PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	MEDication reminder Apps to improve medication adherence in Coronary Heart Disease (MedApp-CHD) Study: A randomised controlled trial protocol
AUTHORS	Santo, Karla; Chow, Clara; Thiagalingam, Aravinda; Rogers, Kris; Chalmers, John; Redfern, Julie

VERSION 1 - REVIEW

REVIEWER	Marcia Vervloet, PhD NIVEL, Netherlands Institute for Health Services Research, in the Netherlands
REVIEW RETURNED	22-May-2017

GENERAL COMMENTS	This well-written paper describes the protocol of an RCT to evaluate the use of a basic and advanced medication reminder app to improve medication adherence in CHD. The authors describe a very interesting study, which is innovative and will expand the fast growing body of literature on the use of smartphone apps for improving health behaviour. It is innovative as it aims to unravel what characteristics of a smartphone app might improve adherence instead of testing a (one of many) newly developed app. The qualitative evaluation the authors aim to do really adds to this. I have two main comments. The first is about the follow-up period, the second about the sample size. Although the authors mention both aspects as limitations of the study, they might need to elaborate more on the choices they made regarding these aspects. 1. After a 3-month-period both adherence and clinical outcomes will be assessed. This is a very short follow-up period. It is well-known that (electronic) reminders have a positive effect on adherence in the short-term, but the long-term effects often remain unknown (see for example this systematic review https://www.ncbi.nlm.nih.gov/pubmed/22534082). In this study it will also remain unknown whether the potential adherence improvement remains over time. The authors need to elaborate more on the choice for this short-term period (as well as its limitation). Furthermore, the PDC will be calculated, but it is not specified over which period. It is not possible to calculate a reliable PDC over 3 months? You need longer time span for this calculation. And how likely is it to detect a (clinically relevant) difference in outcomes as blood pressure and cholesterol levels after 3 months? And how likely is an occurrence of cardiovascular clinical event or hospitalization in 3 months? 2. Around 50 patients per group are needed according to the power analysis. This is based upon an estimated improvement in adherence of 29%. This is a very large improvement, especially if

	you do not select non-adherent patients for your study. For patients who are already doing well, there is not much room for improvement left. Moreover, it is well-known that patients overestimate their adherence. When using a self-report method for measuring adherence (the MMAS-8), it is highly likely that you already end up with patients in your sample who deem themselves (highly) adherent at the start of your trial, making it almost impossible to be able to detect a difference in adherence – let alone an improvement of 29%. The PDC is a more objective adherence measurement, however it is not described over which period this PDC is calculated (see also comment 1). Other (minor) comments: 3. Participants with missing data for adherence will be considered non-adherent. I would suggest to do a sensitivity analysis to show the effect of this choice. 4. I would introduce the expected association between medication knowledge and adherence in the Introduction section. Now research question 4 comes out of the blue.

REVIEWER	Farhad Fatehi Centre for Online Health, The University of Queensland, Australia
REVIEW RETURNED	05-Jun-2017

GENERAL COMMENTS	The manuscript describes the protocol of a 3-arm randomised controlled trial that evaluates the effectiveness of mobile apps on medication adherence for people with coronary heart disease. The study is timely and of interest, the trial has been designed properly, and the protocol has been written very well. Here are a few comments on the protocol: General comments: 1. A common criticism on mobile health interventions is their short duration of intervention and/or follow-up, which is the case with this study as well, but it has been acknowledged in the protocol. 2. It seems from the manuscript that the authors have decided on which mobile app to be used by the basic and advanced groups, but have not mentioned the name of the apps. Is there any reason that the apps have not been disclosed? If not, it would be better to mention the name of the apps that are going to be used in this trial and their developers. If the basic and advanced apps are from two different developers (with significant difference in the design and appearance of the apps), it could be possible that a proportion of any observed difference between the effectiveness of the two apps to be attributed to the user-friendliness of the apps, and not only the difference between their features. Ideally, it would be better to use the same app for both groups, and disable the advanced features for the basic group (or two basic and advanced apps from the same developer), rather than using two different apps with different user-friendliness. 3. In addition to effectiveness, evaluation of several other aspects (feasibility, acceptability, acceptability, utility, engagement, usefulness) of using mobile apps for medication adherence have been mentioned as the aims of this study, but the authors have not given a clear definition for these aspects and how they are going to measure feasibility and acceptability. In Abstract, the main aim of the

