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

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

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

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

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

Date: 04/07/2023
To: "Heidi Moseson" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-23-495

RE: Manuscript Number ONG-23-495

Effectiveness of self-managed medication abortion between 9-22 weeks of pregnancy

Dear Dr. Moseson:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, and STATISTICAL EDITOR COMMENTS (if applicable) below. The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting). Upload the tracked-changes version when you submit your revised manuscript.

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by 04/28/2023, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

Dear Dr. Moseson and co-authors:

Thank you for your submission. Your submission has gone through our external reviewer process and was discussed by our editorial board. We would like to give your paper additional considerations once the reviewers' comments are addressed.

In addition to the comments below, we have the additional requests to consider:
1. It is unclear in the methods if this was a secondary analysis, or planned supplementary study of the primary study. Please clarify. Since the patients in this report are >9 weeks, it seems they would have been ineligible for the primary study. Please clarify under what study methods/circumstances the women in the current report were recruited and followed.
2. Results: Again, it is confusing for the reader to see that 1,594 participants were eligible, but 264 were included in this report without an understanding of the purpose of collecting data on these women >9 weeks.
3. Re: Denominator: please stay consistent. Please explain or clarify in Table 2, why 222/264 = 90.6% for example? What denominator is being used here? Similarly other discrepancies in this table and in paper. Please harmonize.
4. If there is missing data, please provide information on the number of women and characteristics of those with missing data.
5. Please include in your discussion the generalizability and applicability of your study findings to >17 wks GA, to help readers interpret the actual data you have.
6. Please consider changing your title, to be more reflective of the majority of the study population included in this report.
7. Please temper conclusions to be more reflective of the study design, methods, and actual population included in this descriptive study.

Thank you again for your submission. and we look forward to receiving your revised paper.

***Please also note the following:

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

* Figure 1: Please upload as a figure file on Editorial Manager.

REVIEWER COMMENTS:

Reviewer #1:
The authors suggest that self-management of medical abortions up to 22 weeks is a appropriate management. I have major concerns about this study.

1. The sample size is woefully under powered to assess the safety of self-management after 12 weeks in MA. Only 12% or 30 pregnancies were greater than 12 weeks and 1(?) between 17-22 weeks. Thus to make any speculation or suggestion is problematic and dangerous.
2. The authors state that patient's self determination of completeness of a medical abortion is proven to be accurate. However the reference used to support this assertion (ref 16) considered abortions less than 10 weeks. To extrapolate that a patient would be able to determine completeness of a pregnancy greater than 20 weeks is not justified.
3. Patients receiving medical abortions as young as 13 were considered in this study. Where these emancipated minors, where the principal investigators concerned about their safety, etc? I have considerable ethical questions about inclusion of these patients in the study design.
4. The authors state that there is evidence in the literature to support medical abortion in late second trimester (ref 6,8,10). After reviewing these papers, I am unsure how the authors came to this conclusion. Please comment
5. The tables and results sections are confusing. I am unable to tell how many patients at what gestational age were included.

- Ln 1: The title is very misleading. Outcome 1 include 22 weeks gestation as being adequately studied which is assumed by the title. This title in my opinion is dangerous and leads to conclusions that put our patients at risk.
- Ln 46: The study did not prove that the self-management medication abortions are effective. It did not even suggest that they were effective. Please use more appropriate assessment statement.
- Ln 68: I agree the WHO suggest that self-manage pregnancies below 9 weeks are safe, however, implying that this is possible for pregnancies up to 22 weeks is problematic and without basis.
- Ln 97: What is the WHO recommended MA protocol for pregnancies greater than 12 weeks? I did not know that one existed? This is what is a quote from WHO :" There was no research evidence on the cadres performing surgical or medical abortion beyond 12 weeks that allowed for pooled analysis and application of GRADE."

Reviewer #2:
Nicely executed and well written prospective cohort/survey study of a hard to identify and follow population. This research is an important contribution to the field; outcomes of people using self-managed MA after the first trimester has not been previously described in a prospective fashion. It draws on a number of different geographic contexts with low loss to follow up, strengthening their conclusions. Recommend some minor revisions for further clarity/transparity of results - aligning with STAR outcomes https://www.sciencedirect.com/science/article/pii/S0010782421002249?via%3Dihub

ABSTRACT
- Line 34 "Beginning a new self managed abortion". Could just change to initiating a self-managed abortion.

- Line 41 Not all readers may know what a combined regimen is (and that it is more effective).

- Line 42 What happened to the remainder of the individuals undergoing self-managed abortion? 236+14 does not equal 264. How many of the individuals who sought care used a miso only regimen, please provide more demographics regarding your cohort, average age, gestational age range (or absolute numbers in the different categories). As success and complications of medication abortion is related to gestational age and regimen type, its very hard to easily discern if this really is an effective model of care. Maybe your entire cohort was only 14 weeks (I know it wasn't but I can't tell from the abstract and that is what most people read). It really doesn't enable a reader to get a sense of how successful self management is.

