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

TITLE (PROVISIONAL)	A Protocol for a systematic review of Research on HPV and Cervical Cancer in Ghana up until the year 2016: Informing Research and Policy Direction on Cervical Cancer Prevention in Ghana
AUTHORS	Awua, Adolf Kofi Doe, Edna Dzifa

VERSION 1 - REVIEW

REVIEWER	Witness Mapanga
REVIEW RETURNED	11-Nov-2017

GENERAL COMMENTS	Reviewer comments_bmjopen-2017-020183 Abstract Is the protocol not developed according to the PRISMA-P statement? If so, this should be explicitly mentioned under the methods Line 2 under methods should have a "be" between 'will' and 'aggregated' Under ethics and dissemination, correct the spelling of 'publicly' and replace 'sued' with 'used' Objectives Objective number 2: by active, are the authors trying to say current research? The word active is vague Methods May you mention if the protocol is guided by the PRISMA-P statement and if the systematic review that is to be guided by this protocol will be carried out in accordance with PRISMA guidelines? Document about the protocol registration with PROSPERO as well Information sources The documented data sources are few. There is risk of missing other studies, therefore, suggest increasing the number of databases including Embase, Medline, CINAHL Search Strategy Nothing systematic has been mention here. Authors need to have a well thought out search strategy for at least one database. As it is right now, there is no search strategy There is no mention of how the different databases will be search, for example, Cochrane, requires searching via the Cochrane Library using MeSH terms and qualifiers. There is need to use truncation commands (root word) and proximity operators in your search strategies. Citation and reference tracking are also good sources of finding relevant studies. What techniques are to be used in the online databases search – such as free-text synonyms etc?

Study records
Selection process
Include reviewers' initials in the narrative, eg, 'merging of the results of the database searches will be done and two independently working researchers (AAK and EDD)'
There is no mention of a full-text screening form (which should be available) to enable readers to see the criteria used in selecting studies
How many independent researchers are going to be merging the results from the database searches?
How are disagreements and other issues pertaining to the screening process going to be resolved? There is need for a third independent reviewer will mediate the discussions
Dates and related activities
This work plan is not necessary to be included in the manuscript. I suggest the authors remove it
Risk of bias and quality assessment of individual studies
How is potential bias going to be addressed?
Is quality examination going to be carried by one or two researchers?
How are the quality scores going to be accorded? Are two reviewers going to allocate scores independently and then average them?
Are studies going to be excluded based on quality rating?
Data synthesis
'A plot of the total number of publications and number of each type of publication over the study period will be generated' – how are you going to plot these numbers? Is this graphic or statistical?
General comments
There is need to go through the whole manuscript and correct some spellings and a bit of grammar

REVIEWER	Benny Kirschner
REVIEW RETURNED	26-Nov-2017

GENERAL COMMENTS	Does not seem to be a medical research paper, but more a working tool/ guideline for future research. Does need significant revision of language and grammar.

REVIEWER	Peter Rohloff
REVIEW RETURNED	29-Jan-2018

GENERAL COMMENTS	This is an important topic. I did a quick pubmed search of "ghana" and "cervical cancer" and got more than 60 publications, so from a feasibility perspective there is probably enough literature to do this review. Important goals include identifying holes in current research efforts, estimating human resources efforts, and mapping partners and collaborations. These are worthy goals. In the introduction, I think more focus on existing summary literature from Ghana and relevant global health/policy or Africa region literature would be helpful. The reference to Australia

seems somewhat arbitrary. What about recent WHO guidelines, for example, on HPV screening in LMICs and what effect those are having in the AFR region? The framing could be more specific and less general.

The databases to be searched are adequate, but methods for gathering and assessing "other grey literature" are incompletely defined.

Selection process - this is where bias can be introduced, so more specific criteria for inclusion or exclusion would be helpful. Also, how will authors deal with data which may only exist in abstract not full text form? I suspect there will be a lot of this.

OUtcomes and data analysis process - from my review of the 60+ articles on Pubmed on Ghana/cervical cancer, I am struck by the fact that most of these are qualitative. It is not clear to me if the authors have a solid qualitative data analysis plan, and I think that is going to be critical here.

Also "Major Data Items" could be more specific - what does "extent of collaboration" mean, and how will that be assessed, for example?

In terms of quantitative data that might be collected, what are the anticipated data elements that authors will be looking for - screening rates, followup care rates, HPV prevalence rates ,that sort of thing?

Under expected outcomes, I totally agree with authors that mapping gaps in area of study is critical and very important. However, can the authors give us some idea of how they conceptualize the field of HPV and cervical cancer? What scheme or disciplinary taxonomy will be used to categorize research efforts so that we can know where such efforts are distributed, and where they might be missing.

Not all elements of the PRISMA checklist are included in the protocol. In particular some of them are very important, like 15a-c, planned quantitative and qualitative synthesis, and should be addressed in more detail in the protocol.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Witness Mapanga

Abstract
COM   Is the protocol not developed according to the PRISMA-P statement? If so, this should be explicitly mentioned under the methods.
RES: Indicated as suggested: [Line 20 and line 112]

COM   Line 2 under methods should have a "be" between 'will' and 'aggregated'
RES: Corrected as suggested; Line 25

COM   Under ethics and dissemination, correct the spelling of 'publicly' and replace 'sued' with 'used'

RES: Corrected as suggested; Line 27

Objectives
COM   Objective number 2: by active, are the authors trying to say current research? The word active is vague
RES: This has been modified, as well as for objective 4; [Line 99 and 102]

Methods
COM   May you mention if the protocol is guided by the PRISMA-P statement and if the systematic review that is to be guided by this protocol will be carried out in accordance with PRISMA guidelines? Document about the protocol registration with PROSPERO as well
These have been mentioned as suggested. [Lines 111-116]

Information sources
COM   The documented data sources are few. There is risk of missing other studies, therefore, suggest increasing the number of databases including Embase, Medline, CINAHL
RES: Databases have been included, therefore search will be extended to 2017. [Line 155]

Search Strategy
COM   Nothing systematic has been mention here. Authors need to have a well thought out search strategy for at least one database. As it is right now, there is no search strategy. There is no mention of how the different databases will be search, for example, Cochrane, requires searching via the Cochrane Library using MeSH terms and qualifiers. There is need to use truncation commands (root word) and proximity operators in your search strategies. Citation and reference tracking are also good sources of finding relevant studies. What techniques are to be used in the online databases search – such as free-text synonyms etc?
RES: A search strategy has been extensively modified and that for PubMed have been provided as example. The search for the other databases will be conducted according to the specific procedure for each of the databases, including the specific truncation commands, proximity operators etc. This will be reported fully after the review is completed in the related publication. However, citation and reference tracking will not be used for this review, since it is not likely to make any difference in the number of relevant study to be identified for the review. [Lines 168 to 196]

Study records
Selection process
COM   Include reviewers' initials in the narrative, eg, 'merging of the results of the database searches will be done and two independently working researchers (AAK and EDD). There is no mention of a full-text screening form (which should be available) to enable readers to see the criteria used in selecting studies:
RES: This has been mentioned, [Lines 200, 204 and 227].

COM   How many independent researchers are going to be merging the results from the database searches?
RES: An online Zotero account will be used and reviewed by the two independent researchers and a third reviewer when disagreement are not resolved by the researchers. [Line 203]

COM   How are disagreements and other issues pertaining to the screening process going to be resolved? There is need for a third independent reviewer will mediate the discussions.
RES: These have been indicated as suggested. [Lines 211-213].

COM   Dates and related activities - This work plan is not necessary to be included in the manuscript. I suggest the authors remove it.

RES: This has been removed

COM   Risk of bias and quality assessment of individual studies - How is potential bias going to be addressed?
RES: This potential bias will be identified and the differences in the studies included in generated or synthesis specific information will be reported to define the limits thereof. [Lines 298-305].

COM   Is quality examination going to be carried by one or two researchers?
RES: This will carried out by the two and disagreements resolved as indicated earlier. [Lines 279-280].

COM   How are the quality scores going to be accorded? Are two reviewers going to allocate scores independently and then average them?
RES: The two researchers (AKA and EDD) will independently allocate the scores and an average will be determined. [Lines 289-296]

COM   Are studies going to be excluded based on quality rating?
COM   Since the focus of the review is to look at the spectrum of research on cervical cancer and HPV in Ghana and that they may not be a deluge of such studies, No study will be exclude due to quality. However, the quality of the study will be indicated. [Lines 293-296].

Data synthesis
COM   'A plot of the total number of publications and number of each type of publication over the study period will be generated' – how are you going to plot these numbers? Is this graphic or statistical?
RES: This will be done graphically

General comments
COM   There is need to go through the whole manuscript and correct some spellings and a bit of grammar
RES: Conducted as suggested.

