

OBSTETRICS & GYNECOLOGY



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- 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.*

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obgyn@greenjournal.org.

Date: Jul 31, 2020
To: "Dena Goffman" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-1820

RE: Manuscript Number ONG-20-1820

A Novel Vacuum-induced Hemorrhage Control Device For Rapid Treatment of Postpartum Hemorrhage

Dear Dr. Goffman:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

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

REVIEWER COMMENTS:

Reviewer #1: The aim of this multicenter prospective study was to evaluate the safety and effectiveness of a Vacuum-induced Hemorrhage Control (VHC) device for treatment of postpartum hemorrhage (PPH). The use of the VHC device has been previously reported by the Green Journal in 10 cases of PPH after vaginal delivery (Purwosunu Y et al 2016; 128:33-36).

The paper, as currently written, raises some questions that the authors need to address:

- 1) Alydia Health Inc. provided the study design and protocol, supported data collection and study monitoring and "conducted analysis" (lines 121-122). The authors had access to relevant "aggregated" study data (line 123). What does this mean? The use of the word "aggregated" is not clear enough for the reader who may want to know whether the available data (to the authors) were in a format that would allow them to verify the sponsor's results. This should be clarified;
- 2) The authors chose to create a non-inferiority study design with a comparison group which used the Bakri balloon to treat PPH. In order to establish the treatment success for the Bakri group, Discovery Statistics, Inc. (San Clemente, CA) conducted an analysis of "all known publications" reporting the use of Bakri for PPH and they came up with 10 nonrandomized studies (8 retrospective and 2 prospective) involving a total number of 369 patients (Table 1). It is not clear why the authors did not use for comparison the results of the recently published metaanalysis of uterine balloon tamponade studies which included 91 studies (6 RCTs, 1 cluster RCT, 15 nonrandomized studies and 69 case series) and 4,729 patients (Suarez S et al Am J Obstet Gynecol 2020; 222:293.e1-52). The aforementioned metaanalysis includes a much greater number of patients and it has already undergone peer-review so that its results should be more reliable than the results of the Discovery Statistics Inc. (meta)analysis which includes a much smaller number of patients and it has not undergone peer-review;
- 3) The criteria for enrollment with respect to the estimated blood loss should be clarified as there is no agreement between the criteria described in lines 176-177 and those described in lines 185-186;
- 4) Only investigators who were trained on VHC device placement placed the device during the study period. More details should be provided regarding the type of training and prerequisites before being able to apply the device clinically. Was simulation part of the training? How many insertions, on the average, one would need to perform in order to be considered adequately trained?
- 5) It is interesting that uterine artery embolization was included under "non-surgical" treatments. In my opinion, it

should be considered under "surgical" treatments;

- 6) The "modified" intent to treat analysis may be omitted because it violates the principles of the intent to treat analysis. Instances where the device could not be placed properly, i.e. because of fibroid uterus or malfunctioning wall-suction, should be included in a traditional "intent to treat analysis". The use of this new term "modified" is confusing and it does not enhance the value of the paper;
- 7) It is not clear to me what the rectangle-shaped box (filled with questions and answers) placed above line 245 (and above the RESULTS heading) represents or means;
- 8) In the "Discussion", the authors should elaborate regarding the cost of the VHC device;
- 9) In summary, I believe that this device may improve the management of PPH, as compared to the Bakri balloon or other uterine packing methods, because of its more physiologic mechanism of action and also because the ability to observe and monitor ongoing blood loss. The information of this paper should be published but the paper should be simplified by omitting the VHC comparison with the results of an unpublished metaanalysis (i.e. the 10 studies shown in Table 1). Instead, the comparison may be made with the recently published metaanalysis by Suarez S et al (Am J Obstet Gynecol 2020; 222:293.e1-52); the paper will still hold its value because the VHC device results (treatment success 96%; 95% CI: 90%-99%) are very favorable as compared to uterine balloon tamponade results (treatment success 85.9%; 95% CI: 83.9%-87.9%). The study has value even as a descriptive study but if the authors choose a non-inferiority design (which in my opinion is not necessary), the results of the published metaanalysis by Suarez may be the correct comparison.

Reviewer #2:

1. My main concerns lie with the study design. I note "suboptimal", somewhat subjective assessment of inclusion criteria (see later), outcome parameters and the comparison to the study group utilized and published in AJOG (reference #20) regarding success of the intrauterine Bakri balloon (a control group I was never comfortable with). The authors acknowledge and describe these limitations of their study. Clearly the preferred study design would be a randomized study group.

2. I draw your attention to inclusion criteria (lines 175-177), which are not inline with the current ACOG definition of postpartum hemorrhage (PPH) of 1000 mL, irrespective of mode of delivery..

ACOG Practice Bulletin Number 183 (October 2017) states: "The American College of Obstetricians and Gynecologists' (ACOG) reVITALize program defines postpartum hemorrhage as cumulative blood loss greater than or equal to 1,000 mL or blood loss accompanied by signs or symptoms of hypovolemia within 24 hours after the birth process (includes intrapartum loss) regardless of route of delivery. This is in contrast to the more traditional definitions of postpartum hemorrhage as an estimated blood loss in excess of 500 mL after a vaginal birth or a loss of greater than 1,000 mL after a cesarean birth. This new classification is likely to reduce the number of individuals labeled with postpartum hemorrhage. However, despite this new characterization, a blood loss greater than 500 mL in a vaginal delivery should be considered abnormal and should serve as an indication for the health care provider to investigate the increased blood deficit".

The authors attempt to mitigate this discrepancy, the rather vague / opaque statements in lines # 185- stating that "Enrollment could occur when a patient's total EBL reached 500 - 1500 mL within 24 hours after a vaginal delivery or 1000 - 1500 mL with 24 hours after Ceasrean delivery" (see lines # 185 - 186). In my assessment, this is insufficient.

Furthermore, the vast majority of participants (85% of participants) delivered vaginally (and as stated sustained hemorrhages which may not fulfill the well defined current criteria for PPH df 1000mL).

The above concerns contrast the statement in the first line of the Results section (see lines 248-249) stating "A total of 107 subjects were included in the study each diagnosed with PPH(?)...".

This point is especially pertinent given that the study commenced in February 2018, following publication of the above ACOG Practice Bulletin in October 2017.

Overall, the definition of postpartum hemorrhage utilized in the study is notably absent in the Abstract.

In fact, the only objective assessment of amount of hemorrhage is provided regarding the transfusion of four or more units of PRBCs in 5/104 (~5%) of patients. A "contrarian" explanation for the relative low rate of massive blood replacement/transfusion required in this study may lie with the less than 1000 mL of hemorrhage required for the definition of postpartum hemorrhage and lenient or less strict inclusion criteria. Worded more critically, patients may have been included, the device applied and clinical success may have incorrectly been attributed in cases in which postpartum hemorrhage did not occur. In essence this might skew results to reflect success, again to incorrectly include cases where

clinically significant postpartum hemorrhage did not occur / or at least did not merit additional management to the pharmaceutical management of uterine atony, already administered.

While I am aware of the clinical importance of immediate response to even "suspected" PPH preferably prior to the defining loss of 1000 mL. Notwithstanding, it is critically important to establish strict inclusion criteria in the evaluation of novel device to manage PPH prior to this modality becoming a mainstay of current management of PPH.

What were transfusion rates of fewer than 4 units of PRBCs?

3. In addition to the above point, I note the absence of clinical parameters of blood loss or clinical shock (blood pressure, tachycardia, oliguria), or laboratory values [predelivery versus postpartum Hb/Hct, or preferably currently with commercially available, precise, point of care, non-invasive photo-optical based continuous total hemoglobin (SpHb) level assessment device designed specifically for OR or L+D utilization to determine intraoperative hemoglobin levels].

4. Outcome parameters assessed are subjective. For example:

a. (see lines # 195-197), in the absence of strict EBL inclusion criteria of 1000 mL, or clinical parameters of shock, one could argue that endpoint of "subjects successfully treated for PPH defined as the avoidance of other surgical or non-surgical modalities after the device was placed" might have been observed similarly without application of the intrauterine negative pressure device.

b. I question the objectivity of the assessment of "time to uterine cavity collapse" (line # 298). Objective fundal height measurements (before and after application of the device) in centimeters (cm) might have been more objective. Similarly see line # 345, stating "palpable change in the uterine tone".

c. I am not clear what criteria merited the designation of "hemorrhage control" (line 298, and Figure 5)? Postpartum hemorrhage seldom abates completely. What cutoff point was utilized (possibly hemorrhage/unit of time). If so, what were these criteria to determine hemorrhage cessation?

5. I note the absence of data pertaining to the incidence of postpartum hemorrhage during the study periods in the various participating institutions, respectively.

6. A clear prerequisite of application of this (or any other similar device), for the indication of postpartum hemorrhage of any patient is confirming integrity of the uterine musculature, and the absence of cervical or vaginal lacerations. This should be stated clearly early in the manuscript. This is addressed later. Indeed, I note that in one of the failures was attributed to lacerations of the birth canal.

7. I am not clear how in the case of immediate postpartum hemorrhage following vaginal birth, how the previously fully dilated cervix can be truly occluded to create a sealed negative intrauterine pressure?

8. The description of the device as "Vacuum-induced hemorrhage Control", which as stands is somewhat vague, might be enhanced with addition of the descriptive term "Intrauterine", to read "Intrauterine vacuum induced hemorrhage control".

9. Similarly, following that this device is used for / and has been assessed in this study for the indication of "postpartum" hemorrhage, I believe this should be referred to as the title, throughout the text as an "Intrauterine vacuum-induced control of postpartum hemorrhage".

10. The first sentence in the Introduction (lines 86-87) should be referenced.

11. Lines # 113-116: I am unclear with the terminology "physiologic treatment". Possibly, this could be better described by "assisting postpartum uterine contraction", or "convolution of the uterus". Placement of an intrauterine device cannot be described as "physiologic treatment". Later (see line # 138) the authors correct state "facilitate physiologic contraction of the atonic uterus". The latter description is favorable to the former. Notwithstanding the continued statement (see line # 139) I believe it is not the negative pressure that compresses the uterine vessels". Simply enhancing uterine contraction will indirectly assist in compressing uterine vessels.

12. Line # 152: Rather than "a manual sweep of the uterine cavity is customarily performed", I suggest the authors state "uterine integrity and the absence of retained placental components are "confirmed" or are "ascertained" prior to intrauterine or intracavitary placement of the device".

13. In my assessment, the authors should consider another advantage of this novel device is avoiding sharp (or vacuum) postpartum curettage (often applied in cases of postpartum hemorrhage - especially following vaginal birth), which may damage the decidua/endometrium and predispose or lead to subsequent Asherman's Syndrome.

14. Table 1 (previously published publications) is not contributory, and may be referenced without being included.

15. The statement in lines # 334-336, regarding "the potential of the device to mechanically achieve the goal of pharmaceutical uterotonics, contraction of the uterus when this does not occur spontaneously", is unsubstantiated and

speculative in that patients also received uterotonic medications.

16 Abstract: Line # 71: I am not clear with the terminology "Definitive control of hemorrhage".

17. Lines # 370-372: I suggest the authors refrain from self complimentary statements "prospective study design", "rigorously defined protocol". Similarly in lines # 383; "there are numerous additional potential benefits of this novel therapeutic approach". I would simply suffice with the shorter duration of therapy in contrast to the Bakri Balloon. Although possibly correct, the comment regarding application of the device in facilitating maternal-newborn bonding and allowing breastfeed initiation is unsubstantiated, and speculative.

18. Lines 53-54: As mentioned in point # 8, the précis statement should include "intrauterine" or "intracavitary" vacuum-induced hemorrhage control etc...

Reviewer #3: The authors have presented a multicenter prospective study evaluating the safety and efficacy of a new device for the treatment of postpartum hemorrhage (PPH)

Postpartum hemorrhage is an important problem in obstetrics and is a leading cause of pregnancy-related death and morbidity. While several therapeutic options are currently available, they all have their limitations, as discussed in the manuscript. Thus, new, effective therapies are always needed.

The manuscript is very well written and the design is sound. The authors have defined both efficacy and safety end-points. The conclusions are valid.

A few issues:

1. In the abstract conclusion, the "much-needed" is promotion of a commercial product. I suggest removing those words.
2. I also suggest including some wording about the non-inferiority of the VHC in the abstract.
3. The PPH encountered was for the most part mild. How do the authors see this device as working in the context of severe PPH? In other words, it appears that for most patients the device was used early in the PPH cascade. Often the secondary treatments, such as a balloon are used when the PPH is really heavy.
4. The authors mention the financial and other disclosures. I may have missed it, but the only disclosure I saw in the manuscript is that the study was funded by Alydia Health. Since this is an industry funded study with a commercial product, perhaps a more detailed disclosure would be appropriate?

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

Abstract: Need to include CIs for proportions cited on lines 70 (8/107) and 73 (5/104). Need to elaborate on the number of women in whom "definitive control of hemorrhage" and about whom the median 3 mins refers.

lines 214-222, Fig 4: The primary outcome should be the overall success rate with CIs. The comparisons with the meta-analyses for Bakri are complicated. First, the patients in this series predominantly (85% per Table 4) had vaginal deliveries, so comparison with other pooled analyses with higher proportions of PPH after cesarean deliveries is an unfair comparison. Also, as shown in the reference by Suarez et al, the rates of success with Bakri not only varied by delivery (87% vaginal vs 82% cesarean), but by cause of PPH. Also, the method used in the present study to estimate CIs does not appear to be the same method used in the meta-analyses to calculate those CIs. So, the Bakri groups may not be comparable to those in the present study and the statistical methods used to estimate CIs appear to be different, so comparison of the groups for non-inferiority appears faulty. Furthermore, the Authors appear to be using a non-inferiority test for their hypothesis, but then showing in Fig 4 a test for difference, not a test for non-inferiority. Need to formulate, apply and present a consistent test of the hypothesis.

Table 2, 3, 4: Since the total = 107 in almost all cases, should make the table entries more concise by simply entering the data as n(%) for each row entry, rather than repeating x/107 (%) for each entry and noting the exceptions in Table or footnote to Table.

EDITOR'S COMMENTS:

We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues and other relevant topics. Adherence to these requirements with your revision will avoid delays during the revision process by avoiding re-revisions on your part in order to comply with formatting. For instance, there are no subheadings within the major headings, such as "Methods".

Numbers below refer to line numbers.

53. As Vacuum-induced hemorrhage control is not a proprietary name, it should not be capped. Given that you included a relatively small number of women (n=107) the paper is underpowered to assess safety. This should be removed from the precis, and elsewhere. I realize it was one of your objectives, but complications of the comparable balloon device are quite low so you would need a large number of patients to assess safety.

58. VHC is not an acceptable abbreviation. Neither is UBP (105) Please spell out throughout the manuscript.

60. This is known as a primacy claim: yours is the first, biggest, best study of its kind. It should be removed from the abstract and the, in order to make such a claim, in the manuscript please provide the data bases you have searched (PubMed, Google Scholar, EMBASE for example) and the search terms used. IF not done, please edit it out of the paper.

As noted by reviewers, definition of PPH needs to be included.

63. Define 'controlled hemorrhage'. Later, what is "definitive control"?(line 71)

66. How was usability defined?

69. By "non surgical" do you mean no additional uterotonics were given?

70. What do you mean by "unexpected". Please instead describe the adverse events themselves.

72. In the methods you said you would report transfusion rates; here you've only reported transfusion of $> =4$ units. Please provide both overall and major transfusion rates.

92 "new" and "innovate" are redundant.

92. This is an important point as discussed by one of the reviewers. Your definition of PPH is different than that of ACOG and included some women, perhaps, who might be considered to have mild PPH. Here you are indicating that you are trying to treat the PPH before morbidity occurs. Perhaps you could make an argument for earlier intervention than awaiting a 1000 cc blood loss to initiate treatment?

108. Can you give some range of frequency of complications with the uterine balloon? Also, any comment about difficulties placing it? Also, can you comment about whether outward pressure seems physiologic? You make a point of this in favor of the vacuum device on line 114.

116. was the prior study in the US also? You make a point that this one is in the US

123. Your funding statement is quite thorough. One reviewer asked for more details about "aggregate data". Can you comment on this? Does this mean you had individual patient data but not by site?

137-140 is redundant from your introduction. Please pick one place for it.

144. What is a regulated vacuum source? Is this wall suction? Can the vacuum be created by hand for low resource settings?

152. how is it introduced? Is it fed in like a rope? Is there an introducer device? What is the goal placement? Fundal?

153-155. Also previously described above. Please condense your description of the device into one place.

170. Do you recommend use of antibiotics prophylactically? Concomitant use of uterotonics? Fundal massage?

175. Does this mean you excluded women w/ fibroids?

When did you consent women? Please condense information about consent process. I see more online 180-182. During the treatment for PPH or earlier in labor?

178. Will need to point out in the discussion that you only included women with mild to moderate hemorrhage—has not been tested with > 1500 ml

179. Please note that your study was conducted from date 1 to date 2, not between those dates. As written, it would exclude the dates given.

187. For clarity, the device was never placed during a cesarean like one can do w/ a bakri?

Lines 188-192. This is a lot of study personnel to have on hand in the event of a hemorrhage. Where the residents, a lot of faculty considered study personnel or were these study nurses or staff separate from the clinical staff?

204. when was this questioned asked of the clinician?

208. While this is an interesting approach, it seems to mask the fact that you've really have an observational trial. Please reformat the analysis as a descriptive study, eliminating the "non inferiority" approach. As you do not have a comparison arm in your trial, you should just present the descriptive statistics and in the discussion, compare your results to those of the Bakri.

Which treatment effect did you use? 82 or 86%

225. Where did the 3.1% come from ?

229. What do you mean by "independent statistician"?

239. What end points were required at the 6 week visit that warranted a "lost to follow up" concern? I would delete the PP analysis.

I also have concerns about using the mITT for the effectiveness. The effectiveness of the device that is of interest is related to the intention to use the device and how that works out, not how it worked out when failure to place it or some other technical issue prevented its deployment. The primary effectiveness analysis should be reported on the enrolled cohort (n=107); if you want to then as a secondary analysis, report the mITT you are welcome to do so.

The other effectiveness analyses mentioned on 242 can be reported in Supplemental Digital Content.

294. On line 278 you indicated that control was achieved in this group in 95/97. Please clarify

318. Can you clarify that what you are reporting here is related to blood loss after device in use?

Do you have any measure of patient experience? Is this painful on insertion, with vacuum development or with removal?

320. Which study investigators? Please address in the methods.

Discussion needs to be rewritten to discuss comparison with historical literature.

331. Can you tell us what sort of training was needed to be allowed to place the device, to speak to the learning curve.

347. You've not made this assertion before. Is this also true of Bakri collection?

351. This line suggests that the vacuum device may be useful for "non specific" presentations. Isn't it only useful for Atony?

387. I'm not aware that an indwelling Bakri is a contraindication to breastfeeding. Women with a Bakri do, in my experience, have increased discomfort compared to women without one, but I'm not sure if that's related to the Bakri itself or the likely difficult delivery, anemia, etc that they are experiencing. I've taken care of many women with Bakris, however, who are breastfeeding. Either provide some evidence that use of the Bakri precludes initiation of breastfeeding or delete this.