- Results - please include absolute numbers when reporting percentages. Did anyone experience any need for emergency care (yes) and why is that not represented here? I recognize that just because someone seeks care does not mean they actually are having an emergency but you only report on the positive outcomes and not the potentially negative ones (need for hospitalization, need for additional procedures, need for blood transfusion, need for ABX). I think if you aligned with reporting the results like STAR outcomes in the abstract - it would make the results feel more transparent to the reader - then you can get into greater differentiation in the paper. Or if you don't want to present all of the complications in the abstract then at the very list be transparent regarding the proportion that actually needed additional care: 23.5% sought care (what are the absolute #?) of which 67% (num/denominator wanted reassurance of completion and 30% (num/dem) needed further medical intervention or observation?

- Conclusion - I think you need to temper your conclusion to between 12 to 16 weeks appears effective but 17-22 weeks needs more study given small numbers

INTRO
No edits

MAIN METHODS
Line 91 or evidence of a miscarriage?

RESULTS
Line 149 These numbers are not well represented in your abstract
Line 171-172 - The authors could consider here a summary statement of Appendix 7 describing the median time to expulsion for composite or by each regimen.
Line 175 Complete abortion as determined by how? Would note self-report
Line 176 What regimen did most folks use and then receive an MVA
Line 179 Not complete - what gestational age range? And what regimen. Did anyone seek health care for urgent/emergent reasons? (see comment for abstract) It is well outlined in your table but this is a very important result to include in the main text.o
Line 174 - The stated percentage 87.3% does not match Table 2, which states the proportion of participants with a complete abortion at one week without surgical intervention was 86.9%

Line 191 - What is the gestational age range that took the different regimens? this seems important to the outcomes

Table 1 doesn't need p values unless requested by journal
the row entitled "pregnancy duration at baseline" is confusing, as there are patients with ">=9 weeks" column who are recorded as having pregnancies with baseline duration of 6, 7, or 8 weeks.

Is the use of 'at last follow up' - the last time you had contact with the participant or the three week survey? If you are combining responses then please be clear that you are that and what percentage completed each survey and accounts for that combination 'at last follow up'.

Reviewer #3:
-It is not clearly stated how authors' identities relate to the research topic and clarify the authors' limitations in speaking on behalf of the communities in the study. The authors state specific groups involved but not how that may impact the study's validity as a whole.
-Strengths and weaknesses of the study are well thought out and appropriate.

STATISTICAL EDITOR COMMENTS:
lines 174-182 and Fig 1 need to be reconciled. There were in Fig 1, 13 with incomplete or unsure results and 1 missing, or a total of 14 from the overall total of 264. However, the 213 (87.3%) implies a denominator = 244, the 236(89.4%) implies a denominator of 264. The rates of completion, completion with surgery etc all should use the same denominator, namely the total. For lines 180-182, also need to use the same totals (264 overall and 149, 115 for the subsets).

While I appreciate the completeness of the data in Tables 2 and 3, suggest a concise summary in main text and full data set in supplemental material. On the other hand, I would suggest that Appendices 7, 8 and 9 be in main text, but the unadjusted RR should be included (with its CIs), to contrast with the aRR.

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Sincerely,
Vivian W. Sung, MD, MPH
Deputy Editor, Gynecology

The Editors of Obstetrics & Gynecology

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.

Obstetrics & Gynecology,
409 12th Street SW,
Washington, DC 20024-2188

April 27, 2023

Dear Dr. Wright, Deputy Editors, and the *Obstetrics & Gynecology* Editorial Board:

We are grateful for the opportunity to submit our revised research article, entitled "Effectiveness of self-managed medication abortion between 9-16 weeks of pregnancy," to be considered for publication in *Obstetrics & Gynecology*.

In this revised manuscript, we have responded to the thoughtful comments from the editor, statistical editor, and three peer-reviewers. We have substantially revised our presentation of the results to appropriately reframe our findings as relevant for abortions at 9-16 weeks of pregnancy (rather than the full range of 9-22 weeks, as only 3 participants self-managed between 17-22 weeks), to harmonize all denominators, and to shift which tables appear in the main text versus in the supporting information/appendices. We append a detailed response to editors and reviewers below this cover letter, as instructed in the revision checklist.

This revised manuscript is much strengthened by the constructive review process, and we feel more certain that these findings will be a contribution to the literature and of much interest to the readers of *Obstetrics & Gynecology*.
As a reminder, this revised manuscript **presents an in-depth analysis of the experiences of people who self-managed their abortion at later durations of pregnancy than previously studied – specifically, between 9-16 weeks of pregnancy**. Results presented in this manuscript provide new evidence that self-managed medication abortion at these durations of pregnancy is effective, if less so than at <9 weeks, and leads to comparable completion levels as seen in clinical studies of medication abortion use at these stages of pregnancy. We present detailed data on the regimens that the 264 participants used, physical experience of abortion including onset and duration of bleeding and cramping, experiences of pain, time to expulsion, and reasons for healthcare seeking as well as treatment received.

These data fill a critical data gap in our understanding of an increasingly utilized model of abortion care at later durations of pregnancy not previously well studied. All authors have no conflicts of interest to declare, and this paper is not under consideration for publication elsewhere. The research was reviewed and approved by the Allendale Investigational Review Board as the central IRB of record; the Fundación Huésped IRB additionally approved the Argentina-specific protocol. All named persons have provided written consent to be named in the manuscript. 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. These results were presented in an oral abstract at the December 2022 Society of Family Planning Annual Meeting in Baltimore, MD by the first author.

Thank you very much for your consideration and review of our manuscript.