Reviewer: 2
Reviewer Name: Benny Kirschner

COM   Does not seem to be a medical research paper, but more a working tool/ guideline for future research. Does need significant revision of language and grammar.
RES: Conducted as suggested.

Reviewer: 3
Reviewer Name: Peter Rohloff

COM   This is an important topic. I did a quick pubmed search of "ghana" and "cervical cancer" and got more than 60 publications, so from a feasibility perspective there is probably enough literature to do this review. Important goals include identifying holes in current research efforts, estimating human resources efforts, and mapping partners and collaborations. These are worthy goals.
RES: We thank the reviewer for the kind comments

COM   In the introduction, I think more focus on existing summary literature from Ghana and relevant global health/policy or Africa region literature would be helpful. The reference to Australia seems

somewhat arbitrary. What about recent WHO guidelines, for example, on HPV screening in LMICs and what effect those are having in the AFR region? The framing could be more specific and less general.

RES: Although the PRISMA guideline indicated to provide a rational, with little background, we have included a short summary literature on cervical cancer. A full summary literature will be provided in the publication of the review when it is conducted. The Australian example was to indicate one of the most recent use of systematic review to inform policy change, which implies the intension to inform policy in Ghana by this review meets global standard practice. [Lines 48 -85]

COM   The databases to be searched are adequate, but methods for gathering and assessing "other grey literature" are incompletely defined.

RES: Methods for gathering and assessing grey literature have been included. [Lines 190-196 and 205-210].

COM   Selection process - this is where bias can be introduced, so more specific criteria for inclusion or exclusion would be helpful. Also, how will authors deal with data which may only exist in abstract not full text form? I suspect there will be a lot of this.

RES: The eligibility criteria have been expanded to 13 items and these will apply in the selection of relevant records. Abstracts which meet the eligibility criteria will be included in the review. [Lines 119, 137-149].

COM   OUtcomes and data analysis process - from my review of the 60+ articles on Pubmed on Ghana/cervical cancer, I am struck by the fact that most of these are qualitative. It is not clear to me if the authors have a solid qualitative data analysis plan, and I think that is going to be critical here.

RES: The thematic qualitative data analysis will be employed in this review. A detail description is provided, [Lines 314-329].

COM   Also "Major Data Items" could be more specific - what does "extent of collaboration" mean, and how will that be assessed, for example?

RES: These haven been modified and the examples now read, 'Proportion of studies which involved internal and external collaboration' and "Proportion of studies which reported of Ethical conduct". Additional information have been provide to make it more specific. [Lines 244-260].

COM   In terms of quantitative data that might be collected, what are the anticipated data elements that authors will be looking for - screening rates, follow-up care rates, HPV prevalence rates ,that sort of thing?

RES: The data elements that will be looked for in the data extraction are presented as
Age at diagnosed with cervical cancer; Age-specific cervical cancer and lesion prevalence; Age-specific HPV prevalence (indicate participants); Approach to cervical cancer prevention; Awareness of cervical cancer, risk factors, symptom, vaccination; Barrier to screening (individual, national, cost); Cervical cancer type, symptom incidence, and prevalence; Diagnosis and treatment (approaches, option, stage, outcomes); Educational strategy; Facilitators of screening and vaccination; Factors associated with cervical cancer; HPV genotype prevalence (indicate participants); HPV Infection type prevalence (indicate participants); overall HPV prevalence (indicate participants); HPV risk type prevalence (indicate participants); Knowledge of any issues and association; Modelling prevention; Other HPV related cancer prevalence; Perception (cause, risk factors etc); Quality of life; Screening history/rate; Screening strategies and preferences; and Vaccination. [Lines 248-260].

COM   Under expected outcomes, I totally agree with authors that mapping gaps in area of study is critical and very important. However, can the authors give us some idea of how they conceptualize the field of HPV and cervical cancer? What scheme or disciplinary taxonomy will be used to

categorize research efforts so that we can know where such efforts are distributed, and where they might be missing.