Can you comment on cost?

You will need to delete figure 4 based on above comments.

Figure 6 can be moved to SDC.

Table 1 can be moved to SDC

Table 2. The AMA style manual, which the Journal uses, asks that "authors to provide an explanation 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)."

In addition, the the nonspecific "other" as it is sometimes used for comparison in data analysis may also be a "convenience" grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument.

Also, White and Black, as racial categories, are now capitalized.

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.
- B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

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

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

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

4. Obstetrics & Gynecology follows the Good Publication Practice (GPP3)* guideline for manuscripts that report results that are supported or sponsored by pharmaceutical, medical device, diagnostics and biotechnology companies. The GPP3 is designed to help individuals and organization maintain ethical and transparent publication practices.

(1) Adherence to the GPP3 guideline should be noted in the cover letter.

(2) For publication purposes, the portions of particular importance to industry-sponsored research are below. In your cover letter, please indicate whether the following statements are true or false, and provide an explanation if necessary:

(2a) All authors had access to relevant aggregated study data and other information (for example, the study protocol) required to understand and report research findings.

(2b) All authors take responsibility for the way in which research findings are presented and published, were fully involved at all stages of publication and presentation development and are willing to take public responsibility for all aspects of the work.

(2c) The author list accurately reflects all substantial intellectual contributions to the research, data analyses, and publication or presentation development. Relevant contributions from persons who did not qualify as authors are disclosed in the acknowledgments.

(2d) The role of the sponsor in the design, execution, analysis, reporting, and funding (if applicable) of the research has been fully disclosed in all publications and presentations of the findings. Any involvement by persons or organizations with an interest (financial or nonfinancial) in the findings has also been disclosed.

(2e) All authors have disclosed any relationships or potential competing interests relating to the research and its publication or presentation.

(3) The abstract should contain an additional heading, "Funding Source," and should provide an abbreviated listing of the funder(s).

(4) In the manuscript, a new heading—"Role of the Funding Source"—should be inserted before the Methods and contain a detailed description of the sponsor's role as well as the following language:

"The authors had access to relevant aggregated study data and other information (such as study protocol, analytic plan and report, validated data table, and clinical study report) required to understand and report research findings. The authors take responsibility for the presentation and publication of the research findings, have been fully involved at all stages of publication and presentation development, and are willing to take public responsibility for all aspects of the work. All individuals included as authors and contributors who made substantial intellectual contributions to the research, data analysis, and publication or presentation development are listed appropriately. The role of the sponsor in the design, execution, analysis, reporting, and funding is fully disclosed. The authors' personal interests, financial or non-financial, relating to this research and its publication have been disclosed." Authors should only include the above statement if all of it is true, and they should attest to this in the cover letter (see #2, above).

*From Battisti WP, Wager E, Baltzer L, Bridges D, Cairns A, Carswell CI, et al. Good publication practice for communicating company-sponsored medical research: GPP3. *Ann Intern Med* 2015;163:461-4.

5. Your submission indicates that one or more of the authors is employed by a pharmaceutical company, device company, or other commercial entity. This must be included as a statement in the Financial Disclosure section on the title page.

6. Figures 1 and 2:

Tables, figures, and supplemental digital content should be original. The use of borrowed material (eg, lengthy direct quotations, tables, figures, or videos) is discouraged. If the material is essential, written permission of the copyright holder must be obtained.

Both print and electronic (online) rights must be obtained from the holder of the copyright (often the publisher, not the author), and credit to the original source must be included in your manuscript. Many publishers now have online systems for submitting permissions request; please consult the publisher directly for more information. Permission is also required for material that has been adapted or modified from another source. Increasingly, publishers will not grant permission for modification of their material. Creative Commons licenses and open access have also made obtaining permissions more challenging. In order to avoid publication delays, we strongly encourage authors to link or reference to the material they want to highlight instead of trying to get permission to reprint it. For example, "see Table 1 in Smith et al" (and insert reference number). For articles that the journal invites, such as the Clinical Expert Series, the journal staff does not seek permission for modifications of material — the material will be reprinted in its original form.

When you submit your revised manuscript, please upload 1) the permissions license and 2) a copy of the original source from which the material was reprinted, adapted, or modified (eg, scan of book page(s), PDF of journal article, etc.).

If the figure or table you want to reprint can be easily found on the internet from a reputable source, we recommend providing a link to the source in your text instead of trying to reprint it in your manuscript.

7. 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.

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

9. 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).

10. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results

found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words. Please provide a word count.

11. 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.

12. 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.

13. 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 (NNT_h). 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%).

14. 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.

15. Figures

Figures 1-2: Are these figures original to the manuscript? Were they provided by the manufacturer? Were they created by an illustrator for this manuscript? Permission may be necessary for print and online use.

Figure 3: Please consider adding exclusion boxes to the top of the figure.

Figure 4-5: These can be resubmitted as-is.

Figure 6: Please remove all patterned bars, as they do not translate well to print. You are welcome to use any solid colors.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at <http://ong.editorialmanager.com>. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (<http://edmgr.ovid.com/ong/accounts/authors.pdf>), and

* A point-by-point response to each of the received comments in this letter.

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

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

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

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

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: <https://www.editorialmanager.com/ong/login.asp?a=r>). Please contact the publication office if you have any questions.

Re-Submission Date: August 17, 2020

Nancy C. Chescheir, MD
Obstetrics & Gynecology
409 12th Street, SW
Washington, DC 20024

Dear Dr. Chescheir:

We are pleased to re-submit our manuscript now entitled, “**Intrauterine Vacuum-Induced Hemorrhage Control Device for Rapid Treatment of Postpartum Hemorrhage**” for consideration as an “Original Research” publication in *Obstetrics & Gynecology*. We appreciate the feedback from your reviewers and editorial team and recognize that the manuscript is significantly improved based on it.

This manuscript describes our multicenter prospective single arm treatment study of a novel intrauterine device that utilizes low-level vacuum to treat postpartum hemorrhage undertaken at 12 centers in the United States. Based on the feedback of multiple reviewers, we have modified our approach and now present our work as an observational study. We believe this contribution is timely and that this device will provide a new and important additional treatment option for abnormal postpartum uterine bleeding or PPH that is safe and has the potential to assist in the prevention of severe maternal morbidity and mortality.

The trial is registered: Safety and Effectiveness of the Jada System in Treating Primary Postpartum Hemorrhage (PEARLE),
<https://clinicaltrials.gov/ct2/show/NCT02883673?term=jada&draw=2&rank=1>, NCT02883673.
IRB approval was obtained at all sites.

The following table was provided in the methods section of the manuscript but has been removed based on reviewer feedback and is now only included here to reflect the author’s data sharing statement:

Will individual participant data be available (including data dictionaries)? *Yes*.
What data in particular will be shared? Individual participant data that underlie the results reported in this article, after deidentification. Only summary tables, figures, and text will be available.
What other documents will be available? None.
When will data be available (start and end dates)? Beginning 6 months and ending 36 months after article publication.
With whom? Investigators who provide a methodologically sound proposal and whose proposed use of the data has been approved by an independent review committee.
For what type of analyses? For meta-analysis.
By what mechanism? Proposals and requests should be directed to kathryn@alydiahealth.com

Dr. Dena Goffman

CUIMC/NewYork-Presbyterian Morgan Stanley Children's Hospital

[REDACTED]

Good Publication Practice (GPP3) guidelines were followed. The authors had access to relevant aggregated study data (data from each of their individual sites as well as the overall study analysis) and other information (such as study protocol, analytic plan and report, validated data table, and clinical study report) required to understand and report research findings. The authors take responsibility for the presentation and publication of the research findings, have been fully involved at all stages of publication and presentation development including revisions, and take public responsibility for all aspects of the work. All individuals included as authors and contributors who made substantial intellectual contributions to the research, data analysis, and publication or presentation development are listed appropriately. 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 role of the sponsor in the design, execution, analysis, reporting, and funding is fully disclosed. The authors' personal interests, financial or non-financial, relating to this research and its publication have been disclosed. STROBE guidelines were used in manuscript preparation.

The authors affirm that the manuscript is being submitted only to the *Obstetrics & Gynecology*. A closely related manuscript will not be submitted elsewhere while under consideration, has not been submitted or published elsewhere, and, should this manuscript be published in the *Obstetrics & Gynecology*, will not be published elsewhere—either in similar form or verbatim—without permission of the editors. The data from this study is currently under FDA review pending approval.

I have read the Instructions for Authors. Please find our point-by-point response to each of the reviewers' comments included below.

We would like to suggest that Figure 2A be considered as cover art. We will submit by August 31st a video to be available in the publication of this manuscript. It is an animation of the use of the study device.

Thank you for your consideration of our manuscript for publication. We look forward to hearing from you.

Sincerely,

Dena Goffman, MD

Columbia University Irving Medical Center

[REDACTED]

REVIEWER COMMENTS:

Reviewer #1: The aim of this multicenter prospective study was to evaluate the safety and effectiveness of a Vacuum-induced Hemorrhage Control (VHC) device for treatment of postpartum hemorrhage (PPH). The use of the VHC device has been previously reported by the

Green Journal in 10 cases of PPH after vaginal delivery (Purwosunu Y et al 2016; 128:33-36).

The paper, as currently written, raises some questions that the authors need to address:

1) Alydia Health Inc. provided the study design and protocol, supported data collection and study monitoring and "conducted analysis" (lines 121-122). The authors had access to relevant "aggregated" study data (line 123). What does this mean? The use of the word "aggregated" is not clear enough for the reader who may want to know whether the available data (to the authors) were in a format that would allow them to verify the sponsor's results. This should be clarified;

Author response: Thank you. The reference to “aggregated study data” has been removed to avoid confusion. The Sponsor’s role included data analysis by an independent statistician (Advanced Research Associates), and relies on the analysis plan and associated study report submitted to FDA for the Jada System submission. Authors at sites had access to their single-center data and the overall study analysis output.