	study is mentioned as “to evaluate effectiveness, feasibility and acceptability” of the apps, whereas on Page 8 for the 6th aim of the study it says “to determine feasibility of the intervention by evaluating the acceptability, utility, and engagement with the apps”. Having a clear definition of these terms (and how these are measured) will avoid any confusion. Specific comments: 4. Page 15: Perhaps the verbs ‘enter’ or ‘input’ are better terms than ‘insert’ for data entry in mobile apps 5. Page 18, Box 1: the secondary outcome measure for the engagement of the participants (by usage pattern data from the developers, Page 20 Lien 17) should be added to the Box. 6. One (or more?) questionnaires will be used for evaluation of medication knowledge, acceptability and utility (Page 18, Box 1), but the authors provide no information on how these questionnaires have been developed and if the validity of the questionnaire has been studied? Adding the questionnaire(s) to the appendices will be helpful for the readers. 7. Page 19, Line 6-8: Participants with missing data will be considered non-adherent (non-responder imputation). How will these non-adherent participants be determined? How many missing data elements (or percentage of missing data) will be considered non-adherence? 8. Page 19, Line 57: Since the questionnaire will be administered to the users of the apps after three months, it will determine the “usefulness”, not “perceived usefulness”. However, it could be of interest to study the “perceived usefulness” of using a mobile app for medication adherence in control group, and compare the results with the two intervention groups. 9. Pages 23-26: some references (e.g. Ref 17) may need an update to include the latest bibliographic information (volume, issue, page) that have been available recently, and the date of last checked/accessed for the online references should be mentioned. Overall, it will be an interesting trial. Looking forward to seeing the results of this study.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1 comments:

1. a) After a 3-month-period both adherence and clinical outcomes will be assessed. This is a very short follow-up period. It is well-known that (electronic) reminders have a positive effect on adherence in the short-term, but the long-term effects often remain unknown (see for example this systematic review https://www.ncbi.nlm.nih.gov/pubmed/22534082). In this study it will also remain unknown whether the potential adherence improvement remains over time. The authors need to elaborate more on the choice for this short-term period (as well as its limitation).

We agree with the reviewer’s comment that 3 months follow-up is a short follow-up period; however this study was designed as a small study to assess the feasibility and the effectiveness of this

innovative concept of using medication reminder apps to improve medication adherence and whether it has potential to be further evaluated in a larger and longer study. Our study is supported by a Vanguard Grant funded by the National Heart Foundation of Australia, which is a 1- year small research grant to provide funding to test the feasibility of innovative concepts which may lead to larger, more rigorous studies in the future. We hope that the results of this study will allow us to be successful in obtaining a larger research grant to conduct a bigger trial with a longer follow-up period. We have now expanded the Discussion and Conclusion section to include a paragraph on the limitations of the study, including its short-term follow-up as well as a discussion on the future steps if the intervention is shown to be feasible and acceptable (Page 22, lines 458-468).

1. b) Furthermore, the PDC will be calculated, but it is not specified over which period. It is not possible to calculate a reliable PDC over 3 months? You need longer time span for this calculation.

To our knowledge, there is no gold standard in terms of the ideal length of time to calculate the PDC. We plan to calculate the PDC at 3 months as this has been previously done by others,[1-4] but also in longer term at 6 and 12 months. We have now specified this in Methods section, under Study outcomes (Page 16, line 337).

1. c) And how likely is it to detect a (clinically relevant) difference in outcomes as blood pressure and cholesterol levels after 3 months? And how likely is an occurrence of cardiovascular clinical event or hospitalization in 3 months?

We do believe that higher medication adherence to anti-hypertensive medication and statins can be translated in a difference in blood pressure and cholesterol levels after 3 months, therefore, these clinical outcomes will be measured at the 3 months follow-up. We do acknowledge that higher medication adherence, even associated with improvements in the clinical measurements, is not likely to change cardiovascular clinical events and hospitalisation at 3 months. However, we believe that, given the exploratory nature of this trial, these data can provide extra information on trends and correlations between adherence and occurrence of events. We have now added a sentence in the Discussion and Conclusion section to address this issue (Page 22, lines 464-466).

2. Around 50 patients per group are needed according to the power analysis. This is based upon an estimated improvement in adherence of 29%. This is a very large improvement, especially if you do not select non-adherent patients for your study. For patients who are already doing well, there is not much room for improvement left. Moreover, it is well-known that patients overestimate their adherence. When using a self-report method for measuring adherence (the MMAS-8), it is highly likely that you already end up with patients in your sample who deem themselves (highly) adherent at the start of your trial, making it almost impossible to be able to detect a difference in adherence – let alone an improvement of 29%. The PDC is a more objective adherence measurement, however it is not described over which period this PDC is calculated (see also comment 1).

