## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Assessing the Feasibility of a Rapid, High-Volume Cervical Cancer Screening Program using HPV Self-Sampling and Digital Colposcopy in rural regions of Yunnan, China |
| **AUTHORS** | Goldstein, Andrew; Goldstein, Lena; Lipson, Roberta; Bedell, Sarah; Wang, Jue; Stamper, Sarah; Brenner, Gal; Goldstein, Gail; O'Keefe, Karen; O'Keefe, S; O'Keefe, McKenna; O'Keefe, Tierney; Goldstein, Amelia; Zhao, Anna |

## VERSION 1 - REVIEW

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| **REVIEWER** | Christer Borgfeldt<br>Dept Ob-Gyn<br>Region Skåne University Hospital<br>Lund University<br>Sweden |
| **REVIEW RETURNED** | 29-Dec-2019 |

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| **GENERAL COMMENTS** | This study has several interesting and new results. However, several issues should be further reported and discussed, as well as some re-arrangements in the abstract and manuscript should be done.<br><br>Abstract:<br>In the conclusions: only the results from this study should be discussed and commented. The first part of the conclusion belongs to the background. The conclusion in the abstract must be shorter.<br><br>In the “Article Summary” (three bullet points):<br>Only the results from this study should be included – not general comments i.e. “Patient self-swabbing for HPV is crucial…..” there are several cervical screening programs with high compliance using cervical screening (look at the Scandinavian countries)<br>The statement “….differentiate between CIN1 and CIN2 lesions” was not proven by biopsies why this statement cannot be written.<br>The statement low-cost should be compared with other screening methods which probably is as cost-effective as this proposed one stop screening and treat occasion.<br><br>The Introduction should be shortened. The aim of the study must be stated.<br>In M&M the power calculation for the sample size needed should be added.<br>Was there any ethical approval for the study? Please provide the ethical approval number as well as the name and place of the |

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| | ethical committee. How were the women informed of the study? Did they give written informed consent?<br>How was the invitation to participate in the study performed? Please, be much more specific. Could the women get a vaginal self-sample analyzed and not participate in the study?<br>How were the women contacted when they were HPV negative or HPV positive?<br><br>In the discussion:<br>"The authors propose a screen-and-treat model that is low –cost, rapid and capable of being implemented on a large scale, ….."<br>Minor comment – why use "the authors"? I would suggest to write "we"<br>Major comments –<br>Is one-stop screening in this setting able to be implemented on "large scale" with highly educated physicians?<br>Why use one stop – If vaginal self-sampling is used, why is it important to have a "rapid" HPV answer?<br>Why cannot heath workers provide the vaginal self-sample kits or maybe sent it by mail to the women with proper instructions?<br>How will the whole female population in recommended screening ages be screened on a regular basis? Is there any thoughts for the future way to go in this area of China including the logistics?<br>The sensitivity of the HPV analyses are discussed but the meta-analyses by Arbyn et al 2014 and 2018 is not in the list of references. Shorten this part of the discussion and include Arbin et al.<br>Why should women with CIN I (LSIL) be treated? Why not a new vaginal HPV analyze in a 12 months period since the majority of these lesions and HPV infections heal without any treatment? |

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| **REVIEWER** | Ditte Møller Ejegod<br>Hvidovre Hospital, Denmark |
| **REVIEW RETURNED** | 17-Jan-2020 |

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| **GENERAL COMMENTS** | Bmjopen-2019-035153<br>A rapid, high-volume, see-and-treat cervical cancer screening program using HPV self-sampling and digital colposcopy<br>Here the authors present an interesting study presenting data on under screened Chinese women residing in the Yunnan region. The study design entails a novel low-resource see-and-treat approach. The approach includes HPV self-sampling and digital colposcopy of HPV positive women. The paper is well-written, but it is at times a bit hard to follow, a flow chart of the study inclusions, HPV prevalence, DC and perhaps also outcomes would be helpful, as would a table with the results presented in the result section.<br>General comments<br>Please use either digital colposcopy or DC throughout the paper.<br>Suggest using the term ≥CIN2 instead of CIN2+ and hrHPV+ instead of +hrHPV<br>The paper could use some grammatical edit at times e.g. 3th paragraph in introduction, 6th paragraph of introduction,<br>Specific comments<br>Introduction<br>2end paragraph "In general, women living in rural areas are less likely…." Compared to women living in cities or…? |