2) The authors chose to create a non-inferiority study design with a comparison group which used the Bakri balloon to treat PPH. In order to establish the treatment success for the Bakri group, Discovery Statistics, Inc. (San Clemente, CA) conducted an analysis of "all known publications" reporting the use of Bakri for PPH and they came up with 10 nonrandomized studies (8 retrospective and 2 prospective) involving a total number of 369 patients (Table 1). It is not clear why the authors did not use for comparison the results of the recently published metaanalysis of uterine balloon tamponade studies which included 91 studies (6 RCTs, 1 cluster RCT, 15 nonrandomized studies and 69 case series) and 4,729 patients (Suarez S et al Am J Obstet Gynecol 2020;222:293.e1-52). The aforementioned metaanalysis includes a much greater number of patients and it has already undergone peer-review so that its results should be more reliable than the results of the Discovery Statistics Inc.

(meta)analysis which includes a much smaller number of patients and it has not undergone peer-review;

Author response: As the study design was developed and written in 2015 and FDA approved in 2016 the original literature used in the comparison within the protocol and agreed to by the FDA is now outdated and was never published, so we understand the confusion. The Suarez meta-analysis published recently (2020) was referenced with an intent to be more relevant. However, we value the reviewers and Editor feedback suggesting that this study would be better described as “observational”. We have adopted this approach, which streamlines and clarifies the outcomes of the study. We reference the Suarez meta-analysis within the body of the paper, but have modified the methods and results sections to reflect the updated study design as observational rather than a non-inferior trial design. The Suarez article is now referenced in lines 123-124. The observational study design is referenced in line 153.

3) The criteria for enrollment with respect to the estimated blood loss should be clarified as there is no agreement between the criteria described in lines 176-177 and those described in lines 185-186.

Author response: Thank you for finding this discrepancy. The range of EBL for inclusion was clarified and the separate mention of it was removed. Find changes in lines 201-202.

4) Only investigators who were trained on VHC device placement placed the device during the study period. More details should be provided regarding the type of training and prerequisites before being able to apply the device clinically. Was simulation part of the training? How many insertions, on the average, one would need to perform in order to be considered adequately trained?

Author response: The protocol training included two types of training for all investigators: a) didactic training on the instructions for use of Jada and the protocol and b) hands-on training using a uterine model. The manuscript has been updated to include a description of training in lines 222-226.

5) It is interesting that uterine artery embolization was included under "non-surgical" treatments. In my opinion, it should be considered under "surgical" treatments;

Author response: Thank you for noting this and for clarification we have added "open" to surgical description for clarification. See lines 233 and 236 for references to open surgical options.

6) The "modified" intent to treat analysis may be omitted because it violates the principles of the intent to treat analysis. Instances where the device could not be placed properly, i.e. because of fibroid uterus or malfunctioning wall-suction, should be included in a traditional "intent to treat analysis". The use of this new term "modified" is confusing and it does not enhance the value of the paper;

Author response: Thank you for this suggestion. We have removed all references to and analysis of the mITT cohort from the manuscript. The FDA recently responded to the regulatory submission with their questions including discussion specifying that the primary effectiveness analysis must be on the ITT cohort which was pre-defined in the protocol as "All subjects in whom treatment was attempted with Jada (device inserted and vacuum turned on)". FDA also allowed a description of the mITT cohort (and the PP cohort) to remain in the study report and device labeling. According to the protocol and FDA feedback, we have modified the effectiveness endpoint herein to describe use of the Jada System in the pre-planned ITT cohort of 106 subjects in whom treatment was attempted (device inserted and vacuum turned on). We have described the one subject who is removed from this analysis. See Results section lines 262-266 and Figure 3 "Subject Disposition".

7) It is not clear to me what the rectangle-shaped box (filled with questions and answers) placed above line 245 (and above the RESULTS heading) represents or means;

Author response: Thank you. While this language is required to be submitted to the Green Journal, it has been removed from the body of the manuscript and instead placed in the

cover letter.

8) In the "Discussion", the authors should elaborate regarding the cost of the VHC device;

Author response: The device is not yet cleared by FDA and as such the cost is not finalized so is not available for the Discussion section of this manuscript.

9) In summary, I believe that this device may improve the management of PPH, as compared to the Bakri balloon or other uterine packing methods, because of its more physiologic mechanism of action and also because the ability to observe and monitor ongoing blood loss. The information of this paper should be published but the paper should be simplified by omitting the VHC comparison with the results of an unpublished metaanalysis (i.e. the 10 studies shown in Table 1). Instead, the comparison may be made with the recently published metaanalysis by Suarez S et al (Am J Obstet Gynecol 2020; 222:293.e1-52); the paper will still hold its value because the VHC device results (treatment success 96%; 95% CI: 90%-99%) are very favorable as compared to uterine balloon tamponade results (treatment success 85.9%; 95% CI: 83.9%-87.9%). The study has value even as a descriptive study but if the authors choose a non-inferiority design (which in my opinion is not necessary), the results of the published metaanalysis by Suarez may be the correct comparison.

Author response: Thank you for your thorough review and support. As noted above, the manuscript is improved by your suggestions, and is now described as an "observational" study without the confusion of literature comparator or non-inferiority design. The design is described as "observational" in line 153. The meta-analysis by Suarez et. al. is referenced in lines 123-124.

Reviewer #2:

1. My main concerns lie with the study design. I note "suboptimal", somewhat subjective assessment of inclusion criteria (see later), outcome parameters and the comparison to the study group utilized and published in AJOG (reference #20) regarding success of the intrauterine Bakri balloon (a control group I was never comfortable with). The authors acknowledge and describe these limitations of their study. Clearly the preferred study design would be a randomized study group.

Author response: Thank you for your review. Please find point-by-point responses below, and modifications and improvements to the manuscript based on your thoughtful questions and suggestions. We reference the limitation of this study as non-randomized in lines 394-398.

2. I draw your attention to inclusion criteria (lines 175-177), which are not in line with the current ACOG definition of postpartum hemorrhage (PPH) of 1000 mL, irrespective of mode of delivery.

ACOG Practice Bulletin Number 183 (October 2017) states: "The American College of Obstetricians and Gynecologists' (ACOG) reVITALize program defines postpartum hemorrhage

[REDACTED]

as cumulative blood loss greater than or equal to 1,000 mL or blood loss accompanied by signs or symptoms of hypovolemia within 24 hours after the birth process (includes intrapartum loss) regardless of route of delivery. This is in contrast to the more traditional definitions of postpartum hemorrhage as an estimated blood loss in excess of 500 mL after a vaginal birth or a loss of greater than 1,000 mL after a cesarean birth. This new classification is likely to reduce the number of individuals labeled with postpartum hemorrhage. However, despite this new characterization, a blood loss greater than 500 mL in a vaginal delivery should be considered abnormal and should serve as an indication for the health care provider to investigate the increased blood deficit".

The authors attempt to mitigate this discrepancy, the rather vague / opaque statements in lines # 185- stating that "Enrollment could occur when a patient's total EBL reached 500 - 1500 mL within 24 hours after a vaginal delivery or 1000 - 1500 mL with 24 hours after Cesarean delivery" (see lines # 185 - 186). In my assessment, this is insufficient.

Furthermore, the vast majority of participants (85% of participants) delivered vaginally (and as stated sustained hemorrhages which may not fulfill the well-defined current criteria for PPH df 1000mL).

The above concerns contrast the statement in the first line of the Results section (see lines 248-249) stating "A total of 107 subjects were included in the study each diagnosed with PPH(?)...".

This point is especially pertinent given that the study commenced in February 2018, following publication of the above ACOG Practice Bulletin in October 2017.

Overall, the definition of postpartum hemorrhage utilized in the study is notably absent in the Abstract.

In fact, the only objective assessment of amount of hemorrhage is provided regarding the transfusion of four or more units of PRBCs in 5/104 (~5%) of patients. A "contrarian" explanation for the relative low rate of massive blood replacement/transfusion required in this study may lie with the less than 1000 mL of hemorrhage required for the definition of postpartum hemorrhage and lenient or less strict inclusion criteria. Worded more critically, patients may may been included, the device applied and clinical success may have incorrectly been attributed in cases in which postpartum hemorrhage did not occur. In essence this might skew results to reflect success, again to incorrectly include cases where clinically significant postpartum hemorrhage did not occur / or at least did not merit additional management to the pharmaceutical management of uterine atony, already administered.

While I am aware of the clinical importance of immediate response to even "suspected" PPH preferably prior to the defining loss of 1000 mL. Notwithstanding, it is critically important to establish strict inclusion criteria in the evaluation of novel device to manage PPH prior to this modality becoming a mainstay of current management of PPH.

What were transfusion rates of fewer than 4 units of PRBCs?

Author response: Thank you. In response to your request for clarity on the blood loss required for entry in the study, we have modified the manuscript to reflect accurately the inclusion of abnormal postpartum bleeding (500-999 mL) and PPH (1000-1500 mL) by the ACOG guideline definition. This led to multiple changes throughout the manuscript. Notably the title of the paper was not updated to reflect abnormal postpartum uterine bleeding, where we are limited to a character count, making this additional language impossible to add. We believe that “Postpartum Hemorrhage” in the title should attract the right readers to this study with the additional details included within the body of the paper.

There are many instances in the paper making it impractical to list the lines where bleeding is described that might be treated with the intrauterine vacuum-induced hemorrhage control device. This has been changed throughout for consistency.

