PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Evaluation of an innovative mobile health program for the self-management of chronic obstructive pulmonary disease (MH-COPD): protocol of a randomized controlled trial
AUTHORS	Ding, Hang; Karunanithi, Mohan; Ireland, Derek; McCarthy, Lisa; Hakim, Rekha; Phillips, Kirsten; Pradhan, Rahul; Seah, E-Hong; Bowman, Rayleen; Fong, Kwun; Masel, Philip; Yang, Ian

VERSION 1 - REVIEW

REVIEWER	Vicki Johnson-Warrington Complex Interventions team, Leicester Diabetes Centre, Leicester General Hospital, University Hospitals of Leicester NHS Trust, UK
REVIEW RETURNED	30-Jul-2018

GENERAL COMMENTS	This is an important study to undertake in order to provide evidence if a mobile health app can enhance the self-management and quality of life of people with COPD which is a fairly new area of research and will be important for clinical care. It would help if you could provide a bit more detail on what PPI you have carried out and how this has helped your research. Also, how you have developed this app. Have you written a developmental paper/is it reported elsewhere? You say you have designed the intervention to overcome reported barriers - how/what have you done in regards to this? Have you used any psychological theories or specific behavior change techniques within your intervention, if so, I would be interested to find out more. Have you tried/piloted your app? It may be beyond the scope of this paper, but more background detail around this would be useful. Have you trialled any of the individual components previously i.e. the automatic reduction of smoking to 0 over 6 weeks? Could people not personalize their own goals instead? While it would be good to reduce smoking to 0, this may not be manageable for some and it could reduce people's self-efficacy and motivation to try and quit if they are forced into a specific (unrealistic for them) regime? Can you clarify if participants in the intervention arm are self-managing any AECOPDs/are following an automated SM plan via the app or whether HCPs are monitoring this and intervening as each appears to be mentioned within the paper? Is the COPD knowledge questionnaire you plan on using a validated tool? If not, would another tool be helpful i.e. the Bristol COPD knowledge questionnaire which is? Why are you asking the intervention arm to record AECOPD on a paper version as well, as they are already recording via the app? It may be a bit burdensome for them to do it twice?

	Research question - I don't think you can 'increase' someone's self-management (SM), you could enhance it. You state the aim of the intervention/study is to increase SM, improve health outcomes and to test the efficacy of MH-COPD. Could you be clearer on your main aim of the study, consequently you state you have 3 primary outcome measures (which seems a little extreme)- CAT, SGRQ and mMRC but the sample size is based on CAT and SGRQ (no mention of mMRC). (Q4) Could you blind research staff when completing the 6 month assessments to reduce bias and increase the strength of the study? Are research staff part of the clinical staff or separate? if separate, will the clinical staff specifically be aware which arm of the study patients are in and can this be controlled/minimized at all? You mention other studies have been small in number, n<50 in the background and n<100 in the discussion. Will you be able to gain data regarding how often the app is used/how many times the videos etc are viewed etc? It may be interesting to find out and could explain some results at the end of the study (i.e. in terms of engagement). You may be limited by funding, but some qualitative data regarding how participants in the intervention group found the app and intervention could be helpful if possible?

REVIEWER	Roberto Benzo Mayo Clinic USA
REVIEW RETURNED	11-Sep-2018

GENERAL COMMENTS	the study intend to test a mobile technology intervention to improve self management. while there is a lack of effective mobile interventions to improve self management, the ones that are somewhat effective are the one that in addition of technology have some provider interaction. rarely if ever mobile health alone (no provider or coach interaction) improve meaningful outcomes. there is no enough literature to support technology alone to be effective. This study may be the first to prove it . While positive results from the proposed study (technology alone improving outcomes) are needed and need to be published as they will be novel, this reviewer feels that the communication of the protocol will not informative to the reader.

REVIEWER	David Coultas Oregon Health & Science University, USA
REVIEW RETURNED	31-Oct-2018

GENERAL COMMENTS	The protocol described in this manuscript addresses a highly relevant clinical problem with substantial gaps in how to provide self-management support for patients with COPD. Moreover, the comprehensive self-management supported by the MH-COPD intervention, addresses patient perceptions about mHealth and needs of patients with COPD (Korpershoek et al. BMC Health Services Res 2018;18:757). The comprehensive content of the self-management support is a major strength of the protocol. Specific suggestions for improvement of the protocol follow.

	Page 2, line 23: I am not sure what the authors are referring to when they state that self-management resources have “long been available” to patients but they have not been adherent. This is more complex than patient adherence. Healthcare providers, health systems, and health policies all have major roles in ensuring that patients have the support they need. Page 2, line 48: While the trial dates are included in the abstract, suggest also including them in the Methods section. Page 2, line 50: When referring to dissemination through journal publication suggest referencing the CONSORT statement for reporting randomized trials of non-pharmacologic treatments (Boutron et al. Ann Intern Med 2017 doi: 10.7326/M17-0046). Also, consider using the CONSORT checklist to ensure relevant items are included in this protocol. Page 4, lines 7-8: On an annual basis a minority of patients with COPD are impacted by exacerbations. Therefore, I suggest rephrasing and not use the phrase “frequently impacted.” Lines 12-13: Suggest adding social support as a component of self-management support. Page 5, Trial Design and Clinical Setting: The proposed dates are listed in the abstract and need to be included in the Methods section. Page 5, line 28: Limiting patients to the thoracic outpatient unit will limit generalizability. What is the rationale for not including patients from primary care? Page 11, lines 26-37: In addition to clinical researchers a statistician is usually a member of the DMC. Also, interim analyses are performed to be able to examine the rates of serious adverse events rather than a qualitative assessment as suggested. I do not understand the difference between “formal interim statistical analysis” compared to assessing the “rates of serious adverse events.” Moreover, the protocol should describe specific stopping rules for the trial. Page 11, Discussion: Consider including a subsection of limitations and how they will be addressed. One potential limitation was strategies for participant retention discussed on page 10. Another is generalizability.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Nam e: Vicki Johnson-Warrington

Institution and Country: Complex Intervent ions team, Leicester Diabetes Centre, Leicester

General Hospital, University Hospitals of Leicester NHS Trust, UK

Please state any competing interests or state ‘None declared’: No ne declared

Please leave your comments for the authors below

This is an important study to undertake in order to provide evidence if a mobile health app can enhance the self-management and quality of life of people with COPD which is a fairly new area of research and will be important for clinical care.

It would help if you could provide a bit more detail on what PPI you have carried out and how this has helped your research. Also, how you have developed this app. Have you written a developmental paper/is it reported elsewhere?

Response: Detailed development has been undertaken for this app. As we have not written a specific developmental paper, we have extended the following statement in the Methods (new section in bold):

“In this project, we also engaged with clinical nurses, general practitioners, thoracic physicians, and a group of patients with COPD. With this engagement, we identified the care needs for the self-management of COPD. We accordingly designed the interventional components and care processes. Finally we worked with the clinician and patient groups to design the user interface for the mobile app and clinician portal.” (Line 8, page 4)

You say you have designed the intervention to overcome reported barriers - how/what have you done in regards to this? Have you used any psychological theories or specific behavior change techniques within your intervention, if so, I would be interested to find out more. Have you tried/piloted your app? It may be beyond the scope of this paper, but more background detail around this would be useful.

Response: Thank you for these suggestions. Regarding the first question about addressing barriers, we have designed the app to overcome specific barriers to COPD self-management. We have already outlined the barriers addressed in the Introduction (line 17, page 3) with the list of barriers: “limited health knowledge, difficulty to access resources, insufficient clinical support, and lack of motivation”.

In addition, we have now added two sentences to further clarify the strategies to overcome these barriers:

“The MH-COPD program will make it easy for patients to access validated educational materials, and self-manage clinical symptoms. The integration with the clinical service will also enable care providers to support and motivate patients to adhere to the self-management of COPD.” (Line 30-33, page 3)

Regarding the second question, we used well-known mHealth strategies in the design, including a goal-based strategy to improve self-efficacy and personalized intervention. We have not applied psychological theories, and specific behaviour change techniques, as we are seeking to demonstrate efficacy with detailed information provision about how use the app for self-management in routine clinical practice.

Regarding the third question, we have pilot tested the app with clinicians and users. These pilots helped refine the app and clinician portal. We agree with Reviewer 1 that these details are beyond the scope of this protocol paper, and they will be included in the future results paper.

Have you trialled any of the individual components previously i.e. the automatic reduction of smoking to 0 over 6 weeks? Could people not personalize their own goals instead? While it would be good to reduce smoking to 0, this may not be manageable for some and it could reduce people's self-efficacy and motivation to try and quit if they are forced into a specific (unrealistic for them) regime?

Response: Regarding the first question, other than the initial piloting, we have tested the individual components of the app, as the functionality of the app as a whole will be tested in this study. Many of the components, such as smoking cessation and physical activity, have been examined in a cardiac rehabilitation study and two other studies (See references 21 and 27 in line 6, page 4).

Regarding the second and third questions, experienced nurses/clinicians will discuss with individual patients about the goals for smoking cessation. We understand that the goals may not be achieved by all the participants; however, we have set up ambitious targets for quitting, beyond just harm reduction. We expect the mobile app will make it easier for users to track and understand their progress with smoking cessation, compared with paper-based approaches in usual care. We have now accordingly highlighted the clinicians' support to set up and adjust the goals in the trial, with the following sentence in the Methods: "Clinicians in the program will discuss with individual participants to set the goal, and adjust the goal during follow-up." (Line 5, page 7)

Can you clarify if participants in the intervention arm are self-managing any AECOPDs/are following an automated SM plan via the app or whether HC Ps are monitoring this and intervening as each appears to be mentioned within the paper?

Response: In the intervention arm (and usual care arm), AECOPDs will be self-managed by each participant. They will be encouraged to present to their HCP, who will then undertake further diagnosis and treatment as appropriate. The electronic action plan provided in the app will be a general guide to participants (like a hard copy action plan is). In this trial of self-management (as opposed to telemonitoring), HCPs will not be monitoring or intervening (as HCPs are not monitoring app responses).

To clarify this, we have added two sentences to the Methods section (line 29-31, page 6):

"This will make it easy for patients to access and use the action plan. Participants in the intervention program will still be required to engage with care providers to diagnose and treat clinical conditions, including acute exacerbations of COPD, as what they do in usual care."

Is the COPD knowledge questionnaire you plan on using a validated tool? If not, would another tool be helpful i.e. the Bristol COPD knowledge questionnaire which is?

Response: Thank you for this excellent suggestion. The questionnaire we are using in this study is from Lung Foundation Australia, the peak not-for-profit respiratory consumer organisation for COPD in Australia, and has been specifically developed for Australian patients. We will add the Bristol COPD Knowledge Questionnaire (White 2006), as per the kind suggestion from the Reviewer.

Why are you asking the intervention arm to record AECOPD on a paper version as well, as they are already recording via the app? It may be a bit burdensome for them to do it twice?

Response: Whilst we expect that participants in the intervention arm will record their symptoms daily and access the action plan daily, the app will not actually be a diary to record AECOPD events. Therefore we have implemented hard copy diaries for exacerbations in both the intervention and usual care arms. i.e. the intervention group will use the app, on top of usual care procedures. We do not feel that this will be a significant burden for intervention group participants, as exacerbations are likely to be relatively infrequent. Daily symptoms are not being recorded on the hard copy diary card.

Research question - I don't think you can 'increase' someone's self-management (SM), you could enhance it.

Response: Thank you, we have accordingly substituted "enhance" for "increase" (line 33, page 3)

You state the aim of the intervention/study is to increase SM, improve health outcomes and to test the efficacy of MH-COPD. Could you be clearer on your main aim of the study, consequently you state you have 3 primary outcome measures (which seems a little extreme)- CAT, SGRQ and mMRC but the sample size is based on CAT and SGRQ (no mention of mMRC).

Response: We have now added two sentences to explain why three questionnaires will be included in the study:

“The CAT and SGRQ questionnaires will be used because they are responsive to interventions 39. We will also include mMRC because it is essential for assessing dyspnoea, and has been adopted in GOLD 29 and Australian COPD-X guidelines 5.” (Line 10-12, page 8).