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| | 6th paragraph (beginning with “cervicovaginal HPV DNA testing…”) suggest including the reference “Detecting cervical precancer and reaching under-screened women by using HPV testing on self-samples: updated meta-analyses. Arbyn M et al., 2018” in addition to reference 21.<br>Suggest using more resent refences than ref 22-24 in the end of the 6th paragraph<br>Methods<br>How was HPV negative women managed?<br>What is IRB?<br>How was the women with HPV and negative DC followed up, with HPV+DC or only HPV<br>In paragraph 1 the it writes “Cryotherapy was performed the same day when findings were suspicious for CIN1 lesions” and in Paragraph 2 that “women with suspected low-grade lesions (CIN1) were counseled to have repeat HPV testing in 1 year” Did they receive cryotherapy and recommendation for follow-up or… this is a bit unclear.<br>Suggest moving the last paragraph (Patient and public involvement:..) to discussion in a perspective section<br>Results<br>Please refer to figure 1 and 2 in the text.<br>I would suggest generating a flow chart of the study that would make it easier for the reader to follow study the set up.<br>A table showing the data presented in the result section would also be helpful.<br>Was all women with positive DC biopsied this is a bit unclear from the text. |

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| **REVIEWER** | Gisela Helenius<br>Dept of Laboratory Medicine, Faculty of Medicine and Health, Örebro University, Örebro, Sweden |
| **REVIEW RETURNED** | 29-Jan-2020 |

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| **GENERAL COMMENTS** | This manuscript describe a new promising screening strategy for low-income countries without organized screening. It is written clearly and easy to follow. I miss however some information about the HPV-test in the methods part.<br>Describe what kind of selfsampling device that was used.<br>Describe how the HPV-test was performed. How was the result interpreted? How was the sucessrate of the test?<br>In row 50: Define the abbreviation IRB in "IRB approval"<br>In the discussion I would like to an estimation of the total cost of the described screening strategy compared to something relevant, for example a screening strategy used in a country with established organized screening. |

## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Christer Borgfeldt

Abstract:
In the conclusions: only the results from this study should be discussed and commented. The first part of the conclusion belongs to the background. The conclusion in the abstract must be shorter.

DONE, THE ABSTRACT HAS BEEN SHORTENED BY 56 WORDS.

In the “Article Summary” (three bullet points):
Only the results from this study should be included – not general comments i.e. “Patient self-swabbing for HPV is crucial…..” there are several cervical screening programs with high compliance using cervical screening (look at the Scandinavian countries)
The statement “….differentiate between CIN1 and CIN2 lesions” was not proven by biopsies why this statement cannot be written.
The statement low-cost should be compared with other screening methods which probably is as cost-effective as this proposed one stop screening and treat occasion.
THE ENTIRE ARTICLE SUMMARY SECTION WAS DELETED.

The Introduction should be shortened.
DONE, THE ENTIRE DISCUSSION OF VIA WAS REMOVED AS IT IS NOT APPLICABLE TO THIS PAPER
The aim of the study must be stated.
DONE, LINE 199-201
In M&M the power calculation for the sample size needed should be added.
AS THIS WAS NOT A COMPARISON TRIAL A POWER CALCULATION WAS NOT EMPLOYED, HOWEVER, A LONGER DISCUSSION OF PATIENT SELECTION IS DISCUSSED IN LINE 210-212

Was there any ethical approval for the study? Please provide the ethical approval number as well as the name and place of the ethical committee.
DONE, LINES 208-210
How were the women informed of the study?
LINES 210-212
Did they give written informed consent?
YES, LINE 216
How was the invitation to participate in the study performed? Please, be much more specific.
DONE, LINES 210-212

Could the women get a vaginal self-sample analyzed and not participate in the study?
NO, BECAUSE THERE IS NO ABILITY TO DO HPV TESTING IN THIS DISTRICT OUTSIDE OF THIS STUDY AND INFORMED CONSENT WAS REQUIRED FOR HPV TESTING (PER IRB REQUIREMENTS). HOWEVER, WOMEN WERE ABLE TO REFUSE ANY ADDITIONAL TESTING SUCH AS COLPOSCOPY AND BIOPSY (AND SEVERAL DID).

