PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	ref SMARTphone and social media-based Cardiac Rehabilitation and Secondary Prevention (SMART-CR/SP) for patients with coronary heart disease in China: a randomised controlled trial protocol
AUTHORS	Dorje, Tashi; Zhao, Gang; Scheer, Anna; Tsokey, Lhamo; Wang, Jing; Chen, Yaolin; Tso, Khandro; