Author’s response to reviews

Title: Diagnostic Test Accuracy of Diabetic Retinopathy Screening by Physician Graders Using a Hand-held Non-Mydriatic Retinal Camera at a Tertiary Level Medical Clinic

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Diagnostic Test Accuracy of Diabetic Retinopathy Screening by Physician Graders Using a Hand Held Non-Mydriatic Retinal Camera at a Tertiary Level Medical Clinic in a Lower-Middle Income Country Setting

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Replies to the Reviewers.

Dear Editor and Reviewers,

BMC-Ophthalmology

03.02.2019

Thank you very much for all the comments.

This study was one component of a larger feasibility study to develop an integrated diabetic retinopathy (DR) screening program in the Western province of Sri Lanka. We developed this screening modality after assessing the barriers in this local context. The proposed modality has
been developed considering the barriers and enablers identified in the formative qualitative research and following a systematic review of the literature on digital imaging.

We have revised the manuscript according to the comments and our replies and corrections are described below. In addition, we have stated the line numbers of each correction (according to the tracked changes manuscript) within the parentheses after our reply, where applicable.

We would greatly appreciate your comments and opinion on the revised manuscript earliest possible.

Thank you,

Corresponding author.

MMPN Piyasena.

Reviewer reports:

Gökhan Pekel, M.D., Assoc. Prof. Dr., FICO, FEBO (Reviewer 1):

The authors reported a manuscript about using a retinal camera in diabetic retinopathy screening. This is a well-written manuscript. But the topic is not novel. My specific comments are written below.

1. The title may be shortened.

We would like to suggest the shortened new title as follows.

“Diagnostic Test Accuracy of Diabetic Retinopathy Screening by Physician Graders Using a Hand Held Non-Mydriatic Retinal Camera at a Tertiary Level Medical Clinic”.

2. The background of the Abstract may be shortened.

We have reduced the word count of the background of the abstract in the revised version.

[Line no - 82-84]

3. The methods of the abstract may include more data about the devices used and sample population.

We have made the corrections according to the comment.
4. In the Introduction, previous similar studies may be mentioned. We have added a paragraph explaining the previous studies and their limitation in using hand-held cameras in various settings.

5. What are the technical characteristics of the camera used for screening?

The details of the camera used are described in the published protocol paper. In addition, we have added following statements to the summary of the methods, in this revised manuscript.

“The training included the following: capturing retinal fields using a hand-held non-mydriatic fundus camera (Zeiss-Visuscout100®-Germany) ............The hand-held imaging system has the ability to capture colour and red free retinal images in a range of -20 diopters (D) to +20 D, at 40 degree field of view angle. The camera comprised of 9 fixation targets and resolution of the camera is 800 x 480 (5 megapixels)”. 

6. Please discuss the applicability of this screening method for the other regions of the world.

We have added the applicability under the limitations. The new statements are as follows.

“Our proposed DRS modality of using a hand-held non-mydriatic retinal camera at a medical clinic may be more appropriate for a resource poor LMIC setting, with the rising prevalence of DM. However, the caution is quality of the images. Our findings may not applicable to a HIC setting where there are more resources and avenues for development of a population-based DRS program using table-top digital imaging systems. On the other hand, this modality can be piggy back in a population-based program in any setting, to improve the access”.

Alvin Jeffery Munsamy, M.Optom (Reviewer 2):

Response to Author:
In general the manuscript is well constructed and useful for public health eye care. I did find it difficult to follow after one read especially the multifaceted "results section" which is exhaustive and not easy to understand.

We agree with the comment, However, the corresponding author, research student aims to utilize evidence generated in this article for advocacy, planning and implementation of a DRS program in the Western province of Sri Lanka in future. As there are no other published evidence in this topic, authors believe that publication of various levels of diagnostic test accuracies are helpful for future program planning.

This validation study was one component of a larger feasibility study to develop an integrated diabetic retinopathy (DR) screening (DRS) program in the Western province of Sri Lanka. There is no systematic DRS in Sri Lanka at present. The current method of screening is opportunistic intervention only.

In addition, in this low-income setting even the external funders would be interested to see the results of different approaches, before implementing at a program level. Therefore, we have analysed and interpreted the results using more pragmatic approaches for this context.

Moreover, there are different views of presenting the diagnostic accuracy of DR screening among different authors. One such example is, whether to include or exclude ungradable images in the analysis. In order to have fair representation of the evidence, we followed several methods in the analysis, before making recommendations. We hope this would provide a more comprehensive picture of the outcomes of this study to the readership and other stakeholders.

Not sure if figures are possible instead of tables. Otherwise the hard work by the researchers needs an acknowledgement.