(Q4) Could you blind research staff when completing the 6 month assessments to reduce bias and increase the strength of the study? Are research staff part of the clinical staff or separate? if separate, will the clinical staff specifically be aware which arm of the study patients are in and can this be controlled/minimized at all?

Response: To reduce bias, the Methods currently state “Data analysis of outcomes based on questionnaires and diary cards (common to both groups) will be analysed by a researcher not directly involved with recruitment and follow-up. In the analysis, only de-identified data will be provided.” (Line 17, page 9). Clinical staff will be separate from research staff. As this is an open trial, participants and clinical staff will be aware of the allocated study group.

You mention other studies have been small in number, n<50 in the background and n<100 in the discussion.

Response: We have changed “(≤50)” into “(≤100)” in the Background. (Line 25, page 3)

Will you be able to gain data regarding how often the app is used/how many times the videos etc are viewed etc? It may be interesting to find out and could explain some results at the end of the study (i.e. in terms of engagement). You may be limited by funding, but some qualitative data regarding how participants in the intervention group found the app and intervention could be helpful if possible?

Response: We thank you for the recommendation. We will be able track the usage of all features of the app, including the video player (educational video clips), and the electronic action plan. These results will also be analysed, to add to the final outcomes.

We are unable to do qualitative assessments at present because of the limited resources; however, this is an excellent suggestion if further budget becomes available.

Reviewer: 2

Reviewer Nam e: Roberto Benzo

Institution and Country: Mayo Clinic USA

Please state any competing interests or st ate ‘None declared’: no competing interests

Please leave your comments for the authors below

The study intend to test a mobile technology intervention to improve self management. While there is a lack of effective mobile interventions to improve self management, the ones that are somewhat effective are the one that in addition of technology have some provider interaction. rarely if ever mobile health alone (no provider or coach interaction) improve meaningful outcomes. there is no enough literature to support technology alone to be effective. This study may be the first to prove it. While positive results from the proposed study (technology alone improving outcomes) are needed and need to be published as they will be novel, this reviewer feels that the communication of the protocol will not informative to the reader.

Response: We thank Reviewer 2 for this feedback. We expect the MH-COPD program will make it easy for users to self-manage COPD. In addition, it will also enable care providers to support and motivate participants to adhere to the self-management. Therefore, we are reporting the details of the protocol, similar to other protocols from our group for other conditions: Ding H, Jayasena R, Maiorana A, Dowling A, Chen SH, Karunanithi M, Layland J, Edwards I. Innovative Telemonitoring Enhanced Care Programme for Chronic Heart Failure (ITEC-CHF) to improve guideline compliance and collaborative care: protocol of a multicentre randomised controlled trial. BMJ Open. 2017;7(10):e017550.

Reviewer: 3

Reviewer Nam e: David Coultas

Institution and Country: Oregon Health & Science University, USA

Please state any competing interests or state 'None declared': Non e declared

Please leave your comments for the authors below

The protocol described in this manuscript addresses a highly relevant clinical problem with substantial gaps in how to provide self-management support for patients with C OPD. Moreover, the comprehensive self-management supported by the MH-C OPD intervention, addresses patient perceptions about mHealth and needs of patients with C OPD (Korpershoek et al. BMC Health Services Res 2018;18:757). The comprehensive content of the selfmanagement support is a major strength of the protocol. Specific suggestions for improvement of the protocol follow.

Page 2, line 23: I am not sure what the authors are referring to when they state that selfmanagement

resources have "long been available" to patients but they have not been adherent. This is more complex than patient adherence. Healthcare providers, health systems, and health policies all have major roles in ensuring that patients have the support they need.

Response: We have accordingly changed the sentence into. "In outpatient care, the self-management of COPD is essential, but patient adherence to this remains suboptimal." (Line 12-13, page 1)

Page 2, line 48: While the trial dates are included in the abstract, suggest also including them in the Methods section.

Response: We have inserted a sentence in Trial Design and Clinical Setting (Line 18, Page 4), saying "The recruitment and follow-up of the trial will be from Jan 2019 to Dec 2020." The dates are adjusted to ensure we will be using the Methods from this current protocol.