We agree with the reviewer that self-report methods of measuring adherence are usually associated with overestimation of adherence; however, it is the simplest, most inexpensive and most useful method of assessing adherence in clinical setting,[5, 6] and we are using a validated and reliable questionnaire (MMAS-8).[7-9] In addition, as mentioned in the response to the previous comment, we will calculate the PDC, which is a more objective measure of adherence at 3, 6 and 12 months. We have calculated the sample size using an estimated improvement of 29% in adherence using the best available data obtained from previous studies that evaluated a similar intervention (text-message reminders) in the same population of patients (coronary heart disease). Although we acknowledge and agree with the reviewer that this might be a large estimated improvement; we believe that the results from this study will potentially provide a better estimate of effect size of the intervention compared to control arm, enabling accurate powering of a large-scale trial in the future. We have now

added this as a limitation of the study in the Discussion and Conclusion section (Page 22, lines 458-468).

3. Participants with missing data for adherence will be considered non-adherent. I would suggest to do a sensitivity analysis to show the effect of this choice.

As suggested, we have now clarified that we will perform a sensitivity analysis considering those with missing data as non-adherent patients (Page 18, line 373 and Page 19, lines 374-375).

4. I would introduce the expected association between medication knowledge and adherence in the Introduction section. Now research question 4 comes out of the blue.

We have now added a sentence about medication knowledge in the Introduction section (Page 7, lines 141-142)

Reviewer #2 comments:

1. A common criticism on mobile health interventions is their short duration of intervention and/or follow-up, which is the case with this study as well, but it has been acknowledged in the protocol.

As per response to item 1 a) of reviewer #1 comments, we have now included a paragraph on the limitations of the study, including its short-term follow-up, in the Discussion and Conclusion section. (Page 22, lines 458-468).

2. It seems from the manuscript that the authors have decided on which mobile app to be used by the basic and advanced groups, but have not mentioned the name of the apps. Is there any reason that the apps have not been disclosed? If not, it would be better to mention the name of the apps that are going to be used in this trial and their developers.
If the basic and advanced apps are from two different developers (with significant difference in the design and appearance of the apps), it could be possible that a proportion of any observed difference between the effectiveness of the two apps to be attributed to the user-friendliness of the apps, and not only the difference between their features. Ideally, it would be better to use the same app for both groups, and disable the advanced features for the basic group (or two basic and advanced apps from the same developer), rather than using two different apps with different user-friendliness.

The names of the basic and advanced apps being used in the study were reported in our previous paper,[10] in which we described the systematic stepwise process that we used to identify and select the apps to be used in this study. As our intention is not to promote one or two specific apps, but to evaluate the type of features they have, we have decided not mention the name of the apps in this protocol paper. However, as suggested by the reviewer, we have now added the names of the apps in the Acknowledgements section (Page 23, lines 484-486). Although the basic and advanced medication reminder app were developed by two different app developers, during our selection process, both apps were rated high in user-friendliness. We will explore reasons for an eventual difference between the apps in the process evaluation. We have now added extra information about the focus groups that will be conducted with the intervention participants to explore in more depth several aspects of the apps, for example whether the participants liked or disliked the app, whether they found it useful, whether they believe the reminders improved their medication-taking habit, how was their experience of using the app, and which features they used the most (Page 19, line 397 and Page 20, lines 398-406).

3. In addition to effectiveness, evaluation of several other aspects (feasibility, acceptability, acceptability, utility, engagement, usefulness) of using mobile apps for medication adherence have been mentioned as the aims of this study, but the authors have not given a clear definition for these aspects and how they are going to measure feasibility and acceptability. In Abstract, the main aim of the study is mentioned as “to evaluate effectiveness, feasibility and acceptability” of the apps, whereas on Page 8 for the 6th aim of the study it says “to determine feasibility of the intervention by evaluating the acceptability, utility, and engagement with the apps”. Having a clear definition of these terms (and how these are measured) will avoid any confusion.

As suggested by the reviewer, we have now re-worded the text throughout, using these terms more consistently and making it clearer that we will assess whether the intervention is feasible, by evaluating the acceptability, utility and engagement with the intervention. We have now explained in more detail how we are going to assess these aspects in the Process evaluation section (Page 19, lines 392-397 and Page 20, lines 398-415).

4. Page 15: Perhaps the verbs ‘enter’ or ‘input’ are better terms than ‘insert’ for data entry in mobile apps.

We have now changed the term ‘insert’ to ‘input’ and ‘enter’ (Page 15).

5. Page 18, Box 1: the secondary outcome measure for the engagement of the participants (by usage pattern data from the developers, Page 20 Lien 17) should be added to the Box.

We have now added engagement with the intervention in Box 1 (Page 18).

6. One (or more?) questionnaires will be used for evaluation of medication knowledge, acceptability and utility (Page 18, Box 1), but the authors provide no information on how these questionnaires have been developed and if the validity of the questionnaire has been studied? Adding the questionnaire(s) to the appendices will be helpful for the readers.