Under the guidance of an adviser on statistics of this student project, we have tried out developing ‘receiver operating characteristics (ROC) curves for the imaging modality and for each grader. However, since we have only one estimate for each method, this was not an appropriate way of representing data graphically.

Abstract:

Line 80: rephrase "less evidence"

We rephrased the sentence as follows.

“The evidence on diagnostic test accuracy (DTA) of diabetic retinopathy (DR) screening utilising photographic studies by non-ophthalmologist personnel that have used non-ophthalmologist human resources in low and middle-income country (LMIC) settings is scarce”.

[Line no -80-83]
Line 81: rephrase to read "... screening utilising photographic studies by non-ophthalmologist personnel in low and …"

We corrected the statement as suggested in the comment.

[Line no -81]

Line 82: "… first to assess the DTA…" Do you not feel this is definitive and in the event whilst you are in this review process someone else beats you to it, would you rather use less definitive language?

We agree with the comment and we would like to remove this statement, as it would not add any scientific value to the article. In addition, we considered the Reviewer - 1 comment to reduce the content in background and we have deleted this sentence.

[Line no -83-84]

Line 94: "Their mean age…” does not read well rephrase to "The mean age of participants…." We rephrased the statement as suggested.

[Line no -96]

Line 105: "nonmydriatic" should read "non-mydriatic" and re-word all further use in the body of the manuscript.

We have corrected the word “nonmydriatic” as “non-mydriatic” in the whole manuscript.

Line 106: "… following pupil dilation" this is not in line with the conclusion in the manuscript which suggests that only those with ungradable images be dilated see line 500/501.

We agree with the comments and the conclusion in the abstract was corrected in accordance with the main conclusion. New statement is as follows.

“The Physicians grading of images from a digital hand-held non-mydriatic camera at a medical clinic, with dilatation of pupil of those who have ungradable images, provides a valid modality to identify referable level of DR”.

[Line no -107-111]

Background:

Line 133/4: This statement is definitive; consider re-phrasing to say with the use of existing techs it is more possible…
We rephrased statement as follows.

“These recommendations were followed by most of the high-income countries (HICs). The LMICs would also be able to achieve this aim with the adaptation and use of existing technologies according to the local contextual requirements”.

[Line no -133-136]
Line 146: correct to "population-based"
We made the correction as suggested.

Lines 148-150: Please provide evidence that these countries do not have clinics for diabetics who have eye screening as routine follow up. Or is this peculiar to Sri Lanka?

It is a known fact that most of the low and middle-income countries do not have systematic screening. However, there is not enough level of evidence on situational analysis of service delivery from these countries. However most of the review articles have stated the requirement of systematic screening in these countries and possibility of integrating screening services in general medical care.

We have revised this section and added new references here.

[Line no -148-156]
Line 155: support with a citation.
We have revised this statement and added references.

“Retinal fundus photography is the most common DRS method used globally [13] and digital systems are mostly preferred [14]”.

[Line no -162-163]
Line 157: correct to "Hand-held" and correct for whole manuscript
We made the corrections in the whole manuscript.

Line 159: "...which do not require pupil dilation…” is redundant.
We would like to rephrase the statement as follows.

“Non-mydriatic retinal imaging is more convenient for the both service users and providers due to absence of procedures such as pupil dilatation”.

[Line no -167-169]
Line 161: "…published data on this", what are you referring to?

Here we referred to the evidence on DR screening using retinal imaging from the local context (from Sri Lanka). We revised this statement as follows.

“To the authors’ knowledge there is no evidence on DRS using retinal imaging from Sri Lanka”.

[Line no -184-185]

Methods:

Line 169: Please clarify if you obtained gatekeeper consent from National Eye Hospital or ethical approval from both London school and the hospital and is reflect in text if this is not the case.

The validation of DR screening intervention has been conducted as one component of a larger feasibility study conducted by the corresponding author as a fulfilment of a research degree. Therefore, we have obtained ethics approval from the student’s university which is the London School of Hygiene and Tropical Medicine - UK.

In addition, we obtained the ethics approval from the ethics review committee of the National Eye Hospital - Colombo - Sri Lanka.

We amended the statement as follows:

“Ethics approval was obtained from both ethics review committees of …..”

[Line no -194-195]

Line 179: the same retinologists trained and validated?

Yes. There were two trainer retinologists (KB and MD) involved in training of physician graders. One of them conducted the validation study (KB).

Line 188: n is participants or eyes?

The sample size was calculated considering persons and not eyes. Here, ‘n’ denotes the number of people with diabetes (n=700).

[Line no -217]

Line 204: what was "n" for clinical reference test?
Clinical reference test ‘n’ was also n=700, as per diagnostic test accuracy measuring protocol. We performed clinical reference test on all participants who have undergone the index test. However, there were dropouts as stated in the flow chart.

