PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A Protocol for the Study of Cervical-Cancer Screening Technologies in Human Immunodeficiency Virus-Infected Women Living in Rwanda
AUTHORS	Murenzi, Gad; Dusingize, Jean; Rurangwa, Theogene; Sinayobye, Jean d'Amour; Munyaneza, Athanase; Murangwa, Anthere; Zawadi, Thierry; Hebert, Tiffany; Mugenzi, Pacifique; Adedimeji, Adebola; Mutesa, Leon; Anastos, Kathryn; Castle, Philip

VERSION 1 – REVIEW

REVIEWER	Rachel Winer University of Washington School of Public Health
REVIEW RETURNED	05-Dec-2017

GENERAL COMMENTS	The protocol is clearly written and comprehensive. A couple of suggestions are to add information on trial registration (if available), and to include a limitations section. Lack of inclusion of cytology is listed as a weakness in the "strengths and weaknesses" section but it would be useful to also include a brief section on limitations in the text. Additional specific comments follow. -Line 121: 2) should be changed to 3). -Lines 158-163: It's not clear what the criteria were for selecting study sites - did the site need to have a certain number of potential eligible women? Also, "The total is the number of 30-54 year old women receiving care at all selected sites and our study population is an estimate of the women who will actually be eligible according to all inclusion and exclusion criteria." What does "the total" refer to here? -Line 165: Was HIV+ status confirmed by medical record review only, or was an HIV test performed as part of the study? -Line 172: "offer" should be "offers" -Lines 193-194: How is "screen-positive" specifically defined? Also, are there targets for completing hrHPV testing within a certain time frame, and for getting women in for colposcopy within a certain time frame? -Lines 212-216: What is the protocol for adjudicating discrepant biopsy reads between pathologists? And why does CIN 3+ require a consensus diagnosis, but CIN 2+ only by the local pathologist? What if the local pathologist diagnoses CIN 2 and the other pathologist CIN 3? How would that case be coded? -Line 219: ">=+" should this be ">=CIN2+"? -Lines 280-282: What is the rationale for deviating from the protocol used in the China study? -Table 1 describes potential participants per site - over what time period?

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REVIEWER	DR.DORCAS OBIRI-YEBOAH DEPARTMENT OF MICROBIOLOGY, SCHOOL OF MEDICAL SCIENCES, UNIVERSITY OF CAPE COAST, GHANA
REVIEW RETURNED	23-Jan-2018

GENERAL COMMENTS	This is a very important area of research especially in Africa. HPV and cervical cancer screening has entered a phase where there are so many options and newer options being introduced very frequently. hence the question of what is best and what is cost effective is very relevant. For HIV positive women, this becomes even more important, hence I am happy with your team for this research to be carried out. T There are however few areas I believe the protocol could be clearer: 1. What is the explanation for your age range? Particularly the upper limit of 54 years? 2. What informed the choice of screening methods to be evaluated? can you explain this further? There must be some rational. 3. What sampling method is used at each site for recruiting the women? It is not clear to me in the protocol currently. 4. It is important to attach the questionnaire which is going to be administered. And describe how it was developed and will it be pre-tested? who will be used to pre-test it and how many? etc 5. who will be performing the pelvic exams and taking the samples? 6. what are the limitations of the study? this is not mentioned in the protocol. If these few issues are addressed, in my opinion this protocol will be better Best regards

VERSION 1 – AUTHOR RESPONSE

The protocol is clearly written and comprehensive. A couple of suggestions are to add information on trial registration (if available), and to include a limitations section. Lack of inclusion of cytology is listed as a weakness in the "strengths and weaknesses" section but it would be useful to also include a brief section on limitations in the text. Additional specific comments follow.

Response: We have added a section on limitations at the end of the manuscript (Lines 399-410)

-Line 121: 2) should be changed to 3).

Response: Corrected.

-Lines 158-163: It's not clear what the criteria were for selecting study sites - did the site need to have a certain number of potential eligible women? Also, "The total is the number of 30-54 year old women receiving care at all selected sites and our study population is an estimate of the women who will actually be eligible according to all inclusion and exclusion criteria." What does "the total" refer to here?

Response: We have clarified the recruitment and the meaning of the numbers (Lines 157-165)

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-Line 165: Was HIV+ status confirmed by medical record review only, or was an HIV test performed as part of the study?

Response: Medical records.

