Author’s response to reviews

Title: A Systematic Review and Meta-analysis in the Effectiveness of Mobile Phone Interventions used to improve Adherence to Antiretroviral Therapy in HIV Infection

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Author’s response to reviews:
This information has been presented as a letter in supplementary material but also copy and pasted here.

Dear Reviewers,

Re: PUBH-D-18-03072
A Systematic Review and Meta-analysis in the Effectiveness of Mobile Phone Interventions used to improve Adherence to Antiretroviral Therapy in HIV Infection
Reshma Shah; Julie Watson; Caroline Free

Thank you for your detailed and positive comments about this work. I found the responses extremely helpful and have endeavoured to make all the changes. Please see individual comments to all your suggestions that are in the corresponding box next to the comment. All changes have been highlighted in the paper in yellow.

Dear Keshet Ronen,

Thank you for reading and reviewing this paper again.
Line 135 - what does additional disease profiles mean?

Thank you for this comment, I have changed the wording to make it clearer. Line 137

Line 207-209 belong in the previous paragraph

This has been changed now, thank you for the detail. Line 207-210.

Line 208 mentions social cognitive theory of planned behavior - this is not a theory I'm familiar with.

Social cognitive theory and theory of planned behavior are 2 different theories. Please correct or provide an accurate citation. Shet et al 2014 have quoted this theory in their introduction (page 2). The reference for which this theory is based on has been referenced now (reference 47). The authors felt in the interest of keeping the work succinct, full explanations of all the behavioural change theory used by different trials have been omitted. However we hope the reference provided will be satisfactory should readers be interested.

Please double-check references - in places the numbers in the text don't seem to match with the numbers in the references

Thank you for this comment. The references have been checked.

Ref 23 on line 208 is inaccurate - I cannot find ref 23 at all, but the closest publication (Mayer et al 2017) is a meta-analysis and does not discuss behavioral theory.

Apologies for this mistake. The referencing did not link up correctly. The references on line 208 should match 209-210. The paper mentioned in line 209 (now reference 43) is Shet et al 2014 which mentions Social Cognitive theory on page 2.

References on line 207 and lines 208-209 are not the same - shouldn't they match?

This has been addressed above.

Line 373 explain why these studies were not pooled

Text message interventions with interactivity were found in two trials (Line 256) (Ingersoll and Hardy) and both these showed improved adherence. They could not be pooled for two reasons. Firstly they were using different measures of adherence (line 171-174) in methodology).

Table 3 describes the outcome measures and results for all the text message trials. Ingersoll measures pharmacy refill data and Hardy measured pill count and composite adherence score.

Secondly the Hardy trial used an intervention as part of the control group (Line 185-186)

For clarity this has now been added, line 367.
Line 382 - what does 'these' refer to?

‘These’ refers to the characteristics of interactivity being different to link to support. The word characteristics has now been added to line 377.

Dear Gitau Mburu,

Thank you for reading this paper and your detailed comment.

1. Abstract

a. It is somewhat odd that this paper - which has evaluated several RCTs on adherence, and found that there may be some, or no effect depending on the content of what is delivered through mobile phone (or what's measured e.g. viral load outcomes as proxy indicator of adherence) - suggests that evaluation of cost effectiveness should be performed using RCTs. At best, this is the time for implementation of proven interventions and gathering of cost data as part of implementation research

   Thank you for this point. I agree with you the benefits of doing another RCT would be minimally beneficial, but the hope is that future trials should strive to measure clinically important outcomes so we can robustly answer questions like this (and others). Cost effective analysis should be done alongside such trials – I have changed the wording

2. Background

a. I suggest referencing should be improved, for example where authors mention poor adherence can lead to resistance (other places eg hawthorne effect, or analysis methodology can be better referenced too)

   Thank you for this comment, additional references have now been added to the Background section and areas have been updated with the latest figures which have been highlighted in yellow. This includes line 68, 69, 71, 76, 100

3. Methods
a. Best to state at the beginning if this review was conducted according to PRIMA and to attached the required checklist.

This is now mentioned in the opening paragraph of the Methodology, line 125. The prisma flowchart and checklist has now been added as Appendix 1. Line 125.

b. Interventions: As far as I can see, the authors were assessing use of mobile phones as a channels for delivering different interventions, rather than interventions themselves. Thank you for this thought-provoking comment.

Yes the interventions (be it a reminder text message or a telephone call) were administered via a mobile phone. The control group may have owned a mobile phone but did not receive an intervention.

c. Outcomes: Line 162/163. It is confusing when authors speak of attrition as an outcome, when the primary and secondary outcomes are about ingestion of ARVs. Of course attrition can affect verified adherence, and ITT analysis should take care of that, but it does not seem appropriate to include or measure loss to follow up from programs as an outcome.