While enrollment began in 2018, the study was designed in collaboration with FDA in 2015, with full approval in 2016. The identification of sites and study start up took some time, with sites opened in 2017 and enrollment commencing in 2018, as described in the body of the manuscript.

The manuscript describes that the enrolling investigator must have determined that uterotonics and uterine massage alone were not working to control the abnormal bleeding as an inclusion requirement for the study in lines 203-204 and 216-219. Uterotonics in all cases and TXA in some cases were administered prior to enrollment and the study device was only introduced after the provider in each case determined additional treatment was necessary beyond uterotonics and massage.

Thank you for the suggestion of including the rate of fewer than 4 units RBCs. We have updated the manuscript to include the number of subjects in whom 1-3 units of RBCs were transfused. See lines 71 and 317-318.

3. In addition to the above point, I note the absence of clinical parameters of blood loss or clinical shock (blood pressure, tachycardia, oliguria), or laboratory values [predelivery versus postpartum Hb/Hct, or preferably currently with commercially available, precise, point of care, non-invasive photo-optical based continuous total hemoglobin (SpHb) level assessment device designed specifically for OR or L+D utilization to determine intraoperative hemoglobin levels].

Author response: You have noted that we are missing specific clinical parameters of blood loss. With regard to clinical shock, patients were excluded when EBL prior to enrollment was over 1500 mL for this initial study. Therefore, we would not have expected significant abnormalities in vital signs based on the study design. Additionally, we recognized the significant challenges with using change in Hb/Hct as a proxy for blood loss. These values are altered by so many things including hydration/dilution, hemoconcentration in the setting of preeclampsia, transfusion based on clinical status (not lab driven). However, we did collect all adverse events in the study and there were reports of anemia or worsening anemia leading to transfusion and in some cases, abnormal blood pressure or tachycardia was reported in some cases. None of these reports were attributed to the device. We do not account though for the subjects who did receive immediate blood transfusion, and how that

would impact Hct/Hgb counts so a summary of admission and pre-discharge might not be helpful.

4. Outcome parameters assessed are subjective. For example:

a. (see lines # 195-197), in the absence of strict EBL inclusion criteria of 1000 mL, or clinical parameters of shock, one could argue that endpoint of "subjects successfully treated for PPH defined as the avoidance of other surgical or non-surgical modalities after the device was placed" might have been observed similarly without application of the intrauterine negative pressure device.

Author response: As described in #2 above, the manuscript describes that the enrolling investigator must have determined that uterotonics and massage alone were not working to control the abnormal bleeding as an inclusion requirement for the study. Uterotonics in all cases and TXA in some cases were administered prior to enrollment and the study device was only introduced when the provider in each case determined additional treatment was necessary. Therefore, with the clarification of inclusion of abnormal bleeding, and the protocol recommendations that treatment is necessary and can be determined according to the provider, we believe this study outlines a strong case for treating bleeding with the device early to avoid morbidity including the need for blood replacement. See lines 203-204, 217-219, 412-415.

b. I question the objectivity of the assessment of "time to uterine cavity collapse" (line # 298). Objective fundal height measurements (before and after application of the device) in centimeters (cm) might have been more objective. Similarly see line # 345, stating "palpable change in the uterine tone".

Author response: Thank you for this thoughtful suggestion. You are correct that fundal height measurement was not taken before and after application of the device which may have served as an objective measure. However, we have added in lines 224-226 the description that all investigators were trained to palpate or visualize collapse upon vacuum connection and were able to report this occurrence. Practically this collapse indicates that vacuum is applied and the seal placed at the external cervical os is maintaining pressure in the uterine cavity providing the assist to the uterus in regaining tone.

c. I am not clear what criteria merited the designation of "hemorrhage control" (line 298, and Figure 5)? Postpartum hemorrhage seldom abates completely. What cutoff point was utilized (possibly hemorrhage/unit of time). If so, what were these criteria to determine hemorrhage cessation?

Author response: The definition of hemorrhage control was described in the protocol and there was a checkbox on the data collection form used during the case where the provider would report the first of any of the following as having occurred:

- **there is no blood being collected in the tubing or canister, or**
- **the blood loss is observed as leveled off in the canister, or**
- **blood loss at a rate of < 500 ml in 24 hours.**

The third choice was required by FDA and was intended to be checked if bleeding returned to a normal postpartum rate. If a provider did not determine that hemorrhage was controlled by the device and other treatment was needed (i.e. UBT, compression suture, hysterectomy) that treatment was pursued and reported.

The manuscript has been updated to describe this protocol-defined evaluation in lines 180-181.

5. I note the absence of data pertaining to the incidence of postpartum hemorrhage during the study periods in the various participating institutions, respectively.

Author response: While we agree that this would have been interesting to include, it is not relevant to the outcomes of using the intrauterine vacuum-induced hemorrhage control device, and was not captured in this study. 1.5% of the consented subjects overall were enrolled. Enrollment could only occur when a patient who was already consented was found to meet all eligibility criteria, a trained investigator was present to use the device, and a second study-trained individual was present to collect data pertaining to the case in real-time. In order to be ready to enroll as needed, sites underwent extensive training and included as many providers as possible to have appropriate coverage. Over 700 people were trained at the participating centers.

6. A clear prerequisite of application of this (or any other similar device), for the indication of postpartum hemorrhage of any patient is confirming integrity of the uterine musculature, and the absence of cervical or vaginal lacerations. This should be stated clearly early in the manuscript. This is addressed later. Indeed, I note that in one of the failures was attributed to lacerations of the birth canal.

Author response: In the device “Instructions For Use” it is noted that bleeding source(s) must be evaluated prior to initiating treatment. In line 201 we have added “atony-related” to describe bleeding for enrollment. While one subject is accurately noted in your question as a “failure” this subject should not have been enrolled. In this case, communication after insertion of the device clarified that there might be a different source of bleeding and the device was removed so that the cervix could be checked at that time. Only then, was the laceration to the cervix realized and repaired, after which the abnormal bleeding ceased.

7. I am not clear how in the case of immediate postpartum hemorrhage following vaginal birth, how the previously fully dilated cervix can be truly occluded to create a sealed negative intrauterine pressure?

Author response: When the cervical seal of the device is filled with 60 cc saline the diameter of the balloon reaches 5.5 cm. At provider discretion, they can fill to 120 cc, when the diameter widens to 8 cm. The majority of cases were performed with the seal filled to 60 cc, without determining a need to add additional fluid. There were no reports (in the prior feasibility study or in this present study) where the seal was found to not be of adequate diameter to create a seal at the external cervical os. The recommended fill of 60-120 cc is included in line 175.

8. The description of the device as "Vacuum-induced hemorrhage Control", which as stands is somewhat vague, might be enhanced with addition of the descriptive term "Intrauterine", to read "Intrauterine vacuum induced hemorrhage control".

Author response: Thank you for this suggestion. We have modified this generic procedure description to include “intrauterine” throughout the manuscript.

9. Similarly, following that this device is used for / and has been assessed in this study for the indication of "postpartum" hemorrhage, I believe this should be referred to as the title, throughout the text as an "Intrauterine vacuum-induced control of postpartum hemorrhage".

Author response: Thank you for this suggestion. With the addition of the word “intrauterine” we respectfully do not feel the addition of “postpartum” is necessary in what is intended to be a short, generic description of the procedure, similar to “uterine balloon tamponade”.

10. The first sentence in the Introduction (lines 86-87) should be referenced.

Author response: We have updated and referenced this sentence in line 84.

11. Lines # 113-116: I am unclear with the terminology "physiologic treatment". Possibly, this could be better described by "assisting postpartum uterine contraction", or "convolution of the uterus". Placement of an intrauterine device cannot be described as "physiologic treatment". Later (see line # 138) the authors correct state "facilitate physiologic contraction of the atonic uterus". The latter description is favorable to the former. Notwithstanding the continued statement (see line # 139) I believe it is not the negative pressure that compresses the uterine vessels". Simply enhancing uterine contraction will indirectly assist in compressing uterine vessels.

Author response: We agree that “physiologic treatment” is not a stand-alone descriptor, and we have added language to more accurately describe the effect of the vacuum treatment (see lines 131-134 and 185-187).

12. Line # 152: Rather than "a manual sweep of the uterine cavity is customarily performed", I suggest the authors state "uterine integrity and the absence of retained placental components are "confirmed" or are "ascertained" prior to intrauterine or intracavitary placement of the device".

Author response: In lines 168-170 we have updated the description of manual sweep. Thank you for your comment.

13. In my assessment, the authors should consider another advantage of this novel device is avoiding sharp (or vacuum) postpartum curettage (often applied in cases of postpartum hemorrhage - especially following vaginal birth), which may damage the decidua/endometrium and predispose or lead to subsequent Asherman's Syndrome.

Author response: Thank you. In lines 359-362 we have added this as a potential benefit at your suggestion.

14. Table 1 (previously published publications) is not contributory, and may be referenced without being included.

Author response: Thank you. The reference to this group of publications has been removed as we agree it is not contributory, especially with our modified approach.

15. The statement in lines # 334-336, regarding "the potential of the device to mechanically achieve the goal of pharmaceutical uterotonics, contraction of the uterus when this does not occur spontaneously", is unsubstantiated and speculative in that patients also received uterotonic medications.

Author response: We believe it is important to describe that the device is designed to work to collapse the uterus and this is also the goal of uterotonics, both aimed at solving the abnormal bleeding that results from atony. We hope that it is allowable to include this in the discussion section of the manuscript, however we have slightly modified the sentence in lines 338-341. It would be interesting in future study to randomize the device to treatment with uterotonics which might be informative for comparisons of initial intervention.