-Line 172: "offer" should be "offers"

Response: Corrected.

-Lines 193-194: How is "screen-positive" specifically defined? Also, are there targets for completing hrHPV testing within a certain time frame, and for getting women in for colposcopy within a certain time frame?

Response: We have defined screen-positive in the text (Line 204).

-Lines 212-216: What is the protocol for adjudicating discrepant biopsy reads between pathologists? And why does CIN 3+ require a consensus diagnosis, but CIN 2+ only by the local pathologist? What if the local pathologist diagnoses CIN 2 and the other pathologist CIN 3? How would that case be coded?

Response: We corrected this statement. There is no plan for adjudication since the distances are great. We have clarified the algorithm for treatment. (Lines 224-231)

-Line 219: ">=+" should this be ">=CIN2+"?

Response: Corrected

-Lines 280-282: What is the rationale for deviating from the protocol used in the China study?

Response: Deviation is the wrong term and has been corrected. (Lines 297-299)

-Table 1 describes potential participants per site - over what time period?

Response: We have clarified that these are the numbers of HIV-infected women receiving care at those sites at the beginning of the study. (Lines 157-165)

This is a very important area of research especially in Africa. HPV and cervical cancer screening has entered a phase where there are so many options and newer options being introduced very frequently. hence the question of what is best and what is cost effective is very relevant. For HIV positive women, this becomes even more important, hence I am happy with your team for this research to be carried out.

There are however few areas I believe the protocol could be clearer:

1. What is the explanation for your age range? Particularly the upper limit of 54 years?

Response: We have clarified this in the write-up. We went above the WHO recommendations because the optimal upper age limit for cervical-cancer screening of HIV-infected women is less certain. (Lines 168-171)

2. What informed the choice of screening methods to be evaluated? can you explain this further? There must be some rational.

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Response: Yes, these are WHO recommended methods and technically might be implemented in these settings. (Lines 147-148)

3. What sampling method is used at each site for recruiting the women? It is not clear to me in the protocol currently.

Response: This was a convenience sample from each site (Lines 164-165).

4. It is important to attach the questionnaire which is going to be administered. And describe how it was developed and will it be pre-tested? who will be used to pre-test it and how many? Etc

Response: We have added the questionnaire (Figure 2) and explained the rationale for the included questions (Lines 191-197)

5. who will be performing the pelvic exams and taking the samples?

Response: Study nurses. (Lines 184-186)

6. what are the limitations of the study? this is not mentioned in the protocol.

Response: We have added a section on limitations at the end of the manuscript. (Lines 399-410)

VERSION 2 – REVIEW

REVIEWER	Rachel Winer University of Washington School of Public Health, USA
REVIEW RETURNED	05-Apr-2018

GENERAL COMMENTS	The authors have sufficiently addressed the comments from the original review.

REVIEWER	DR. DORCAS OBIRI-YEBOAH DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY, SCHOOL OF MEDICAL SCIENCES, UNIVERSITY OF CAPE COAST
REVIEW RETURNED	01-Apr-2018

GENERAL COMMENTS	MY COMMENTS HAVE MOSTLY BEEN ADDRESSED BUT I STILL HAVE FEW ISSUES THAT NEED CLARIFICATION. 1.THE TONE OF THE DOCUMENT CURRENTLY GIVES THE IMPRESSION THAT THE WOMEN HAVE ALREADY BEEN RECRUITED. WHERE AS THE ABSTRACT AND OTHER PORTIONS SUGGESTS FUTURE EVENTS. SO EXACTLY WHAT IS THE CURRENT SITUATION? ARE WOMEN ALREADY RECRUITED, CURRENTLY BEING RECRUITED OR YET TO BE? 2. THE QUESTIONNAIRE IS GENERALLY GOOD BUT FOCUSES ON MALARIA AND TUBERCULOSIS. WHEREAS THERE IS A CLEARLY ESTABLISHED LINK BETWEEN OTHER STIs AND HPV BUT THE QUESTIONNAIRE IS COMPLETELY SILENT ON THAT.SO THIS IS WHERE THE ISSUE NEEDS TO BE CLEAR AGAIN, THAT IF RECRUITMENT IS YET TO START, THEN ADDITIONAL QUESTIONS ON STIs COULD BE INCLUDED BUT IF ALREADY HAS BEEN USED THEN, IT MAY BE TOO LATE.