Heidi Moseson, PhD MPH
Principal Investigator, the SAFE Study
First and corresponding author

(Response to reviewers and editors begins on the following page)

EDITOR COMMENTS:

Dear Dr. Moseson and co-authors:

Thank you for your submission. Your submission has gone through our external reviewer process and was discussed by our editorial board. We would like to give your paper additional considerations once the reviewers' comments are addressed.

In addition to the comments below, we have the additional requests to consider:
1. It is unclear in the methods if this was a secondary analysis, or planned supplementary study of the primary study. Please clarify. Since the patients in this report are >9 weeks, it seems they would have been ineligible for the primary study. Please clarify under what study methods/circumstances the women in the current report were recruited and followed.
This is an important and appreciated question. To clarify, the analysis presented in this manuscript is a planned supplementary study of the primary study. The primary aim of the SAFE study was to assess the non-inferiority of self-managed medication abortion as compared to clinician-managed medication abortion outcomes for pregnancies <9 weeks gestation. However, knowing that people self-manage their abortions beyond 9 weeks and that little is known about these experiences, we designed the study protocol to allow enrollment of individuals who self-managed at 9+ weeks with the intent of analyzing their outcomes separately to see what could be learned from these lesser studied, but increasingly of-interest, experiences. Indeed, we stated this planned supplementary analysis in our protocol paper, published in the BMJ in 2020 (Moseson H, et al. *BMJ Open* 2020;10:e036800. doi:10.1136/bmjopen-2020-036800). Thus, the individuals we analyze in this paper were not included in the main non-inferiority analysis previously published. Thus, the methods/circumstances in which participants in this current report were recruited and followed were identical to the methods/circumstances in which participants in the larger SAFE study were recruited/followed. To clarify this, we have added language in the methods section in lines 194-196 that reads: “Among those who enrolled, 264 participants (19.5%) took the first dose of their MA at or beyond nine weeks of pregnancy, and thus were eligible for this planned supplementary analysis of outcomes among those who self-managed at >9 weeks. These participants were recruited and followed identically to those in the full study, but were slightly younger, had lower educational attainment, and were more likely to have confirmed pregnancy duration via ultrasound than were participants who had their abortions prior to nine weeks (Table 1).”

2. Results: Again, it is confusing for the reader to see that 1,594 participants were eligible, but 264 were included in this report without an understanding of the purpose of collecting data on these women >9 weeks.
This point is well taken, and we hope that the language we added (above) will clarify this.

3. Re: Denominator: please stay consistent. Please explain or clarify in Table 2, why 222/264 = 90.6% for example? What denominator is being used here? Similarly other discrepancies in this table and in paper. Please harmonize.

Initially, we had utilized the denominator of all those who completed that specific follow-up (rather than the full sample). However, per the reviewer and editor feedback, we have revised all proportions to use 264 as the denominator throughout – all numbers have been harmonized on this front.

4. If there is missing data, please provide information on the number of women and characteristics of those with missing data.
Only 1 of the 264 participants was fully lost to follow up. We have added information on missing data by time point and overall to the first section in the results, in lines 199-202: "Among the 264 participants included in this analysis, 92.8% (245/264) completed the one-week survey, and 87.1% (230/264) completed the three-week survey; across these two follow-ups, 99.6% (263/264) completed at least one follow-up survey."

5. Please include in your discussion the generalizability and applicability of your study findings to >17 wks GA, to help readers interpret the actual data you have.
This point is well taken. We have added the following text, in lines 270-278 to better unpack this limitation: "Finally, the sample size of participants who self-managed between 17 and 22 weeks is quite small (n=3), and therefore limits the inference that can be drawn for self-managed abortions that occur in the range of 17-22 weeks gestation. As a result, additional research is needed to evaluate the safety and effectiveness of self-managed medication abortion beyond 17 weeks. Prior retrospective research on experiences of people who have self-managed at 17+ weeks and those who support them to do so,[10,21] indicates that the physical and emotional support needs at these gestations differ from those who self-manage earlier in pregnancy, and may require more pain management and other physical support for passing the pregnancy and managing delayed placental expulsion."

6. Please consider changing your title, to be more reflective of the majority of the study population included in this report.
We have revised the title to: "Effectiveness of self-managed medication abortion between 9-16 weeks of pregnancy".

7. Please temper conclusions to be more reflective of the study design, methods, and actual population included in this descriptive study.
We have gone through the discussion and conclusion paragraph to temper conclusions and ensure the statements made are fully grounded in the data we have, the study design, and the population. We welcome additional feedback if there are further revisions to be made.

Thank you again for your submission. and we look forward to receiving your revised paper.

***Please also note the following:

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making

the applicable edits to your manuscript.

* Figure 1: Please upload as a figure file on Editorial Manager.

We have uploaded this as a figure to Editorial Manager.

REVIEWER COMMENTS:

Reviewer #1:
The authors suggest that self-management of medical abortions up to 22 weeks is a appropriate management. I have major concerns about this study.