Page 2, line 50: When referring to dissemination through journal publication suggest referencing the CONSORT statement for reporting randomized trials of non-pharmacologic treatments (Boutron et al. Ann Intern Med 2017 doi: 10.7326/M17-0046). Also, consider using the CONSORT checklist to ensure relevant items are included in this protocol.

Response: We have revised the sentence, stating "The study outcomes will be disseminated according to the CONSORT statement 1 through a journal publication, approximately 6 months after finishing data collection." (Line 31, page 1). Furthermore the CONSORT checklist has been used and included with the original manuscript submission.

Page 4, lines 7-8: On an annual basis a minority of patients with COPD are impacted by exacerbations. Therefore, I suggest rephrasing and not use the phrase “frequently impacted.” Lines 12-13: Suggest adding social support as a component of self-management support.

Response: We have changed this into “often experience”. (Line 4, page 3)

Regarding the comment for adding “Social support”, we have changed the sentence into “The self-management of COPD through clinical and social support, such as optimal use of medicines, lifestyle modification and avoidance of risk factors, is essential to improve health outcomes and prevent COPD progression” (Line 7, page 3; new text is shown in bold here)

Page 5, Trial Design and Clinical Setting: The proposed dates are listed in the abstract and need to be included in the Methods section.

Response: We have inserted a sentence in Trial Design and Clinical Setting (Line 19, Page 4), saying “The recruitment and follow-up of the trial will be from Jan 2018 to Dec 2020.”

Note: This comment is that same as the previous comment of “Page 2, line 48: While the trial dates are included in the abstract, suggest also including them in the Methods section.”

Page 5, line 28: Limiting patients to the thoracic outpatient unit will limit generalizability. What is the rationale for not including patients from primary care?

Response: The research partnership for this study was established between a tertiary referral hospital and the Australian eHealth Research Centre, CSIRO, with funding from The Prince Charles Hospital Foundation for a hospital-based study. We propose to demonstrate feasibility and efficacy initially with hospital-based outpatients (this study), and then extend future studies to primary care.

Page 11, lines 26-37: In addition to clinical researchers a statistician is usually a member of the DMC .

Also, interim analyses are performed to be able to examine the rates of serious adverse events rather than a qualitative assessment as suggested.

I do not understand the difference between “formal interim statistical analysis” compared to assessing the “rates of serious adverse events.” Moreover, the protocol should describe specific stopping rules for the trial.

Response: Regarding the first question, we have inserted a sentence saying “The statistical analysis methods and outcomes will be reviewed by a statistician.” (Line 28, page 10)

Regarding the second comment, the risks of using mobile health apps is low. Therefore, specific qualitative assessment has not been included in this study. The Trial Monitoring section (Page 10) already includes quantitative analysis of the rates of serious adverse events, as well as severity.

Regarding the third comment, we have clarified the “interim statistical analysis” and added a stopping rule. The revised sentences are “If there are substantial differences in rates of serious adverse events (including mortality) or hospitalisation between the MH-COPD and UC-COPD groups, the DMC will investigate the potential reasons for the differences. If significant adverse events are caused by the MH-COPD program, the DMC will recommend to terminate the trial early.” (Line 31, page 10)

Page 11, Discussion: Consider including a subsection of limitations and how they will be addressed. One potential limitation was strategies for participant retention discussed on page 10. Another is generalizability.

Response: We have accordingly added a subsection of limitations (Line 36, page 10):

A number of potential limitations should be considered. This study is limited to a 6-month intervention duration, which may be insufficient to reflect long-term effects of the intervention. The study is also not blinded to participants and clinicians, although analysis of 6 month outcomes will be blinded. This is a hospital-based study, which limits generalisability; however, future studies will address initiating of mHealth for patients with COPD in primary care.

As participant retention has already been discussed in a separate section on page 10 (Strategies for Participant Retention), we have not duplicated those statements here.

VERSION 2 – REVIEW

REVIEWER	David Coultas Oregon Health & Science University
REVIEW RETURNED	24-Jan-2019

GENERAL COMMENTS	The authors have responded appropriately to the initial reviewers' comments.