How were the women contacted when they were HPV negative or HPV positive?
WOMEN WHO WERE HPV+ WERE CONTACTED VIA CELL PHONE. LINE 231.

In the discussion:
“The authors propose a screen-and-treat model that is low –cost, rapid and capable of being implemented on a large scale, …..”
Minor comment – why use “the authors”? I would suggest to write “we”
DONE

Major comments –
Is one-stop screening in this setting able to be implemented on “large scale” with highly educated physicians?

NURSE OR OTHER SKILLED HEALTH CARE WORKERS COULD BE TRAINED TO PERFORM COLPOSCOPY AND ABLATIVE PROCEDURES. CURRENTLY, EXCISIONAL PROCEDURES MUST BE DONE BY PHYSICIAN IN CHINA. LINE 353.

Why use one stop – If vaginal self-sampling is used, why is it important to have a “rapid” HPV answer?
RAPID HPV TESTING ALLOWS FOR A SEE-AND-TREAT APPROACH WHICH LIMITS LOSS-TO-FOLLOW-UP.A MORE THOROUGH DISCUSSION IS GIVEN IN LINES 318-323

Why cannot heath workers provide the vaginal self-sample kits or maybe sent it by mail to the women with proper instructions?
MANY OF THE WOMEN SCREENED IN THIS STUDY ARE ILLITERATE FARMERS AND/OR SEMI-NOMADIC. THEY DO NOT HAVE ADDRESSES (PER SE) OR MAIL SERVICE.

How will the whole female population in recommended screening ages be screened on a regular basis?
I BELIEVE THAT THE ANSWER TO THIS QUESTION IS BEYOND THE SCOPE OF THIS PAPER AS IT IS DEPENDANT ON ECONOMIC AND SOCIETAL FACTORS. AS I AM SURE YOU ARE AWARE, CHINA IS A VAST AND EXTREMELY DIVERSE NATION. IT IS UNLIKELY THAT ONE SCREENING STARTEGY CAN BE IMPLIMENTED THROUGHOUT CHINA.

Is there any thoughts for the future way to go in this area of China including the logistics?
THIS IS ALSO PROBABLY BEYOND THE SCOPE OF THIS PAPER. IF FEASIBILITY STUDIES SUCH AS THESE CONTINUE TO BE SUCCESSFUL THEN PROPOSALS TO REGIONAL HEALTH MINISTRIES CAN BE MADE AND THEN FUNDING AND RESOURCES MUST BE ALLOCATED.

The sensitivity of the HPV analyses are discussed but the meta-analyses by Arbyn et al 2014 and 2018 is not in the list of references
ADDED, REFERENCES 21,22

Why should women with CIN I (LSIL) be treated? Why not a new vaginal HPV analyze in a 12 months period since the majority of these lesions and HPV infections heal without any treatment?
THESE ARE NOT BIOPSY PROVEN LESIONS. ADDITIONALLY, THERE IS NO (CURRENT) ABILITY TO RETEST THESE WOMEN IN ONE YEAR FOR HPV. THEREFORE, THE CURRENT W.H.O. GUIDELINE RECOMMEND AN ABLATIVE PROCEDURE. LINES 373-376.

Reviewer: 2
Reviewer Name: Ditte Møller Ejegod
The paper is well-written, but it is at times a bit hard to follow, a flow chart of the study inclusions, HPV prevalence, DC and perhaps also outcomes would be helpful, as would a table with the results presented in the result section.
DONE, SEE FIGURE 3.