1. The sample size is woefully under powered to assess the safety of self-management after 12 weeks in MA. Only 12% or 30 pregnancies were greater than 12 weeks and 1(?) between 17-22 weeks. Thus to make any speculation or suggestion is problematic and dangerous.
Many thanks to the reviewer. A first point of clarification is that we report here on 66 participants (as opposed to 30, as the reviewer stated above) who self-managed their abortions at 12+ weeks of pregnancy, and 3 between 17-22 weeks. Due to the small sample size at 17-22 weeks, we have revised the title and all conclusions to focus on the outcomes at 9-16 weeks, and comment at some length about the insufficiency of the sample size at 17+ weeks leading us not to draw any conclusions about this group (see lines 270-278 in the discussion, where the added text reads as follows: "Finally, the sample size of participants who self-managed between 17 and 22 weeks is quite small (n=3), and limits inference that can be drawn for these pregnancy durations. As a result, additional research is needed to evaluate the safety and effectiveness of self-managed medication abortion beyond 17 weeks. Prior retrospective research on experiences of people who have self-managed at 17+ weeks and those who support them to do so,[11,22] indicates that the physical and emotional support needs at these gestations differ from those who self-manage earlier in pregnancy, and may require more pain management and other physical support for passing the pregnancy, disposing of pregnancy tissue, and managing delayed placental expulsion."

Secondly, the primary outcome of the larger study (of which the data analyzed in this manuscript are a subset) was the non-inferiority of abortion completion without procedural intervention following self-managed abortion with misoprostol-only, or in combination with mifepristone, as compared to clinician-managed medication abortion use. Thus, the study was powered to detect a 5% margin of non-inferiority for abortion completion as the primary outcome. Safety outcomes (such as hospitalization or transfusion) were not the primary outcomes, and sample size calculations thus did not focus on having sufficient power to detect them. Due to the rare incidence of adverse safety events following use of medication abortion (eg, hospitalization, blood transfusions, etc), this study - like other medication abortion studies -- was not powered to detect a difference in safety outcomes, but we did document the occurrence of these rare events. No medication abortion studies, even the pilot studies on

which the FDA approval of mifepristone was based, were powered to detect rates of rare occurrences such as transfusion or hospitalization (Winikoff et al, 2012: https://pubmed.ncbi.nlm.nih.gov/23090524/; ANSIRH: https://www.ansirh.org/sites/default/files/publications/files/mifepristone_safety_4-23-2019.pdf) due to the prohibitively large sample size that would require.

2. The authors state that patient's self determination of completeness of a medical abortion is proven to be accurate. However the reference used to support this assertion (ref 16) considered abortions less than 10 weeks. To extrapolate that a patient would be able to determine completeness of a pregnancy greater than 20 weeks is not justified.
The reviewer correctly notes that the reference for the statement about self-assessment refers to pregnancies at or below 10 weeks, and that similar research has not been conducted among people who have abortions 10 weeks or above. This is due, in large part, because the consensus in the literature (as well as decades of clinical experience) is that abortion completion becomes increasingly easier to assess as gestational age increases as the completion of the process is evident in the form of a visibly expelled fetus.

3. Patients receiving medical abortions as young as 13 were considered in this study. Where these emancipated minors, where the principal investigators concerned about their safety, etc? I have considerable ethical questions about inclusion of these patients in the study design.
The reviewer is correct that individuals as young as 13 were eligible for participation in the study – however, the youngest individual in the 264 participants who self-managed at 9+ weeks was a single participant aged 15, the next youngest were 4 participants aged 17 years, followed by 4 who were 18. The decision to include minors in this study reflected the reality that accompaniment groups support young people with unwanted pregnancies at these ages, and indeed that young people who do not receive accompaniment support at these ages present at clinics and hospitals with severe maternal morbidity or mortality because of unsafe abortion at these ages (in the absence of the information and support provided by accompaniment groups). Given the unique vulnerability and needs of young people, it felt unethical to NOT include them in the study, and to not measure what unique support or other needs they may have. The investigators were indeed highly attentive to the needs and safety of these younger participants. During training for study personnel involved in subject recruitment, special emphasis was placed on how to evaluate the ability of participants <18 years of age to give consent to participate in this study. In compliance with international guidance on assent/consent from minors to participate in research, study recruiters spent particular time with any potential participant <18 years of age to ensure that the young person understood the benefits and risks of participation, and recruiters asked the young person to demonstrate this understanding by being able to report back /describe to the recruiter the expected benefits and risks of research. During training, study recruiters were given sample scripts to improve/hone to insure that discussion of the informed consent information related to participation was clear and understandable even for young people. To help the young person understand what participation might be like, recruiters were trained to focus on conveying an accurate picture of what the actual experience of participation in the research was likely to be in language that was familiar / understandable, focusing on describing how the study team would contact them,

what types of questions they would ask and how long it would take, as well as how many times the study team would contact them. Special emphasis was also placed on describing the protections in place for individual identifiers, and the purpose of the research, in words familiar to and geared toward young people. Trainers emphasize that the young person must actively show their willingness to participate in the research, rather than merely failing to object to it. The IRBs involved in the study reviewed and approved the inclusion of these ages.

4. The authors state that there is evidence in the literature to support medical abortion in late second trimester (ref 6,8,10). After reviewing these papers, I am unsure how the authors came to this conclusion. Please comment

There is indeed robust evidence in the literature to support medication abortion throughout the second trimester; the robustness of this evidence is reflected in the fact that the updated 2022 medical management of abortion guidelines from the WHO include recommendations for medication abortion at ≥12 weeks of pregnancy.