One questionnaire, divided in two parts, is being used to evaluate medication knowledge, acceptability and utility of the intervention. The first part is assessing medication knowledge and was adapted from a previously validated questionnaire.[11] The second part is assessing acceptability and utility of the intervention and it was adapted from a questionnaire/survey that assessed acceptability and utility of a text-message intervention, previously published. [12, 13] We have now added information on these questionnaires (Page 17, line 342 and Page 19, line 396). We have also added the questionnaire as an Appendix of the manuscript.

7. Page 19, Line 6-8: Participants with missing data will be considered non-adherent (non-responder imputation). How will these non-adherent participants be determined? How many missing data elements (or percentage of missing data) will be considered non-adherence?

Participants with missing data will be the ones that did not complete the MMAS-8 at 3 months follow-up, e.g. patients who withdrew from the study or were loss of follow-up. We have now re-worded the sentence to make it clearer (Page 18, line 373 and Page 19, lines 374-375).

8. Page 19, Line 57: Since the questionnaire will be administered to the users of the apps after three months, it will determine the “usefulness”, not “perceived usefulness”. However, it could be of interest to study the “perceived usefulness” of using a mobile app for medication adherence in control group, and compare the results with the two intervention groups.

We have now removed the term ‘perceived usefulness’.

9. Pages 23-26: some references (e.g. Ref 17) may need an update to include the latest bibliographic information (volume, issue, page) that have been available recently, and the date of last checked/accessed for the online references should be mentioned.

We have now updated Ref 17 to include volume, issue and page. We have also updated Refs 7 and 10 adding the date of access.

References:

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10. Santo K, Richtering SS, Chalmers J, Thiagalingam A, Chow KC and Redfern J. Mobile Phone Apps to Improve Medication Adherence: A Systematic Stepwise Process to Identify High-Quality Apps. JMIR mHealth and uHealth. 2016; 4: e132.
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13. Redfern J, Santo K, Coorey G, et al. Factors Influencing Engagement, Perceived Usefulness and Behavioral Mechanisms Associated with a Text Message Support Program. PloS one. 2016; 11: e0163929.

VERSION 2 – REVIEW

REVIEWER	Marcia Vervloet, PhD NIVEL Netherlands Institute for Health Services Research, The Netherlands
REVIEW RETURNED	31-Jul-2017

GENERAL COMMENTS	I thank the authors for addressing the issues I raised during the first review of the manuscript. I am satisfied with the changes they made to the manuscript in response to my comments. I would, however, like to repeat my concerns on one comment: the reliability of calculating the PDC over 3 months. I am glad that the authors have added that they will calculate the PDC at 6 and 12 months as well. However, they will still calculate the PDC at 3 months. Maybe it just needs some clarification /elaboration on the prescription length issued for chronic medication in Australia. That might take away my concerns about the reliability. Because in the Netherlands, a refill prescription for a chronic medication such as for CHD is given for a period of 90 days. Therefore, in the Netherlands, calculating a PDC over a period of 3 months is not relevant or reliable. Maybe in Australia, refill prescriptions are given for a shorter period of time, enabling to take into account multiple prescriptions in a PDC over 3 months? Only when this is the case, it is justifiable to calculate a PDC over 3 months.

REVIEWER	Farhad Fatehi Centre for Online Health, The University of Queensland, Brisbane, Australia
REVIEW RETURNED	27-Jul-2017

GENERAL COMMENTS	No further comments. Well done.

VERSION 2 – AUTHOR RESPONSE

Reviewer #1 comment:

I would, however, like to repeat my concerns on one comment: the reliability of calculating the PDC over 3 months. I am glad that the authors have added that they will calculate the PDC at 6 and 12 months as well. However, they will still calculate the PDC at 3 months.
Maybe it just needs some clarification /elaboration on the prescription length issued for chronic medication in Australia. That might take away my concerns about the reliability. Because in the Netherlands, a refill prescription for a chronic medication such as for CHD is given for a period of 90 days. Therefore, in the Netherlands, calculating a PDC over a period of 3 months is not relevant or reliable. Maybe in Australia, refill prescriptions are given for a shorter period of time, enabling to take into account multiple prescriptions in a PDC over 3 months? Only when this is the case, it is justifiable to calculate a PDC over 3 months.

In Australia, a prescription refill for cardiovascular medications and the majority of chronic disease medications is given for a period of 28 to 30 days, meaning that the patients need to return to the pharmacy to collect their medication every month. Therefore, we believe calculating PDC at 3 months is feasible and relevant. We have now added a sentence in the manuscript, describing the

prescription refill length in Australia (Page 16, lines 323-325), as follows:

“In Australia, prescription refills for cardiovascular medications are dispensed every month at the pharmacy as a 28 or 30-day supply, and a record of each dispensing is included in the PBS data, enabling the calculation of PDC at 3, 6 and 12 months.”