16. Abstract: Line # 71: I am not clear with the terminology "Definitive control of hemorrhage".

Author response: Thank you for this question. Definitive control connotes an absence of recurrence or need for additional escalation of treatment. We have included this in the Methods section, in lines 181-182, for clarity.

17. Lines # 370-372: I suggest the authors refrain from self-complimentary statements "prospective study design", "rigorously defined protocol". Similarly, in lines # 383; "there are numerous additional potential benefits of this novel therapeutic approach". I would simply suffice with the shorter duration of therapy in contrast to the Bakri Balloon. Although possibly correct, the comment regarding application of the device in facilitating maternal-newborn bonding and allowing breastfeed initiation is unsubstantiated, and speculative.

Author response: The protocol design is correct as described, but as noted in earlier responses, has been revised to “observational”. The potential benefits are described in the discussion in an effort to describe potential benefits in a more holistic way including perspectives of the provider, the patient and the healthcare system. We have removed the breastfeeding reference in lines 409-412, although do believe that by decreasing time moms are on L&D, thereby minimizing mother-newborn separation that this could impact bonding and breastfeeding. While we do not wish to be perceived as “going too far” we believe that some comment of the potential benefits in the discussion should be included to provide food for thought for the reader. We hope that future studies will include these perspectives as well – patient, provider, healthcare system.

18. Lines 53-54: As mentioned in point # 8, the précis statement should include "intrauterine" or

"intracavitary" vacuum-induced hemorrhage control etc...

Author response: In the precis statement, we have added “intrauterine” according to your suggestion. Thank you for helping us improve this manuscript.

Reviewer #3: The authors have presented a multicenter prospective study evaluating the safety and efficacy of a new device for the treatment of postpartum hemorrhage (PPH)

Postpartum hemorrhage is an important problem in obstetrics and is a leading cause of pregnancy-related death and morbidity. While several therapeutic options are currently available, they all have their limitations, as discussed in the manuscript. Thus, new, effective therapies are always needed.

The manuscript is very well written and the design is sound. The authors have defined both efficacy and safety end-points. The conclusions are valid.

A few issues:

1. In the abstract conclusion, the "much-needed" is promotion of a commercial product. I suggest removing those words.

Author response: In response to this critique, we have removed “much needed” from the abstract conclusion.

2. I also suggest including some wording about the non-inferiority of the VHC in the abstract.

Author response: In response to the reviewers’ comments we have removed the descriptor “non-inferiority” from the design in this manuscript.

3. The PPH encountered was for the most part mild. How do the authors see this device as working in the context of severe PPH? In other words, it appears that for most patients the device was used early in the PPH cascade. Often the secondary treatments, such as a balloon are used when the PPH is really heavy.

Author response: According to FDA requirement, we excluded bleeding > 1500 mL in this initial study. Future research should include more severe hemorrhage as well, but the authors hope that in most cases, the intrauterine vacuum-induced hemorrhage control device could be used earlier, before a patient faces morbidity associated with her bleeding. It would be interesting to study severe hemorrhage to assess effectiveness for further understanding of the technology. There was a single case in this study who was enrolled (violating inclusion criteria) at 2300 mL. Her PPH was controlled in 2 minutes after connection to vacuum. While overall conclusions cannot be made from this single case, it was a positive outcome in the setting of heavy bleeding. Studying the device in severe hemorrhage is added as a suggestion for the future in the Discussion section, lines 398-400.

4. The authors mention the financial and other disclosures. I may have missed it, but the only disclosure I saw in the manuscript is that the study was funded by Alydia Health. Since this is an

[REDACTED]

industry funded study with a commercial product, perhaps a more detailed disclosure would be appropriate?

Author response: The disclosures are thorough. A statement has been included in the revised manuscript to disclose clearly that one author is an employee at the Sponsor – see line 40. We will work with the Green Journal to add any other detail requested.

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

Abstract: Need to include CIs for proportions cited on lines 70 (8/107) and 73 (5/104). Need to elaborate on the number of women in whom "definitive control of hemorrhage" and about whom the median 3 mins refers.

Author response: The 2 proportions cited in original lines 70 and 73 have been removed. The median of 3 minutes to control refers to the women in whom abnormal bleeding or PPH was controlled with the device and the sentence has been modified for clarity in lines 67-68.

lines 214-222, Fig 4: The primary outcome should be the overall success rate with CIs. The comparisons with the meta-analyses for Bakri are complicated. First, the patients in this series predominantly (85% per Table 4) had vaginal deliveries, so comparison with other pooled analyses with higher proportions of PPH after cesarean deliveries is an unfair comparison. Also, as shown in the reference by Suarez et al, the rates of success with Bakri not only varied by delivery (87% vaginal vs 82% cesarean), but by cause of PPH. Also, the method used in the present study to estimate CIs does not appear to be the same method used in the meta-analyses to calculate those CIs. So, the Bakri groups may not be comparable to those in the present study and the statistical methods used to estimate CIs appear to be different, so comparison of the groups for non-inferiority appears faulty. Furthermore, the Authors appear to be using a non-inferiority test for their hypothesis, but then showing in Fig 4 a test for difference, not a test for non-inferiority. Need to formulate, apply and present a consistent test of the hypothesis.

Author response: In response to reviewer input, the manuscript no longer refers to a comparator and is instead written as an observational study, so this question is no longer relevant.

Table 2, 3, 4: Since the total = 107 in almost all cases, should make the table entries more concise by simply entering the data as n(%) for each row entry, rather than repeating x/107 (%) for each entry and noting the exceptions in Table or footnote to Table.

Author response: Thank you for this feedback. The Tables have been revised accordingly.

EDITOR'S COMMENTS:

We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues and other relevant topics. Adherence to these requirements with your revision will avoid delays during the revision process by avoiding re-revisions on your part in order to comply with formatting. For instance, there are no subheadings within the major headings, such as “Methods”.

Author response: Thank you for this feedback. We have removed the subheadings from the “Methods” section accordingly. The Instructions for Authors has been read and applied.

Numbers below refer to line numbers.

53. As Vacuum-induced hemorrhage control is not a proprietary name, it should not be capped. Given that you included a relatively small number of women (n=107) the paper is underpowered to assess safety. This should be removed from the precis, and elsewhere. I realize it was one of your objectives, but complications of the comparable balloon device are quite low so you would need a large number of patients to assess safety.

Author response: Thank you. The term for the procedure name has been revised accordingly. The number of subjects was the maximum allowed per the study design and FDA IDE approval at 107 subjects. The study was approved to evaluate both effectiveness and safety. With at least 96 subjects, the study was powered to identify any risk that would occur at a rate of 3.1% or greater, which is described in line 240. The primary safety endpoint was the incidence, severity, and seriousness of device-related adverse events, described in lines 62-63 and 237-238. The safety evaluation is included in the FDA submission and in this manuscript. We have added a sentence into the discussion section in lines 400-401 that safety of the device should continue to be monitored with additional research studies.

58. VHC is not an acceptable abbreviation. Neither is UBP (105). Please spell out throughout the manuscript.

Author response: We have amended the manuscript accordingly.

60. This is known as a primacy claim: yours is the first, biggest, best study of its kind. It should be removed from the abstract and the, in order to make such a claim, in the manuscript please provide the data bases you have searched (PubMed, Google Scholar, EMBASE for example) and the search terms used. IF not done, please edit it out of the paper.

Author response: Line 60 was the first sentence of the abstract – Methods and described the study design. We do describe the device itself as “novel”. Please clarify if there is something that requires further edits.

As noted by reviewers, definition of PPH needs to be included.

Author response: This has been discussed thoroughly in the responses to reviewer comments and a definition of bleeding included in this study has been included in multiple places within this re-submission.

63. Define ‘controlled hemorrhage’. Later, what is “definitive control”?(line 71)

Author response: The definition of hemorrhage control was described in the protocol and there was a checkbox on the data collection form used during the case where the provider would report the first of any of the following as having occurred:

- there is no blood being collected in the tubing or canister, or
- the blood loss is observed as leveled off in the canister, or
- blood loss at a rate of < 500 ml in 24 hours.

The third choice was required by FDA and was intended to be checked if bleeding returned to a normal postpartum rate. If a provider did not determine that hemorrhage was controlled by the device and other treatment was needed (i.e. UBT, compression suture, hysterectomy) that treatment was pursued and reported.

The manuscript has been updated to describe this protocol-defined evaluation in lines 180-181.

Definitive control connotes an absence of recurrence or need for additional escalation of treatment. We have included this in the Methods section, in lines 181-182, for clarity.

66. How was usability defined?

Author response: Usability was completed by the investigator using the device in each case at the conclusion of the case. It was collected using six questions with a 5-point Likert Scale for response. The questions were:

1. The Instructions for Use and Device Training clearly explained insertion, use, and removal of the device.
2. The Jada System was easy to insert and properly position within the uterus.
3. The Jada System was easy to remove from the uterus once the vacuum was turned off.
4. The Jada System did not prohibit the normal treatment activities of the attending personnel.
5. Overall, the Jada System was easy to use.
6. I would recommend the Jada System to treat postpartum hemorrhage.

The data on each of these questions is shown in Figure 5.

69. By “non surgical” do you mean no additional uterotonics were given?

Author response: “Non-surgical” with regard to characterization of a failure included: UBT, uterine packing, UAE. This is described in lines 235-236. The continuation of

uterotonics was allowed per protocol without impact on the effectiveness evaluation as per standard of care. This is described in lines 208-209.

70. What do you mean by “unexpected”. Please instead describe the adverse events themselves.

Author response: Thank you. We have removed reference to “unexpected” for clarity.

72. In the methods you said you would report transfusion rates; here you’ve only reported transfusion of ≥ 4 units. Please provide both overall and major transfusion rates.

Author response: Thank you. Transfusion rates in the 1-3 unit category and the 4 or more category are included in lines 71-72 and 317-318.