The three references that the reviewer mentioned represent comprehensive summaries of this literature and of their conclusion that medication abortion in the late second trimester is safe and effective, and thus why we selected them for inclusion in the manuscript. Specifically:

- **Reference 6** (Whitehouse et al, 2020) is a systematic review and meta-analysis of 8284 women from 43 randomized clinical trials on management of second-trimester medical abortion, of which 40 of the 43 RCTs evaluated ongoing pregnancy at 24-48 hours following use of medication abortion up to AT LEAST 20 weeks gestation, with 18 of those RCTs following people beyond 20 weeks, up to 28 weeks at the highest end. This review concludes that both the combined regimen, and misoprostol-only regimens, are safe and effective methods of pregnancy termination at 12-28 weeks of gestation. More specifically, their review of the evidence endorses the use of mifepristone 200 mg 1 to 2 days before misoprostol 400 mcg vaginally every 3 h at ≥ 12 weeks' gestation; and that, when mife is unavailable, providers can use misoprostol only. The authors find vaginal misoprostol administration to be most efficacious with fewest side effects, but sublingual and buccal routes are also acceptable.
- Further, **Reference 8** (a 2011 Cochrane review by Wildschut et al.) evaluated ~40 RCTs on medication abortion regimens at 12 to 28 weeks of gestation and concluded that it is a safe and effective method for pregnancy termination, and that the optimal regimen was mifepristone plus misoprostol vaginally every 3 h. The review highlights that while the combined regimen led to shorter time to abortion completion, the need for surgical intervention, pain management, etc did not differ between misoprostol-only versus mifepristone+misoprostol regimens at these gestations.
- **Reference 10** (Moseson et al, 2020) details the outcomes following self-managed use of medication abortion from 13-24 weeks (in contrast to the RCTs summarized in refs 6 and 8) – including 58 participants who used medication abortion at 20-24 weeks of pregnancy, and concludes that medication abortion at these gestations is an effective and safe option for abortion beyond the first trimester, particularly in legally restrictive settings where alternatives for abortion at these gestations come with extremely high risk of morbidity and mortality. Specifically, the study reports that: “Medication alone resulted in 241 complete abortions (76%); 37 (12%) individuals underwent manual vacuum aspiration or dilation and curettage within the formal health system, and 16 people (5%) required an additional medication abortion attempt at

a later date, resulted in ongoing pregnancy, or were lost to follow-up. After accounting for additional interventions or monitoring at a healthcare facility, 302 of 318 (95%) abortion attempts completed overall."

To address the reviewer's concern about lack of data on late second trimester medication abortion, we have added an additional reference to the manuscript – an RCT that evaluated the combined regimen versus misoprostol-only for medication abortion specifically just in the late second trimester (18-23 weeks gestation). This review found that both regimens were highly effective and safe, while the combined regimen significantly reduced the induction time (Kapp et al, 2007: https://pubmed.ncbi.nlm.nih.gov/18055725/).

5. The tables and results sections are confusing. I am unable to tell how many patients at what gestational age were included.

This point is well taken. We have updated Table 1 to present gestational age at the time of the abortion, rather than at the time of enrollment (for some people, it took them several weeks to obtain and take the pills – thus, there was a difference between their gestational age at the time of enrollment versus the time of the actual abortion. We have updated to the time of actual abortion, as that is most relevant for this analysis.

- Ln 1: The title is very misleading. Outcome 1 include 22 weeks gestation as being adequately studied which is assumed by the title. This title in my opinion is dangerous and leads to conclusions that put our patients at risk.

This point is also well taken, and thus we have modified the title to better reflect the data we have – 9-16 weeks of pregnancy, instead of 9-22 weeks (as only 3 participants had abortions at 17-22 weeks of pregnancy).

- Ln 46: The study did not prove that the self-management medication abortions are effective. It did not even suggest that they were effective. Please use more appropriate assessment statement.

From among 264 people who self-managed their abortion with medication at 9+ weeks of pregnancy, 89.4% had a complete abortion without procedural intervention. From our perspective, ~90% completion can be considered "effective"; indeed, systematic and Cochrane reviews of medication abortion in the second trimester have considered completion levels of this range to be "effective". To the reviewer's valid points about the small sample of individuals who self-managed between 17-22 weeks, we have revised the abstract conclusion to better reflect the gestational age range in which most participants fell – the line in question now reads as follows: "Self-managed medication abortion can be an effective model of abortion care between 9-16 weeks of pregnancy; outcomes between 17-22 weeks may require more study due to few participants."

- Ln 68: I agree the WHO suggest that self-manage pregnancies below 9 weeks are safe, however, implying that this is possible for pregnancies up to 22 weeks is problematic and without basis.