General comments
Please use either digital colposcopy or DC throughout the paper.
DONE

Suggest using the term ≥CIN2 instead of CIN2+ and hrHPV+ instead of +hrHPV
DONE

The paper could use some grammatical edit at times e.g. 3th paragraph in introduction, 6th paragraph of introduction
DONE

Specific comments
Introduction
2end paragraph “In general, women living in rural areas are less likely….” Compared to women living in cities or…?
DONE, LINES 129-130

6th paragraph (beginning with “cervicovaginal HPV DNA testing…”) suggest including the reference “Detecting cervical precancer and reaching under-screened women by using HPV testing on self-samples: updated meta-analyses. Arbyn M et al., 2018” in addition to reference 21.
DONE

Suggest using more resent refences than ref 22-24 in the end of the 6th paragraph
DONE, SEE NEW REFERENCES 22,23

Methods
How was HPV negative women managed?
IT WAS SUGGESTED THAT THEY BE RETESTED IN 3 YEARS- THOUGH NO CURRENT SYSTEM IS AVAILABLE FOR THIS.

What is IRB?
LINE 209-210

How was the women with HPV and negative DC followed up, with HPV+DC or only HPV
In paragraph 1 the it writes “Cryotherapy was performed the same day when findings were suspicious for CIN1 lesions” and in Paragraph 2 that “women with suspected low-grade lesions (CIN1) were counseled to have repeat HPV testing in 1 year” Did they receive cryotherapy and recommendation for follow-up or… this is a bit unclear.
WE HAVE TRIED TO MAKE THIS CLEARER, LINES 240-252. ADDITIONALLY, THE RESULTS CHART FIGURE 1 ALSO CLARIFIES THIS.

Suggest moving the last paragraph (Patient and public involvement:..) to discussion in a perspective section
THE JOURNAL’S POLICY IS TO HAVE THIS IN THE METHODS SECTION.

Results
Please refer to figure 1 and 2 in the text.
DONE, LINES 153, 298.

I would suggest generating a flow chart of the study that would make it easier for the reader to follow study the set up.
DONE, FIGURE 3

A table showing the data presented in the result section would also be helpful.
FIGURE 3 CONTAINS ALL RESULTS

Was all women with positive DC biopsied this is a bit unclear from the text.
LINE 240-241.

Reviewer: 3

Reviewer Name: Gisela Helenius

Please leave your comments for the authors below
This manuscript describe a new promising screening strategy for low-income countries without organized screening. It is written clearly and easy to follow. I miss however some information about the HPV-test in the methods part.
Describe what kind of selfsampling device that was used.
NOW DESCRIBED IN LINES 218-219.

Describe how the HPV-test was performed. How was the result interpreted? How was the sucessrate of the test?
I'M AFRAID I DON'T UNDERSTAND THIS QUESTION. THE RESULTS ARE BETTER ILUSTRATED IN THE CHART OF RESULTS FIGURE 3.

In row 50: Define the abbreviation IRB in "IRB approval"
DONE

In the discussion I would like to an estimation of the total cost of the described screening strategy compared to something relevant, for example a screening strategy used in a country with established organized screening.
UNFORTUNATELY, THIS STUDY WAS NOT SET UP AS A COST-EFFECTIVENESS STUDY. I HAVE ADDED AN EXTENSIVE DISCUSSION OF THIS ISSUE ON LINES 450-468.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Christer Borgfeldt<br>Department of Obstetrics and Gynecology<br>Skåne University Hospital<br>Lund University<br>Sweden |
| **REVIEW RETURNED** | 15-Feb-2020 |

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| **GENERAL COMMENTS** | Improved manuscript |

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| **REVIEWER** | Ditte Møller Ejegod<br>Hvidovre Hospital, Denmark |
| **REVIEW RETURNED** | 13-Feb-2020 |

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| **GENERAL COMMENTS** | The authors have done a good job at responding to the comments from the reviewer and the paper is in my opinion ready for publication<br>The only comment I have is regarding the strength and limitations part after the abstract which in my opinion only appears to include points regarding the strength of the study not the limitations. |

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| **REVIEWER** | Gisela Helenius<br>Department of Laboratory Medicine, School of Medical Sciences, Örebro University, Sweden |
| **REVIEW RETURNED** | 12-Feb-2020 |

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| **GENERAL COMMENTS** | The reviewer completed the checklist but made no further comments. |

**VERSION 2 – AUTHOR RESPONSE**

I appreciate Reviewer 2's comment and added a significant limitation of the study to this section of the abstract. Specifically:

• "The careHPVTM system, which relies on signal amplification technology, may be less sensitive than PCR based systems to detect ≥CIN2 lesions on self-swabs."