92 “new” and “innovate” are redundant.

Author response: Thank you. We have removed “new” from line 90.

92. This is an important point as discussed by one of the reviewers. Your definition of PPH is different than that of ACOG and included some women, perhaps, who might be considered to have mild PPH. Here you are indicating that you are trying to treat the PPH before morbidity occurs. Perhaps you could make an argument for earlier intervention than awaiting a 1000 cc blood loss to initiate treatment?

Author response: Thank you. We have modified the manuscript to reflect accurately the inclusion of abnormal bleeding (500-999 mL) and PPH (1000-1500 mL) by the ACOG guideline definition. This led to multiple changes throughout the manuscript. See paragraph added to introduction in lines 92-101 and additionally, we have modified the manuscript in many places as indicated to include both PPH (according to ACOG definition) and abnormal postpartum uterine bleeding were included.

108. Can you give some range of frequency of complications with the uterine balloon? Also, any comment about difficulties placing it? Also, can you comment about whether outward pressure seems physiologic? You make a point of this in favor of the vacuum device on line 114.

Author response: Thank you for these suggestions. The frequency of complications attributed to uterine balloon tamponade use was low (up to 6.5%) in the recent meta-analysis by Suarez et al. which is now described in lines 123-124. Reported complications included: Seven studies reported a total of 29 cases of fever or infection after the placement of a UBT device among 445 women (6.5%). Three studies reported a total of 7 cases of endometritis attributed to the use of UBT among 308 women (2.3%) infection as the most common cervical tears (2 among 120 women; 1.7%), acute colonic pseudo-obstruction (1 among 49 women; 2.0%), laceration of the lower segment of the vagina (1 among 21 women; 4.8%), uterine incision rupture (1 among 53 women; 1.9%), and uterine perforation (1 among 49 women; 2.0%).

Complexities of placement of effective balloon tamponade has been added in lines 344-349.

Outward pressure, such as in UBT, does not seem physiologic, as the uterus should naturally contract, thereby controlling bleeding. The contrast is described in lines 341-344.

116. was the prior study in the US also? You make a point that this one is in the US

Author response: The prior feasibility study was conducted outside the U.S.. This detail was added for clarity in line 134.

123. Your funding statement is quite thorough. One reviewer asked for more details about “aggregate data”. Can you comment on this? Does this mean you had individual patient data but not by site?

Author response: The term “aggregate data” was removed for clarity. The authors had access to their individual site raw data in addition to the reported analyzed data for the study.

137-140 is redundant from your introduction. Please pick one place for it.

Author response: Thank you. We have revised accordingly. Please see this in lines 131-134 of the introduction (and it has been removed from the Methods section).

144. What is a regulated vacuum source? Is this wall suction? Can the vacuum be created by hand for low resource settings?

Author response: Thank you. Vacuum source has been clarified in lines 160-161, as related to this study. Vacuum sources available in low-resource settings is a topic of interest being explored currently by the manufacturer of the device.

152. how is it introduced? Is it fed in like a rope? Is there an introducer device? What is the goal placement? Fundal?

Author response: Thank you. The description of placement has been revised for clarity including both the way it is introduced and the goal of placement in lines 170-174.

153-155. Also previously described above. Please condense your description of the device into one place.

Author response: Thank you. The description of the device has been condensed in lines 157-166, without repetition of the design description of the cervical seal.

170. Do you recommend use of antibiotics prophylactically? Concomitant use of uterotonics? Fundal massage?

Author response: Thank you. Antibiotics were not required per protocol, but instead investigators were asked to consider local protocols for coverage with antibiotics for

intrauterine devices and use at their discretion. This is also described in the “Instructions For Use” of the device. Concomitant use of uterotonics was allowed per provider discretion per protocol. Uterine massage was required prior to enrollment and considered to not be working alone with uterotonics and could continue concomitant with device use per provider discretion.

175. Does this mean you excluded women w/ fibroids?

Author response: Thank you for this question. No, fibroids were not excluded per se. However, in one case on study, the provider could not place the device as the path for placement was obstructed by a fibroid.

When did you consent women? Please condense information about consent process. I see more online 180-182. During the treatment for PPH or earlier in labor?

Author response: Thank you. The description of consent timing and the consenting process overall was amended in the manuscript. See lines 214-216.

178. Will need to point out in the discussion that you only included women with mild to moderate hemorrhage—has not been tested with > 1500 ml

Author response: Thank you. Yes, lines 398-400 were added to clarify that severe hemorrhage was not included in this study for safety concerns in the first large study of the device.

179. Please note that your study was conducted from date 1 to date 2, not between those dates. As written, it would exclude the dates given.

Author response: Thank you. The sentence on dates of enrollment was amended in line 211.

187. For clarity, the device was never placed during a cesarean like one can do w/ a bakri?

Author response: Thank you. The device was used after c-sections in 16 subjects, placed transvaginally after the hysterotomy was closed. The placement after cesarean is described in lines 202-203. As it is a lower rate of device use in cesarean compared to after vaginal delivery, it is noted as a limitation of the study in lines 402-404.

Lines 188-192. This is a lot of study personnel to have on hand in the event of a hemorrhage. Where the residents, a lot of faculty considered study personnel or were these study nurses or staff separate from the clinical staff?

Author response: Thank you. Yes, there were over 700 individuals trained at the participating sites overall. Residents, fellows and attendings were included in study trainings for device use. A second investigator or trained research staff could fill out the data collection during the case.

204. when was this questioned asked of the clinician?

Author response: Thank you. The questionnaire was completed at the conclusion of the case and this has been clarified in line 244.

208. While this is an interesting approach, it seems to mask the fact that you've really have an observational trial. Please reformat the analysis as a descriptive study, eliminating the "non inferiority" approach. As you do not have a comparison arm in your trial, you should just present the descriptive statistics and in the discussion, compare your results to those of the Bakri.

Author response: Thank you. The manuscript has been modified according to the reviewer comments, eliminating the non-inferior approach, and instead describing the study as “observational”.

Which treatment effect did you use? 82 or 86%

Author response: Thank you. The manuscript is now formatted as an observational study.

225. Where did the 3.1% come from?

Author response: Thank you. This came from our statistical analysis plan and determination of number of subjects required to evaluate adverse events for safety.

229. What do you mean by “independent statistician”?

Author response: Thank you. The statistician team was from Advanced Research Associates. They are a statistics support company, and are contracted for this expertise and statisticians are not employed directly by the study Sponsor.

239. What end points were required at the 6 week visit that warranted a “lost to follow up” concern? I would delete the PP analysis.

I also have concerns about using the mITT for the effectiveness. The effectiveness of the device that is of interest is related to the intention to use the device and how that works out, not how it worked out when failure to place it or some other technical issue prevented its deployment. The primary effectiveness analysis should be reported on the enrolled cohort (n=107); if you want to then as a secondary analysis, report the mITT you are welcome to do so.

Author response: Thank you. We have agreed to remove the mITT and PP cohort analyses. The analysis cohort that is primary is the ITT cohort, which was also pre-specified in the protocol and approved by FDA, including subjects where treatment was initiated with vacuum.

The other effectiveness analyses mentioned on 242 can be reported in Supplemental Digital Content.

Author response: Thank you. The manuscript has been revised to include 2 cohorts, enrollment, ITT and overall, the study reported as observational. Thank you for your assistance which in our eyes has made it more concise.

294. On line 278 you indicated that control was achieved in this group in 95/97. Please clarify.

Author response: Thank you. The Per Protocol cohort has been removed.

318. Can you clarify that what you are reporting here is related to blood loss after device in use?

Author response: The sentence is clarified that blood evacuation during device use is low in line 319-321.

Do you have any measure of patient experience? Is this painful on insertion, with vacuum development or with removal?

Author response: We have mentioned in the Discussion section in lines 401-402 that a lack of patient-centric data is a limitation of this study. There were no adverse events reported of pain related to the device or the procedure.

320. Which study investigators? Please address in the methods.

Author response: Thank you. We have clarified in the Methods section that the investigators include those who used the device in line 323.

Discussion needs to be rewritten to discuss comparison with historical literature.

Author response: Thank you. The description of the study has been updated according to the reviewer comments to an observational study.

331. Can you tell us what sort of training was needed to be allowed to place the device, to speak to the learning curve.

Author response: Thank you. The description of training for the study is included now in lines 222-226.

347. You've not made this assertion before. Is this also true of Bakri collection?

Author response: Thank you, this is another potential approach that can be explored and was done in one case on the study. We are not aware of cell salvage being done with Bakri.

351. This line suggests that the vacuum device may be useful for "non specific" presentations. Isn't it only useful for Atony?

Author response: Thank you. The statement there (now lines 370-372) is meant to describe that current treatments are each not a catch-all for every patient presentation, and an introduction to more discussion on that topic. However, the device in the study is appropriate only for atony, and this is described specifically throughout the manuscript.

387. I'm not aware that an indwelling Bakri is a contraindication to breastfeeding. Women with a Bakri do, in my experience, have increased discomfort compared to women without one, but I'm not sure if that's related to the Bakri itself or the likely difficult delivery, anemia, etc that they are experiencing. I've taken care of many women with Bakris, however, who are breastfeeding. Either provide some evidence that use of the Bakri precludes initiation of breastfeeding or delete this.

Author response: Thank you. We agree that Bakri is not a contraindication to breastfeeding, however we wrote this as related to a short procedure (vacuum device) versus a longer procedure that takes 12-24 hours (balloon tamponade). In our collective experience women with Bakri balloon require more intensive observation, longer duration of higher level of care and more often newborn separation. The specific reference to breastfeeding has been removed from lines 409-412 and more general benefits of facilitating recovery mentioned.

