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)	African Breast Cancer - Disparities in Outcomes (ABC-DO): Protocol of a multi-country mHealth prospective study of breast cancer survival in sub-Saharan Africa
AUTHORS	McKenzie, Fiona; Zietsman, Annelle; Galukande, Moses; Anele, Angelica; Adisa, Charles; Cubasch, Herbert; Parham, Groesbeck; Anderson, Benjamin; Abedi-Ardekani, Behnoush; Schuz, Joachim; dos Santos Silva, Isabel; McCormack, Valerie

VERSION 1 - REVIEW

REVIEWER	Dr. Eva J. Kantelhardt Institute for medical Epidemiology, Statistics and Informatics Martin Luther-Universität Halle Ernst-Grube Str. 40 06097 Halle Germany
REVIEW RETURNED	25-Feb-2016

GENERAL COMMENTS	This well written manuscript describes the study protocol of a very interesting study on breast cancer (BC) in sub Saharan Africa. The study protocol (ABC-DO) is a prospective hospital based cohort study. The study is conducted in five African countries and investigates overall survival, quality of life and the patient pathways. This recruitment started in 2014 and will continue until 2016. The study will significantly contribute to knowledge on outcome and understanding of factors influencing outcome. Factors from the patient side, social and health system side as well as tumor characteristics are studied. The participating hospitals are thoroughly described and the mHealth approach is explained. Some minor comments: Abstract: Introduction: The first sentence mentions breast cancer as “treatable” disease. I suggest to use e.g. “potentially treatable” since of course many cases are rather palliative cases. Methods: 1) The first sentence says “…journey to diagnosis.” I am sure the authors mean “…journey to diagnosis and treatment.” 2) The next sentence says “… clinically … confirmed.” Breast cancer cannot be clinically confirmed, I suggest to re-write the sentence. 3) Second paragraph in Methods: “Responses… captured on mobiles” – In the later text I understood that the baseline interview is actually face-to-face and only later it is mobil phone interviews? 4) Possibly the authors may want to mention the hospital levels involved in recruitment. Background: 1) In the second paragraph it is mentioned that factors have the

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	potential to "…save lives if stage migration could be achieved." Possibly use "…downstaging…" instead of stage migration since the latter is more often use when the stage increases (rather than decreases). 2) Third paragraph: therapy availability is important but I suggest to add also quality of therapy. 3) Same paragraph: consider to add "lack of radiotherapy" as a problem. 4) Page 4 list of hypothesis: problem of linking centralized oncology care with rural areas/health centers could be mentioned. Methods and analysis 1) Participant inclusion/exclusion first paragraph: how do you handle patients with recurrences? 2) Please justify why patients with diagnosis of D05 are included in the study? These have different expected treatment and outcome. Usually outcome analysis is restricted to cancer. 3) clinical, pathological and treatment information: are there any measures to know about metastatic situation? Is that clinically/patient complaints? Is staging done (chest x-ray, liver ultrasound and bone scan)? How does the study design account for differences in metastatic workup at point of diagnosis between centers because the proportion of M1 patients will differ depending on the investigations done. M1 patients will have very reduced survival probabilities. 4) Bio specimen: is it certain that no therapy is given before sample acquisition? Table 1: lasr row – what about radiology and bone scan? Figure 1: Endpoint survival at 3 years seems ambitious since drop-out is expected, the definition in "data analysis plan" has better description Figure 2: the term "Pre-study enrolment" is not clear to me.

REVIEWER	Sulma Mohammed Purdue University West Lafayette IN 47906 USA
REVIEW RETURNED	26-Feb-2016

GENERAL COMMENTS	**1. I think the way the paper is written is not clear and the description does not explain the objectives** "The author stated that understanding context –specific societal, health system and women level barriers to early detection, diagnosis and appropriate treatment are needed to inform strategies to improve survival". However, the manuscript did not address the above objectives but described a processes or a protocol to collect data – this should be clearly stated – the above sentence should be the rational The author should state his/her objectives by starting with "this manuscript describe a protocol to collect data ----------" **2. The authors described a protocol to collect information on women and why they present late** – since no outcomes or results described we do not know the value of this protocol – I think is too early to publish this protocol without showing its success.