The reviewer is correct that the WHO endorses self-managed abortions at <12 weeks – however, the WHO has cited a lack of data on the safety of self-managed abortion >12 weeks. This need for more research is one of the motivating factors for why we enrolled individuals with pregnancies at later gestations into this study – so that we could assess and evaluate experiences and outcomes for people at these later gestations, and contribute to the evidence base. We have revised the text in the introduction to clarify this important distinction, and to highlight the age range for which the WHO endorses self-managed medication abortion (line 78): "A growing body of literature has demonstrated that self-managed MA is similarly safe and effective, and the World Health Organization (WHO) recently updated their guidance to fully recommend self-managed MA for pregnancies up to 12 weeks as part of a full range of safe, effective options for abortion care.[10]"

- Ln 97: What is the WHO recommended MA protocol for pregnancies greater than 12 weeks? I did not know that one existed? This is what is a quote from WHO :" There was no research evidence on the cadres performing surgical or medical abortion beyond 12 weeks that allowed for pooled analysis and application of GRADE."
The WHO does indeed have a recommended MA protocol for pregnancies greater than 12 weeks. In the updated guidelines released in March 2022, the text of the recommended protocol is as follows:
"For medical abortion at ≥ 12 weeks:

a. Suggest the use of 200 mg mifepristone administered orally, followed 1–2 days later by repeat doses of 400 µg misoprostol administered buccally, sublingually or vaginally every 3 hours.* The minimum recommended interval between use of mifepristone and misoprostol is 24 hours
b. When using misoprostol alone: Suggest the use of repeat doses of 400 µg misoprostol administered vaginally, sublingually or buccally every 3 hours.*

Remarks:

- The combination regimen (Recommendation 29a) is more effective than use of misoprostol alone.
- Evidence suggests that the vaginal route is the most effective. Consideration for patient and provider preference suggests the inclusion of all routes.
- Pregnancy tissue should be treated in the same way as other biological material unless the individual expresses a desire for it to be managed otherwise.

* Misoprostol can be repeated at the noted interval as needed to achieve success of the abortion process. Providers should use caution and clinical judgement to decide the maximum number of doses of misoprostol in pregnant individuals with a prior uterine incision. Uterine rupture is a rare complication; clinical judgement and health system preparedness for emergency management of uterine rupture must be considered with later gestational age. Source: Recommendation 3b carried forward from WHO (2018) (120)." (This can be found here in the digital version: https://srhr.org/abortioncare/chapter-3/abortion-3-4/medical-management-of-induced-abortion-recommendations-27-30-3-4-2/)

Reviewer #2:

Nicely executed and well written prospective cohort/survey study of a hard to identify and follow population. This research is an important contribution to the field; outcomes of people using self-managed MA after the first trimester has not been previously described in a prospective fashion. It draws on a number of different geographic contexts with low loss to follow up, strengthening their conclusions. Recommend some minor revisions for further clarity/transparity of results - aligning with STAR outcomes
https://www.sciencedirect.com/science/article/pii/S0010782421002249?via%3Dihub

ABSTRACT
- Line 34 "Beginning a new self managed abortion". Could just change to initiating a self-managed abortion.
We have made this change – the text in line 34 now reads: "We recruited callers to three abortion accompaniment groups in Argentina, Nigeria, and Southeast Asia who were initiating a self-managed medication abortion."

- Line 41 Not all readers may know what a combined regimen is (and that it is more effective).
We have revised this text to clarify that the combined regimen includes both mifepristone and misoprostol – the updated text in line 41 now reads: "…56% used the combined regimen (mifepristone+misoprostol)." Due to word limitations in the abstract, we do not address regimen effectiveness in the abstract.

- Line 42 What happened to the remainder of the individuals undergoing self-managed abortion? 236+14 does not equal 264. How many of the individuals who sought care used a miso only regimen, please provide more demographics regarding your cohort, average age, gestational age range (or absolute numbers in the different categories). As success and complications of medication abortion is related to gestational age and regimen type, its very hard to easily discern if this really is an effective model of care. Maybe your entire cohort was only 14 weeks (I know it wasn't but I can't tell from the abstract and that is what most people read). It really doesn't enable a reader to get a sense of how successful self management is.
These points are well taken. We presented outcomes for all 264 participants in the full results section but due to space had not initially included all outcomes in the abstract. To address the reviewer's question, we have updated the abstract to include this information. The updated abstract results section in lines 74-80 now reads: "Between 2019-2020, we enrolled 1,352 participants, 19.5% (264/1352) of whom self-managed their abortion at >9 weeks of pregnancy: 75.0% (198/264) at 9-11 weeks, 19.3% (51/264) at 12-14 weeks, and 5.7% (15/264) between 15-22 weeks. Participants were 26 years old on average (SD 5.6); 56% (149/264) used the combined regimen (mifepristone+misoprostol), and 44% (115/264) used misoprostol-only. At last follow-up, 89.4% (236/264) completed without procedural intervention, 5.3% (14/264) completed with MVA or D&C, 4.9% (13/264) were incomplete, and 0.4% (1/264) participants were missing."

- Results - please include absolute numbers when reporting percentages. Did anyone experience any need for emergency care (yes) and why is that not represented here? I recognize that just because someone seeks care does not mean they actually are having an

emergency but you only report on the positive outcomes and not the potentially negative ones (need for hospitalization, need for additional procedures, need for blood transfusion, need for ABX). I think if you aligned with reporting the results like STAR outcomes in the abstract - it would make the results feel more transparent to the reader - then you can get into greater differentiation in the paper. Or if you don't want to present all of the complications in the abstract then at the very list be transparent regarding the proportion that actually needed additional care: 23.5% sought care (what are the absolute #?) of which 67% (num/denominator wanted reassurance of completion and 30% (num/dem) needed further medical intervention or observation?