RES: These are as follows

Biological research: ☐ HPV biology, ☐ Genome analysis, ☐ Cancer cell biology. ☐Cervical cancer biomarker

Primary prevention research: ☐ Group Education, ☐ Health professional Training, ☐ Knowledge, Attitude & Perception, ☐ Risk group assessment, ☐ Risk factor assessment, ☐ Psychosocial factors and health seeking behaviour, ☐ Vaccination

Secondary Prevention research: ☐ Prevalence of HPV/HPV screening, ☐ Pap screening/Prevalence cervical lesions or cancer, ☐ VIA screening, ☐ Co-testing, ☐ Factors influencing screening attendance

Tertiary Prevention/Clinical Research: ☐ Diagnosis, ☐ Reporting, ☐ Clinical manifestation, ☐ Treatment ☐ Quality of life ☐ Palliative care, ☐ Incidence/Survival/Mortality studies, ☐ Cancer registry data ☐ Factors influencing treatment seeking

COM   Not all elements of the PRISMA checklist are included in the protocol. In particular some of them are very important, like 15a-c, planned quantitative and qualitative synthesis, and should be addressed in more detail in the protocol.
RES: These have been addressed. [Lines 314 to 335].

Additional change by Authors
The limit on study period has been extended to 2017 and the time for the search modified, since the reviewers suggested more databases to be added, and therefore the search will be repeated.

VERSION 2 – REVIEW

REVIEWER	Witness Mapanga
REVIEW RETURNED	16-Mar-2018

GENERAL COMMENTS	Reviewer comments
	Abstract
	Line 18: Consider rewording the aim of the protocol. Protocols usually report the plan for a systematic review rather than identify research gaps, prevent unnecessary duplication of work and hopefully enable collaboration
	Line 26: "Although publicly available data is be used for this review…." Add "to" between 'be and used'
	Strengths and limitations
	Line 35: 'The selection method used allows for a comprehensive review by the inclusion of almost all publications on cervical cancer and HPV, without limitations on study design" – This statement is vague, consider re-wording it
	Line 37: 'The review covers a wide range of potential source of information hence reduces the potential for publication bias" – how does this reduce potential publication bias?
	Line 39: 'The comprehensive selection method will result a in list of relevant publications useful for researchers and students seeking for research ideas' – Are you trying to make the available literature accessible by everyone or you want to use this literature for your systematic review?
	Introduction

Line 52: 'In Ghana, it is one the two leading causes (the other is breast cancer) of cancer cases and death.' – Put 'of' between 'it is one of the two leading causes….'

Eligibility criteria

Line 146, point 12: 'All grey literature for which a full-text article is available shall be not be eligible' – Is it shall be eligible or shall not be eligible?

Information Sources

Line 153: replace 'search' with 'searched'

****The manuscript has a number of grammar mistakes that require attention.

PRISMA-P Checklist

Item number 2: The protocol is registered with PROSPERO, therefore, indicate so on the information reported

REVIEWER	Peter Rohloff
REVIEW RETURNED	29-Mar-2018

GENERAL COMMENTS	The authors have substantially improved the manuscript, with a lot of important methodological details.

I have some additional recommendations.

1. I am conflicted a bit about the choice to exclude most of the grey literature ("excluding "not research studies"). I think this needs to be revisited or more strongly justified. Many NGO or government or policy documents may not be strictly research, but still have a lot of important insights particularly in the more qualitative arena (barriers/facilitators to care; knowledge, attitudes and practices). If the authors feel that including this literature is not justifiable or feasible, then I think they need to make the case for this more strongly.

2. The qualitative data analysis plan is better, but I think we are still unclear on what types of data that the authors expect to find in this part of the work (as compared to the more quantitative data). Some of these elements are now presented in the paragraph on quantitative data (e.g., "barrier to screening") but I still am unclear on how the authors will triangulate this with the quantitative data. Maybe separately addressing the types of data from the more quantitative vs. more qualitative reports would be helpful.

3. The authors document a taxonomy for classifying research in the response letter, but this doesn't seem to be addressed in the revised manuscript.

4. I would recommend a close and extensive edit for grammar and style and succinctness. The quality of the English is uneven, and this has been made worse because of the many important methodological additions the authors have made to the text. This is not a critique of the scientific content, but the readability of the manuscript in its current format is low.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Witness Mapanga
Institution and Country: Centre for Health Policy, University of Witwatersrand, South Africa
Please state any competing interests: None declared

Abstract
COM: Line 18: Consider rewording the aim of the protocol. Protocols usually report the plan for a systematic review rather than identify research gaps, prevent unnecessary duplication of work and hopefully enable collaboration
ANS: [Lines 18-20; 92, 97-99;]. The aim of the protocol has been stated and clearly differentiated form the objectives of the intended systematic review to be guided by the protocol.