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	3. The study is hospital – based and did not capture all women with breast cancer – so we can not generalize as there are some that do not make it to the hospital (and those are the important ones) 4. Standardization of sample handling, fixation, reagents used in fixation, immunohistochemistry protocol and reagent 5. Important part of the protocol is not provided i- which is the questions used in the protocol – those should be included as part of the protocol and what are languages used

REVIEWER	Shahin Sayed Aga Khan University Nairobi,Kenya
REVIEW RETURNED	06-Mar-2016

GENERAL COMMENTS	"the study itself does not fund, and thus does not require, histo(cyto)pathological confirmation" Why then are biospecimens being collected for analysis for histopathology and IHC ? There is clearly a contradiction here. Please clarify.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Dr. Eva J. Kantelhardt

Minor comments:

Abstract:
Introduction: The first sentence mentions breast cancer as “treatable” disease. I suggest to use e.g. “potentially treatable” since of course many cases are rather palliative cases.

Response: The wording is amended as per the reviewer’s suggestion.

Methods:
1) The first sentence says “…journey to diagnosis.” I am sure the authors mean “…journey to diagnosis and treatment.”

Response: The wording is amended as per the reviewer’s suggestion.

2) The next sentence says “… clinically … confirmed.” Breast cancer cannot be clinically confirmed, I suggest to re-write the sentence.

Response: Some of the patients are only diagnosed clinically. We have changed the wording to women … “with a new clinical or histo-cytological diagnosis of primary BC…”

3) Second paragraph in Methods: “Responses… captured on mobiles” – In the later text I understood that the baseline interview is actually face-to-face and only later it is mobile phone interviews?

Response: All interviews are captured on mobile devices, whether face-to-face or telephone. In the abstract and methods-ABC-DO mHealth application section, we have added the word face-to-face for

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the baseline interview, and clarified the use of the app for data capture during the follow-up period.

4) Possibly the authors may want to mention the hospital levels involved in recruitment.

Response: We have mentioned secondary and tertiary hospitals in the abstract.

Background:
1) In the second paragraph it is mentioned that factors have the potential to "…save lives if stage migration could be achieved." Possibly use "…downstaging…" instead of stage migration since the latter is more often use when the stage increases (rather than decreases).

Response: We have amended this term as per Reviewer's suggestion.

2) Third paragraph: therapy availability is important but I suggest to add also quality of therapy.

Response: Quality of therapy has now been included.

3) Same paragraph: consider to add "lack of radiotherapy" as a problem.

Response: Indeed, radiotherapy has very low coverage in much of sub-Saharan Africa. We have added a sentence to highlight this important point.

4) Page 4 list of hypothesis: problem of linking centralized oncology care with rural areas/health centers could be mentioned.

Response: We have spelled out further the problem of access into the background. In the hypothesis, we consider that this point is covered in the first hypothesis concerning "late stage at diagnosis" and "lack of access to treatment".

Methods and analysis
1) Participant inclusion/exclusion first paragraph: how do you handle patients with recurrences?

Response: During patient enrolment, if there is uncertainly whether a woman presents with a second primary breast cancer or a recurrence, rather than leaving this important decision to the enrolling nurse, we have asked RAs to include a patient if there is any such uncertainty. Information is collected on all previous breast problems including previous breast cancer, thus an evaluation of the potential that a woman has a recurrence rather than an incidence cancer will be jointly assessed across all sites and, if necessary, women will be excluded at time of analyses. The end of the paragraph "Participant inclusion/exclusion" has been changed to reflect this.

2) Please justify why patients with diagnosis of D05 are included in the study? These have different expected treatment and outcome. Usually outcome analysis is restricted to cancer.

Response: The simple documentation of the expected rarity of in situ breast cancers in this setting, or even any small increase in situ cancers and gaining information on how such cancers come about to be diagnosed would in itself be informative. All analyses will of course be stage-stratified and many will be restricted to invasive malignancies only. The 'Data analysis plan' has been altered to reflect this.

3) Clinical, pathological and treatment information: are there any measures to know about metastatic situation? Is that clinically/patient complaints? Is staging done (chest x-ray, liver ultrasound and bone scan)? How does the study design account for differences in metastatic workup at point of diagnosis

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between centers because the proportion of M1 patients will differ depending on the investigations done. M1 patients will have very reduced survival probabilities.