The recommendation to follow the STAR outcomes reporting is an excellent one. We have revised the presentation of health care seeking results to report a more complete set of health care treatment outcomes of interest, not just the most common. The revised results text in the abstract in lines 80-85 now reads: "Some participants (23.5%; 62/264) sought healthcare during or after their self-managed abortion, most commonly to confirm completion (15.9%; 42/264); 9.1% (24/264) needed further medical intervention (procedural evacuation, antibiotics, additional misoprostol, intravenous fluids, blood transfusion, or stayed overnight in the facility)."

- Conclusion - I think you need to temper your conclusion to between 12 to 16 weeks appears effective but 17-22 weeks needs more study given small numbers

We have revised the conclusion statement accordingly – the updated text in lines 86-87 now reads: "Self-managed medication abortion can be an effective model of abortion care between at nine or more9-16 weeks of pregnancy where linkages to healthcare is accessible ifexist when needed."

INTRO

No edits

MAIN METHODS

Line 91 or evidence of a miscarriage?

Correct – we excluded anyone with signs of ongoing abortion attempt or evidence of a miscarriage – we have updated the text to reflect this. The updated language in line 133-134 now reads: "Exclusion criteria included anyone experiencing ongoing symptoms from a prior abortion attempt or ongoing miscarriage (bleeding, cramping), symptoms suggestive of ectopic pregnancy, or not wanting to be contacted by study staff."

RESULTS

Line 149 These numbers are not well represented in your abstract

We have updated the abstract per the reviewer's recommendation to add more detail on numerator and denominator for core outcomes. If further numbers still feel missing, we welcome that feedback.

Line 171-172 - The authors could consider here a summary statement of Appendix 7 describing the median time to expulsion for composite or by each regimen.
This is a helpful suggestion. We have added the following summary statement in lines 220-222: "Participants expelled the pregnancy between 0 hours to 3.5 days after the first dose of misoprostol; median time to expulsion was slightly faster for users of the combined regimen, but more variable, as compared to those who used misoprostol-only (Appendix 7)."

Line 175 Complete abortion as determined by how? Would note self-report
In the methods section, we specify that abortion completion is ascertained via self-report. To remind readers of this, we have added the descriptor "self-" in front of each mention of "reported" in the results. The updated text, now in lines 224-228 reads as follows: "One week after taking the pills, 80.7% (95%CI: 75.3%-85.3%; 213/264; Table 2) of participants self-reported a complete abortion without procedural intervention; by three weeks, 89.4% (95%CI: 85.04%-92.89%; 236/264) of participants self-reported a complete abortion without procedural intervention, and 5.3% (14/264) completed with MVA or D&C (13 who used the combined regimen, 1 who used misoprostol-only).

Line 176 What regimen did most folks use and then receive an MVA
Most of the participants who received an MVA used the combined regimen (13 of the 14 used the combined regimen, 1 used misoprostol-only). We have added this detail to the text where indicated by the reviewer, and the updated text in lines 227-228 now reads: "…and 5.3% (14/264) completed with MVA or D&C (13 who used the combined regimen, 1 who used misoprostol-only)." This may reflect the well-established relationships between the accompaniment group in Argentina and trusted clinical providers there (where most of the combined regimen users lived), versus in Nigeria (where most misoprostol-only users lived) where the accompaniment group did not have strong relationships with trusted clinical providers to whom they could refer participants.

Line 179 Not complete - what gestational age range? And what regimen. Did anyone seek health care for urgent/emergent reasons? (see comment for abstract) It is well outlined in your table but this is a very important result to include in the main text.
To clarify the gestational age range for those who were not complete and unsure, we have added back into table 2 a row with these data. We have also added it to the text, now in line 230-231: "Those who reported that the abortion was not complete (n=5, 1.9%; at 9, 11 or 13 weeks gestation) cited a positive pregnancy test (home or facility-based)."

Per the question about seeking healthcare for urgent/emergent reasons, we have the following language (pulled from table 3, now Appendix 8) in the narrative results section under the "healthcare-seeking" sub-section. This language, in lines 237-242, reads as follows: "Overall, 23.5% (62/264) of participants sought healthcare at a clinic or hospital during or after their self-managed abortion, most commonly to confirm completion (n=42, 15.9%, 42/264), followed by concerns about bleeding (3.0%, 8/264), pain (1.8%, 5/264), or fever/discharge (1.8%, 5/264; Appendix 8). Participants most frequently received an ultrasound, antibiotics, or pain

medications; 5% (14/264) of participants received an MVA or D&C to complete their abortion and 1.5% (4/264) received a blood transfusion."

Line 174 - The stated percentage 87.3% does not match Table 2, which states the proportion of participants with a complete abortion at one week without surgical intervention was 86.9%
We have updated the text and tables to ensure the correct numbers are reported in the text and tables. We also adjusted to report the completion finding among those without procedural intervention (rather than overall). The updated text in lines 224-228 now reads: "One week after taking the pills, 80.7% (95%CI: 75.3%-85.3%; 213/264; Table 2) of participants self-reported a complete abortion without procedural intervention; by three weeks, 89.4% (95%CI: 85.0%-92.8%; 236/264) of participants self-reported a complete abortion without procedural intervention, and 5.3% (14/264) completed with MVA or D&C (13 who used the combined regimen, 1 who used misoprostol-only)."

Line 191 - What is the gestational age range that took the different regimens? this seems important to the outcomes
We agree this is an important outcome. The gestational age range that took the different regimens is presented in Table 2, alongside outcomes for each regimen/gestation combination. We have added in the total n for each gestational group within each regimen to make this clearer.