We corrected this.

[Line no -239-240]

Line 205: only a single retinologist? What is "experienced"?

One of the trainer retinologists (KB) who conducted the training program, conducted the reference test. He has worked in public sector as a trainer retinologists for more than 10 years.

We understand that ideal reference test for this study would be the 7 filed Early Treatment Diabetic Retinopathy Study (ETDRS) imaging strategy. However, this was out of the remit of this student project due to resources constraints. Moreover, the retinologist’s slit-lamp biomicroscopic examination considered to be the accepted reference standard for this local context.

We wanted to emphasise that retinologist has enough experience to conduct the reference test as this was the locally accepted reference standard.

[Line no -235-237]

Line 231: "… different to referable criteria" please clarify what was different?

As this was one component of a larger feasibility study, we planned to define criteria for referring a person with diabetic retinopathy from the medical clinic to the eye clinic. As this validation study supposed to generate evidence for this decision making we analysed the results using different referral criteria, i.e., such as pupil status, level of DR, level of visual acuity and presence of macular signs.

We identified that these referable criteria can be developed based on various results at the index test.

[Line no -263-264]

Line 232: "ophthalmologist's clinic" suggests the ophthalmologist is the owner, maybe say "eye clinic"

We agree with the comment, and have corrected the statement.

Results:

Line 239: instead of using "a third" just say 27.9% (195/700)"
We have corrected the manuscript.

[Line no -272]

Line 241: "11(1.6%)" instead say 1.6% (11) to align with preceeding text for type 2.

We have corrected the manuscript.

[line no -274]

Table 1: Fasting blood glucose and HbA1c do not have units in column 3; Age at diagnosis of hypertension- column 3 has "%" not years?

Corrections were done according to the comment.

[Line no -281]

Line 264: "… are described in Table 2…” please elaborate in this paragraph what table 2 is communicating especially column 1 as this is not very easy to follow.

We have made the corrections as suggested.

[Line no -297-300]

Line 311: resource not "resources"

We have made the corrections.

[Line no -345]

Discussion:

Line 375: is the percentages quoted for detecting any DR or referable DR? effect in the sentence if the numbers are referring to which of the above.

These DTA values were for referable level of DR. We have made the corrections in the statement.

[Line no -410-411]

Line 379: ">80%"; ">95%" doesn't read well

We have corrected this statement.

[Line no -415-416]
Line 382: "the requirement of refer those..." does not read well.

We have corrected this statement.

[Line no -419]

Line 384/386/7: By starting with the point that the "strain on the system" suggests that all pts who are diabetic are referred to the eye clinic (again "ophthalmologist's clinic" suggests ownership)? Is this an accurate statement?

Yes, In the current system in this local context all people with diabetes presented at the medical clinic are referred to the eye clinic / ophthalmologist’s clinic without any risk stratification.

This was observed during the formative research work conducted before this study as well (service provider’s perspective article is being reviewed under BMC - Health Services Research - open source).

Furthermore I would think that "proposed imaging strategy" would allow for early detection and management of DR to mitigate preventable DR blindness?

Yes, we agree with the comment.

We made the corrections according to the comments.

Line 417-419: Please re-phrase as it is not clear what you are trying to convey.

We have rephrased the statement.

[Line no - 454-458]

Line 433: cross-section not "cross section"

Corrected.

Line 439/440: What do you mean?

The validation of the proposed screening modality has been conducted under an environment of a research project supported by a team of research assistants and investigators. However, the same level of accuracy may not be observed when we apply the intervention at population level (population as the all people with diabetes attending at outpatient medical clinics, not at community level). Therefore, it would be more appropriate to assess the effectiveness of the proposed screening modality before making specific recommendations for the same.

Line 442-458: Comparisons are made to China; Israel; Singapore; Australia however the income status of these countries are not discussed. When comparing to these countries can you elude to
the impact of your findings in a LMIC country vs HIC (Australia/China) especially if the findings are the same.

We agree with the comment and we added more relevant studies from low income settings. In addition, we used the high-income setting studies for comparison. However, the studies from low income settings are scarce as observed in our literature survey.

[Line no - 494-507]

Conclusion:

In light that this is an abbreviated conclusion, is it possible to write out the abbreviations in full. It is very difficult to follow throughout the manuscript, and I feel the gravity of the conclusion may be lost in translation with the numerous abbreviations especially STDR.

We have revised the conclusion.

[Line no -557-563]

References:

I cannot access ref#5- please provide.

We noted that this is a conference preceding abstract only.

Therefore, we added a new reference relevant for the statement in the Introduction.

[End of Replies]