Response: The study is entirely and deliberately observational, so that it will provide estimates of survival for the present situation, using the methods of diagnosis available in the settings included. Diagnostic capabilities will have a large impact on staging, thus in addition to recording stage data, we obtain information on methods of ascertainment of diagnostic staging, including of confirmed or suspected metastases. The timings of stage information in relation to surgery, chemo, etc., is also being recorded. Thus, there may be systematic differences in the ability to accurately stage between sites, but in analyses we will still be able to compare stage distributions between sites in women who have undergone similar diagnostic investigations of metastatic spread.

4) Bio specimen: is it certain that no therapy is given before sample acquisition?

Response: Data regarding the timing of the specimen in relation to therapies is being collected, thus we will be able to identify tumor specimen that are obtained after neoadjuvant chemotherapy. We have added this detail to the 'biospecimen' text.

Table 1: last row – what about radiology and bone scan?
Response: Imaging facilities have been added to the table.

Figure 1: Endpoint survival at 3 years seems ambitious since drop-out is expected, the definition in "data analysis plan" has better description

Response: The primary endpoint is 3-year survival. This will be estimated in the present study set-up, as interviewers will be employed for at least 3 years since enrolment of the first patient. Losses-to-follow-up are indeed expected, but use of active follow-up methods using mobile phones should reduce these losses. We will of course be able to analyse 1-year and 2-yeaer survival

Figure 2: the term "Pre-study enrolment" is not clear to me.

Response: Pre-study enrolment refers to time/events that happened before women enter the study – this has been added as a note at the bottom of the diagram.

Reviewer: 2
Sulma Mohammed

Response: As the reviewer does not seem familiar with the publication of study protocols, we have followed the editor's instructions, and do not respond to points 1 and 2 below.

1. I think the way the paper is written is not clear and the description does not explain the objectives. "The author stated that understanding context –specific societal, health system and women level barriers to early detection, diagnosis and appropriate treatment are needed to inform strategies to improve survival". However, the manuscript did not address the above objectives but described a processes or a protocol to collect data – this should be clearly stated – the above sentence should be the rational. The author should state his/her objectives by starting with "this manuscript describe a protocol to collect data ----------"

2. The authors described a protocol to collect information on women and why they present late – since no outcomes or results described we do not know the value of this protocol – I think is too early to publish this protocol without showing its success.

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3. The study is hospital – based and did not capture all women with breast cancer – so we can not generalize as there are some that do not make it to the hospital (and those are the important ones).

Response: This is indeed true, that this is a hospital based study and won't be representative of all women with breast cancer. We acknowledge this in the last point of 'Strengths and limitations'. This will be further discussed in individual ensuing results papers. Through working with population-based cancer registries in the South African and Ugandan settings, we will be able to obtain estimates of the proportions of all women diagnosed with breast cancer represented by these hospital-based series.

4. Standardization of sample handling, fixation, reagents used in fixation, immunohistochemistry protocol and reagent.

Response: This study is an observational study, and is funded to compare current processes across the participating sites. Details of processing at each site are being obtained.

5. Important part of the protocol is not provided i- which is the questions used in the protocol – those should be included as part of the protocol and what are languages used.

Response: The questionnaire has been built within a mobile application, and the series of questions are logic driven depending on previous sets of answers – the complex nature makes it difficult to include in a manuscript; however, the authors are happy to discuss if contacted by interested parties. As mentioned in the Ethics and Dissemination section, the main languages at each site are used and if additional ones are required local translators are sourced.

Reviewer: 3 -Shahin Sayed

"the study itself does not fund, and thus does not require, histo(cyto)pathological confirmation"
Why then are biospecimens being collected for analysis for histopathology and IHC ? There is clearly a contradiction here. Please clarify.

Response: Because this is an observation study, we do not require a histological confirmation of breast cancer for inclusion of a woman into ABC-DO. However, for women for whom a tumour block is obtained by the hospital as part of her routine diagnostic work-up, consent to use that block for research purposes is being requested. We have clarified the text accordingly (last line before METHODS - 'Enrolment and baseline interview' section).

VERSION 2 – REVIEW

REVIEWER	Eva Johanna Kantelhardt Martin Luther University Halle, Germany
REVIEW RETURNED	09-Apr-2016

GENERAL COMMENTS	This very nice manuscript is clear, informative and definitely of interest to the scientific community. I recommend to accept manuscript.

REVIEWER	Shahin Sayed Aga Khan University Hospital, Nairobi, Kenya
REVIEW RETURNED	11-May-2016

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GENERAL COMMENTS	This is an important study as it will help shed light on the disparities in breast health outcomes within sub Saharan Africa

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