Table 1 doesn't need p values unless requested by journal
We will consult with the journal editor about removing these, and remove if recommended.

the row entitled "pregnancy duration at baseline" is confusing, as there are patients with ">=9 weeks" column who are recorded as having pregnancies with baseline duration of 6, 7, or 8 weeks.
This point is well taken. We have revised Table 1 to instead report the gestational age at the time of taking the medication abortion pills, rather than at baseline. Some participants took several weeks to obtain the pills and take them – thus, for some, gestational age at baseline is <9 weeks, even though by the time they took the pills, they were at 9+ weeks. To avoid this confusion, we revised Table 1 to report only gestational age at the time of the abortion itself.

Is the use of 'at last follow up' - the last time you had contact with the participant or the three week survey? If you are combining responses then please be clear that you are that and what percentage completed each survey and accounts for that combination 'at last follow up'.

The reviewer is correct that the "last follow-up" time point combines those who completed the 3 week follow-up with those who were missing the three week follow up (and we only have their 1 week follow up data). Given that not everyone completed the three week survey, we report the last abortion outcome we have for participants. We have 264 (100%) responses at baseline, 245 (92.8%) at the first follow up (missing 19 participants), and then we have 230 (87.1%) who completed the ~3 week follow-up. Between the 245 and 230, we have 263 (99.6%) who completed at least one follow-up, with only one participant among the 264 lost to follow-

up. We have added this information to the tables in a footnote to clarify, as well as in the first paragraph of the results. The newly added language in lines 199-202 reads: “Among the 264 participants included in this analysis, 92.8% (245/264) completed the one-week survey, and 87.1% (230/264) completed the three-week follow-up; across these two follow-ups, 99.6% (263/264) completed at least one follow-up survey.”

Reviewer #3:
-It is not clearly stated how authors' identities relate to the research topic and clarify the authors' limitations in speaking on behalf of the communities in the study. The authors state specific groups involved but not how that may impact the study's validity as a whole.
We have added a sentence to the methods section to provide input into the positionality of the authors’ identities and how they relate to the research topic. The added sentence, in lines 124-126, reads as follows: “The authorship team includes researchers and leaders of sexual and reproductive health organizations who have expertise in self-managed medication abortion and accompaniment models in a range of legal and cultural settings.”

-Strengths and weaknesses of the study are well thought out and appropriate.
Thank you.

STATISTICAL EDITOR COMMENTS:
lines 174-182 and Fig 1 need to be reconciled. There were in Fig 1, 13 with incomplete or unsure results and 1 missing, or a total of 14 from the overall total of 264. However, the 213 (87.3%) implies a denominator = 244, the 236(89.4%) implies a denominator of 264. The rates of completion, completion with surgery etc all should use the same denominator, namely the total. For lines 180-182, also need to use the same totals (264 overall and 149, 115 for the subsets).
This point is well taken, and we have updated all results to use 264 for the denominator (rather than the denominator that responded at each timepoint). All numbers in the tables and text have been updated to reflect this. The updated results section in these lines (224-235) now reads as follows: “One week after taking the pills, 80.7% (95%CI: 75.3%-85.3%; 213/264; Table 2) of participants self-reported a complete abortion without procedural intervention; by three weeks, 89.4% (95%CI: 85.0%-92.8%; 236/264) of participants self-reported a complete abortion without procedural intervention, and 5.3% (14/264) completed with MVA or D&C (13 who used the combined regimen, 1 who used misoprostol-only). Those who were unsure (n=6, 2.3%) said that they were still bleeding, experiencing discharge, having intermittent cramping, had not felt the fetus expel, or had not yet taken a pregnancy test. Those who reported that the abortion was not complete (n=5, 1.9%; at 9, 11 or 13 weeks gestation) cited a positive pregnancy test (home or facility-based). Completion was high across both regimens: 84.6% (95%CI: 77.7%-90.0%) without procedural intervention among users of the combined regimen (93.3% inclusive of procedural intervention), and 95.7% (95%CI: 90.1-98.6%) among users of misoprostol-only (96.5% inclusive of procedural intervention).”

While I appreciate the completeness of the data in Tables 2 and 3, suggest a concise summary in main text and full data set in supplemental material. On the other hand, I would suggest that Appendices 7, 8 and 9 be in main text, but the unadjusted RR should be included (with its CIs), to contrast with the aRR.

This is a thoughtful suggestion. We propose a hybrid adjustment. Given that the primary outcome of this analysis is effectiveness of self-managed medication abortion at these gestations, it feels important to present abortion completion outcomes in the main body of the paper (Table 2). However, we agree that the details in Table 3 (reasons for health care seeking and treatment received) could be moved to the appendix in lieu of the other material proposed by the editor. Is it allowable to keep the current Figure 1, Table 1 and Table 2, move Table 3 to an appendix, and replace the original Table 3 with a combined table that presents the results from Appendix 8 and 9 (odds ratio, as well as predicted risks and unadjusted plus adjusted RRs)? This is what we have done in this updated version. However, if the editors feel strongly that we move Table 2 (with abortion completion outcomes) to the appendix, and bring Appendix 7 (the box plot with time to completion) into the main text as a Figure 2, we are happy to do so. We welcome feedback on what is most of interest to the journal's readers.