Can you comment on cost?

Author response: No, as the device is not FDA cleared for market at this time, the cost has not yet been established.

You will need to delete figure 4 based on above comments.

Author response: Thank you. It has been deleted.

Figure 6 can be moved to SDC.

Author response: Thank you. With the deletion of Figure 4, we are hopeful we can keep previously titled Figure 6 where it is (at "Figure 5").

Table 1 can be moved to SDC

Author response: Thank you. This table has been deleted according to the modifications in this current draft.

Table 2. The AMA style manual, which the Journal uses, asks that "authors to provide an explanation 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)."

Dr. Dena Goffman

CUIMC/NewYork-Presbyterian Morgan Stanley Children's Hospital

Author response: Thank you. The description of process on capture of race and ethnicity has been added in lines 211-214.

In addition, the nonspecific “other” as it is sometimes used for comparison in data analysis may also be a “convenience” grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument.

Author response: The category “Other” was available on the research data collection form and has been captured as such in the database.

Also, White and Black, as racial categories, are now capitalized.

Author response: Thank you. Yes, they are written as described in the above comment.

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.

B. OPT-OUT: No, please do not publish my point-by-point response letter.

Author response: OPT-IN. Please publish my point-by-point response letter.

2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

Author response: Thank you for this reminder. This has been done.

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

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

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

Author response. Thank you. This has been addressed in above questions.

4. Obstetrics & Gynecology follows the Good Publication Practice (GPP3)* guideline for manuscripts that report results that are supported or sponsored by pharmaceutical, medical device, diagnostics and biotechnology companies. The GPP3 is designed to help individuals and organization maintain ethical and transparent publication practices.

(1) Adherence to the GPP3 guideline should be noted in the cover letter. **DONE**

(2) For publication purposes, the portions of particular importance to industry-sponsored research are below. In your cover letter, please indicate whether the following statements are true or false, and provide an explanation if necessary:

TRUE

(2b) All authors take responsibility for the way in which research findings are presented and published, were fully involved at all stages of publication and presentation development and are willing to take public responsibility for all aspects of the work. **TRUE**

(2c) The author list accurately reflects all substantial intellectual contributions to the research, data analyses, and publication or presentation development. Relevant contributions from persons who did not qualify as authors are disclosed in the acknowledgments. **TRUE**

(2d) The role of the sponsor in the design, execution, analysis, reporting, and funding (if applicable) of the research has been fully disclosed in all publications and presentations of the findings. Any involvement by persons or organizations with an interest (financial or nonfinancial) in the findings has also been disclosed. **TRUE**

(2e) All authors have disclosed any relationships or potential competing interests relating to the research and its publication or presentation. **TRUE**

(3) The abstract should contain an additional heading, "Funding Source," and should provide an abbreviated listing of the funder(s). **DONE**

(4) In the manuscript, a new heading—"Role of the Funding Source"—should be inserted before the Methods and contain a detailed description of the sponsor's role as well as the following language:

"The authors had access to relevant aggregated study data and other information (such as study protocol, analytic plan and report, validated data table, and clinical study report) required to understand and report research findings. The authors take responsibility for the presentation and publication of the research findings, have been fully involved at all stages of publication and presentation development, and are willing to take public responsibility for all aspects of the work. All individuals included as authors and contributors who made substantial intellectual contributions to the research, data analysis, and publication or presentation development are listed appropriately. The role of the sponsor in the design, execution, analysis, reporting, and

[REDACTED]

funding is fully disclosed. The authors' personal interests, financial or non-financial, relating to this research and its publication have been disclosed." Authors should only include the above statement if all of it is true, and they should attest to this in the cover letter (see #2, above).

DONE

*From Battisti WP, Wager E, Baltzer L, Bridges D, Cairns A, Carswell CI, et al. Good publication practice for communicating company-sponsored medical research: GPP3. *Ann Intern Med* 2015;163:461-4.

5. Your submission indicates that one or more of the authors is employed by a pharmaceutical company, device company, or other commercial entity. This must be included as a statement in the Financial Disclosure section on the title page.

Author response: The above have been included in the manuscript. There was one question of whether “aggregate data” were available to authors. The investigator authors had the protocol, overall study analysis report, and direct access to individual site raw data (for each of them for their site and each of them attesting to the quality and completeness of their site data). The statement has been amended for clarity.

6. Figures 1 and 2:

Tables, figures, and supplemental digital content should be original. The use of borrowed material (eg, lengthy direct quotations, tables, figures, or videos) is discouraged. If the material is essential, written permission of the copyright holder must be obtained.

Both print and electronic (online) rights must be obtained from the holder of the copyright (often the publisher, not the author), and credit to the original source must be included in your manuscript. Many publishers now have online systems for submitting permissions request; please consult the publisher directly for more information. Permission is also required for material that has been adapted or modified from another source. Increasingly, publishers will not grant permission for modification of their material. Creative Commons licenses and open access have also made obtaining permissions more challenging. In order to avoid publication delays, we strongly encourage authors to link or reference to the material they want to highlight instead of trying to get permission to reprint it. For example, "see Table 1 in Smith et al" (and insert reference number). For articles that the journal invites, such as the Clinical Expert Series, the journal staff does not seek permission for modifications of material — the material will be reprinted in its original form.

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If the figure or table you want to reprint can be easily found on the internet from a reputable source, we recommend providing a link to the source in your text instead of trying to reprint it in your manuscript.

Author response: The figures and tables included here are all original. The illustrations are owned by the Sponsor of the study.

7. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://urldefense.proofpoint.com/v2/url?u=https-3A_www.acog.org_practice-2Dmanagement_health-2Dit-2Dand-2Dclinical-2Dinformatics_revitalize-2Dobstetrics-2Ddata-2Ddefinitions&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=zKJos-K6iCZCjIms308l4vcVvPEdpVbAFzjv8dIrI7c&m=4De7pXTmp6kYhr_Bb7MDX3P-oAQfNB43_O3BREGeis&s=Yjke9dU7jpMwcf8UitliPo6PdSi24npd6kSUxTymJi4&e= and the gynecology data definitions at https://urldefense.proofpoint.com/v2/url?u=https-3A_www.acog.org_practice-2Dmanagement_health-2Dit-2Dand-2Dclinical-2Dinformatics_revitalize-2Dgynecology-2Ddata-2Ddefinitions&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=zKJos-K6iCZCjIms308l4vcVvPEdpVbAFzjv8dIrI7c&m=4De7pXTmp6kYhr_Bb7MDX3P-oAQfNB43_O3BREGeis&s=AIqc7FeZ0TB-e6VKgSIDYsANBrScQEXTZ9mPXPB0VQ0&e=. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

Author response: The reVITALize definitions are referenced in this paper in the Introduction.

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

Author response: Thank you for this guidance.

9. 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

Dr. Dena Goffman

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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).

Author response: Thank you. All the above have been included, as appropriate.

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

In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words. Please provide a word count.

Author response: The abstract is in line with the description and conclusions of the manuscript. The abstract word count is 294.

11. Only standard abbreviations and acronyms are allowed. A selected list is available online at https://urldefense.proofpoint.com/v2/url?u=http-3A_edmgr.ovid.com_ong_accounts_abbreviations.pdf&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=zKJos-K6iCZCjIms308l4vcVvPEdpVbAFzjv8dIrI7c&m=4De7pXTmp6kYhr_Bb7MDX3P-oAQfNB43_O3BREGeis&s=jpu8VNrpedxNzJWLpA1Wkk6jZPpQ5Bo1rICvjamTkW4&e=. 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.

Author response: Many changes were made based on the comments about acronyms. Thank you.

12. 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.

Author response. Thank you. We have removed any use of the virgule symbol in sentences.

13. 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%").

Author response: Thank you.

14. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here:

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Author response: Thank you.

15. Figures

Figures 1-2: Are these figures original to the manuscript? Were they provided by the manufacturer? Were they created by an illustrator for this manuscript? Permission may be necessary for print and online use.

Author response: The figures are owned by and were provided by the manufacturer.

Figure 3: Please consider adding exclusion boxes to the top of the figure.

Author response: Exclusions are indicated from the ITT cohort within the figure.

Figure 4-5: These can be resubmitted as-is.

Author response: Thank you.

Figure 6: Please remove all patterned bars, as they do not translate well to print. You are welcome to use any solid colors.

Author response: Figure 4 and 5 are re-submitted with this revision in color and without patterns.

16. The web editor has reviewed your manuscript and would like to encourage you to submit a video to accompany your manuscript. The video file may be uploaded with your revised submission as "supplemental digital content." Acceptable file types include .wmv, .swf, .flv, .mov, .mp4, .avi, .mpg, .mpeg, or .m4v. The file may not exceed 100 MB. The video will accompany your article as supplemental digital content on the Green Journal web site, be displayed in the journal's video gallery, and also be uploaded to the journal's YouTube channel (if deemed appropriate by the editors). If you have questions prior to submission, please contact the journal's production editor at obgyn@greenjournal.org.

Dr. Dena Goffman

CUIMC/NewYork-Presbyterian Morgan Stanley Children's Hospital

Author response: A video will be submitted by August 31st. It will display an animation of the use of the intrauterine vacuum-induced hemorrhage control device.

17. 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 https://urldefense.proofpoint.com/v2/url?u=http-3A__links.lww.com_LWW-2DES_A48&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=zKJos-K6iCZCjIms308l4vcVvPEdpVbAFzjv8dIrI7c&m=4De7pXTmp6kYhr_Bb7MDX3P-oAQfNB43_O3BREGeis&s=cRAuF4tXHLDSx2qxmKFYiQ35RXNmKDIRCbyreh35DqQ&e= .

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Author response: Thank you. We will request open access if notified of acceptance.