Apologies for the confusion. Attrition is not considered an outcome. The primary and secondary outcome are objective and subjective measures of adherence respectively. This sentence is in relation to the risk of bias (Table 2) and if more than 10% of participants were lost to follow-up, the trial was marked as high risk of bias. The reasoning for each risk of bias outcome including attrition (6th column) can be found in Appendix 5. These levels have been set in accordance to the standard Cochrane risk of bias (reference 26).

d. How many authors were contacted? Since the review is completed, this information can be disclosed. When authors mention that no discrepancies were observed, it creates the impression that authors already had the data they needed, so it is not clear what additional data were acquired from contacting authors. This could be made clear. Thirteen authors were contacted. Authors were contacted for two reasons. Firstly to understand more about the content of the intervention so the analysis could be more accurate. For e.g voice calls made to patients, some used a script, we requested access to the crib sheet to see if the content included themes of social support/ prompt etc as per the Abraham and Michie Taxonomy. This is mentioned in the discussion line 438-441

Secondly for ease of comparison, we wanted all the data to be reported in the same way (RR/SMD). If papers did not present enough information for this to be teased out then we requested the raw data so we could run our own analysis on it.
There were no discrepancies as the authors that responded were those that presented sufficient information in their paper so the additional information they offered did not change the analysis.

As this sentence does not add value in the methodology section it has been deleted.

e. The inclusion of search strategy and search text words / search strings as an appendix is very useful. Thank you

f. To add clarity onto this review, I would suggest that PICO questions should be explicitly stated. For example, did the authors only look at certain populations? Adults, adolescents etc? what precisely were the exclusion criteria? Was it only related to different disease profiles?

    PICO has been reintroduced to this paper, we hope the inclusion and exclusion is clearer now. All populations were included. Line 128-138

g. When was the review conducted? What were the cut off dates? Were publications of all languages considered? This review was initially conducted in July 2015 and then updated in October 2017 as advised by BMC public health, this is reflected in the search strategy dates. The cut off dates were 1990 to October 2017 (please see line 142). There were no language restrictions line 136.

4. Data analysis and synthesis:

a. My understanding is that the authors refer to RR of adherence. Could odds ratios been more appropriate? If not, why not? Give a reference. It is generally advisable to use RR as a more meaningful method of communication and standard reporting when assessing RCT. There is a risk of overestimation when reporting OR. This has been explained in the following BMJ article.

    1. Robert L Grant. Converting an odds ratio to a range of plausible relative risks for better communication of research findings. BMJ 2014;348:f7450

b. I concur with the authors, that all lost to follow up would contribute to assumed non adherence using ITT approach, but this is the reason why the above statement (under outcomes) needs to be clarified. This has been clarified in response 3c.

c. would sensitivity analysis have been useful? Why or why not? Sensitivity analysis has been used within each category (text message, voice call, imagery, mixed) to see if characteristics including interactivity, link to support and involvement of three or more BCT were reasons behind the intervention being successful. To make this clearer additional sentence has been added in line 152.

5. Results
a. PRISMA diagram should be included to show how studies were selected.

This has now been included in Appendix 1.

b. Interventions: I am unsure why social support measures feature here. do the authors suggest that calls, text messages etc contained social support, or were social support, or were delivered alongside social support? if the interventions were delivered outside or alongside mobile interventions in only one arm, then the results could be biased, and might not necessarily e measuring the effect of stand-alone mobile interventions. Three additional areas were looked at in this study (please see section data extraction line 153-162) to see if characteristics of the intervention can be narrowed down so that we can replicate successful components of the intervention. This included looking at link to support. Your point about mobile interventions is the foundation for why this work was done. Previous reviews do not differentiate the nuances between mobile phone interventions. A telephone call may include difference support mechanisms to a reminder text message. Previous systematic reviews group all mobile interventions together which will result in bias. This work tries to tease out elements of the content of the intervention to see if there were characteristics that improved adherence. We looked at three additional areas interactivity, link to support and involvement of three or more BCT. Discussion 376-386.

c. The section titled study quality should probably just be renamed to publication bias.

Quality involves other elements (eg recall bias, attrition bias, etc) which were not assessed and authors should add that as a limitation in the discussion.

All risk of bias measures were assessed as per Cochrane risk of bias tool. Please see Table 2 and Appendix 5.

6. Discussion

a. Authors rightly point out the limitation of RCT in not reflecting real world data. Could authors give a reference to the kind of pragmatic trials they refer to mitigate this issue? The authors have themselves excluded studies that were not randomised clinical trials, but it begs a reader to wonder if previous (and cited) reviews that gave shown more positive impacts included more observations (and therefore real world) circumstances

The use of non-randomised trials would increase bias and risk overestimating the effect. To consider more real world applicability one could consider cluster randomised trials. Individual trials that showed impact should be replicated more closely.
b. line 590. I think that the authors need to be clear here that WHO may have depended on all kind of evidence, including non RCT studies to arrive at their conclusion. Did the authors look at the kind of evidence that WHO used? In addition, the authors might be are conflating text messages here with mobile as a delivery mechanism. If not, precisely what do they suggest WHO guidelines need to state?

The WHO based their evidence on the Cochrane systematic review which looked at two RCT’s. Only RCT’s were included in the Cochrane review. We have mentioned this Cochrane review in our introduction line 109. For e.g. as mentioned line 242 highlights that weekly text message as conducted in the Mbugbaw trial did not improve adherence (contrary to WHO advice) and hence we suggest the evidence is more nuanced than suggested by them. This review looks at a total of 9 RCT for interventions delivered by text message and separates the components (interactivity and more than three BCT) that showed improvements in adherence.

Thank you again for your time and effort in reading this paper. We hope you find all the changes made to your satisfaction and we hope this paper is successful for publication.

We look forward to hearing back,

Yours sincerely

Dr Reshma Shah

On behalf of Julie Watson and Dr Caroline Free.