COM: Line 26: "Although publicly available data is be used for this review…." Add "to" between 'be and used'
ANS: corrected as indicated

Strengths and limitations
COM: Line 35: 'The selection method used allows for a comprehensive review by the inclusion of almost all publications on cervical cancer and HPV, without limitations on study design" – This statement is vague, consider re-wording it.
ANS: [Lines 36-44]. The section on Strengths and limitations has been extensively revised.

COM Line 37: 'The review covers a wide range of potential source of information hence reduces the potential for publication bias" – how does this reduce potential publication bias?
ANS: [Lines 36-44]. The section on Strengths and limitations has been extensively revised.

COM: Line 39: 'The comprehensive selection method will result in a list of relevant publications useful for researchers and students seeking for research ideas' – Are you trying to make the available literature accessible by everyone or you want to use this literature for your systematic review?
ANS: [Lines 36-44]. The section on Strengths and limitations has been extensively revised.

Introduction
COM: Line 52: 'In Ghana, it is one the two leading causes (the other is breast cancer) of cancer cases and death.' – Put 'of' between 'it is one of the two leading causes….'
ANS: corrected as indicated.

Eligibility criteria
COM: Line 146(now 151), point 12: 'All grey literature for which a full-text article is available shall be not be eligible' – Is it shall be eligible or shall not be eligible?
ANS: this has been corrected to "shall be eligible"

Information Sources
COM: Line 153 (now 179): replace 'search' with 'searched'
****The manuscript has a number of grammar mistakes that require attention.
ANS: efforts have been to improve all of such mistakes.
PRISMA-P Checklist

COM: Item number 2: The protocol is registered with PROSPERO, therefore, indicate so on the information reported.
ANS: This has now been indicated in the abstract.

Reviewer: 3
Reviewer Name: Peter Rohloff
Institution and Country: Brigham and Women's Hospital USA, Maya Health Alliance, Guatemala
Please state any competing interests: None declared

COM 1. I am conflicted a bit about the choice to exclude most of the grey literature ("excluding "not research studies"). I think this needs to be revisited or more strongly justified. Many NGO or government or policy documents may not be strictly research, but still have a lot of important insights particularly in the more qualitative arena (barriers/facilitators to care; knowledge, attitudes and practices). If the authors feel that including this literature is not justifiable or feasible, then I think they need to make the case for this more strongly.
ANS: [lines 154-160]; The following justification was provided, "As implied by the title "…systematic review of research…..", the protocol is for a review of research, therefore policy documents with no direct relation to research in Ghana cannot be included, and for those for which there is a direct link with research in Ghana, if its articles are included, then there will be no need to include the policy document. Furthermore, to the best of our knowledge, there is only one such NGO publication, which has most of its information published in different research articles by the collaborating researchers on that project."

COM 2. The qualitative data analysis plan is better, but I think we are still unclear on what types of data that the authors expect to find in this part of the work (as compared to the more quantitative data). Some of these elements are now presented in the paragraph on quantitative data (e.g., "barrier to screening") but I still am unclear on how the authors will triangulate this with the quantitative data. Maybe separately addressing the types of data from the more quantitative vs. more qualitative reports would be helpful.
ANS: It actually not clear what exact types of data we are likely to find in respect of this part of the work, therefore, we will be collecting all available qualitative data. However, the qualitative and quantitative elements have been separated and some further detail have indicated for some of the qualitative elements.

COM 3. The authors document a taxonomy for classifying research in the response letter, but this doesn't seem to be addressed in the revised manuscript.
ANS: These have been included in the section on outcomes.

COM 4. I would recommend a close and extensive edit for grammar and style and succinctness. The quality of the English is uneven, and this has been made worse because of the many important methodological additions the authors have made to the text. This is not a critique of the scientific content, but the readability of the manuscript in its current format is low.
ANS: Efforts have been made to improve the readability of the manuscript.

VERSION 3 – REVIEW

REVIEWER	Witness Mapanga
REVIEW RETURNED	18-May-2018

GENERAL COMMENTS	The paper will benefit more from revision by an English editor to improve grammar and flow of the ideas.

REVIEWER	Peter Rohloff
REVIEW RETURNED	22-May-2018

GENERAL COMMENTS	The authors have addressed my concerns. the manuscript is much improved.