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	3. ON THE QUESTION ABOUT MALARIA, HOW PRACTICAL IS IT TO ASK THESE WOMEN, HOW MANY TIMES THEY HAVE HAD MALARIA? I SURELY CAN NOT ANSWER FOR MYSELF AND WONDER ABOUT THE PARTICIPANTS. SO IT WILL BE GREAT TO DEFINITELY PRE-TEST THE QUESTIONNAIRE AND MODIFY APPROPRIATELY. BUT AGAIN THAT DEPENDS ON IF RECRUITMENT HAS ALREADY HAPPENED OR NOT. SAYING " THE QUESTIONNAIRE WAS NOT PRETESTED" IMPLIES IT HAS ALREADY BEEN USED WHICH IS NOT IN AGREEMENT WITH STATEMENTS SAYING WOMEN "WILL BE RECRUITED".

VERSION 2 – AUTHOR RESPONSE

1.THE TONE OF THE DOCUMENT CURRENTLY GIVES THE IMPRESSION THAT THE WOMEN HAVE ALREADY BEEN RECRUITED. WHERE AS THE ABSTRACT AND OTHER PORTIONS SUGGESTS FUTURE EVENTS. SO EXACTLY WHAT IS THE CURRENT SITUATION? ARE WOMEN ALREADY RECRUITED, CURRENTLY BEING RECRUITED OR YET TO BE?

Response: We apologize for the lack of clarity due to the misuse of tenses. We have gone through the text and edited the tenses to indicate what has been accomplished, what is on-going, and what will happen in the future. The enrollment and clinical follow-up are underway and ongoing.

2. THE QUESTIONNAIRE IS GENERALLY GOOD BUT FOCUSES ON MALARIA AND TUBERCULOSIS. WHEREAS THERE IS A CLEARLY ESTABLISHED LINK BETWEEN OTHER STIs AND HPV BUT THE QUESTIONNAIRE IS COMPLETELY SILENT ON THAT.SO THIS IS WHERE THE ISSUE NEEDS TO BE CLEAR AGAIN, THAT IF RECRUITMENT IS YET TO START, THEN ADDITIONAL QUESTIONS ON STIs COULD BE INCLUDED BUT IF ALREADY HAS BEEN USED THEN, IT MAY BE TOO LATE.

Response: Since STI testing is not generally available in Rwanda, we elected not to ask questions about it. As the study is underway, we cannot change the questionnaire even if STI testing was available.

3. ON THE QUESTION ABOUT MALARIA, HOW PRACTICAL IS IT TO ASK THESE WOMEN, HOW MANY TIMES THEY HAVE HAD MALARIA? I SURELY CAN NOT ANSWER FOR MYSELF AND WONDER ABOUT THE PARTICIPANTS. SO IT WILL BE GREAT TO DEFINITELY PRE-TEST THE QUESTIONNAIRE AND MODIFY APPROPRIATELY. BUT AGAIN THAT DEPENDS ON IF RECRUITMENT HAS ALREADY HAPPENED OR NOT. SAYING " THE QUESTIONNAIRE WAS NOT PRETESTED" IMPLIES IT HAS ALREADY BEEN USED WHICH IS NOT IN AGREEMENT WITH STATEMENTS SAYING WOMEN "WILL BE RECRUITED".

Response: Again, we have tried to clarify that some aspects of the study, like IRB approvals, are completed, while the study enrollment and clinical procedures are ongoing and analyses will be in the future. An association of malaria with high-grade disease was found in one of our previous studies in

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Rwanda so we wanted to confirm the association or not. TB has been found in other studies and could be an immune modulator. We did not feel the need to pretest the questionnaire as we have successfully conducted several studies, including ones on HPV and high-grade cervical abnormalities, in Rwanda with similar questions and questionnaires.

VERSION 3 – REVIEW

REVIEWER	Dr. Dorcas Obiri-Yeboah Department of Microbiology and Immunology, School of Medical Sciences, University of Cape Coast, Cape Coast, Ghana
REVIEW RETURNED	04-Jun-2018

GENERAL COMMENTS	Please reject the change you made on line 426 under "limitations". I also saw Figure 1 legend but did not see the figure so kindly ensure it is attached. And Kindly do a final proof reading. Thank you

VERSION 3 – AUTHOR RESPONSE

We have made the changes to the title, done further editing, etc. We are not certain what the issue was with Figure 1, which was uploaded.

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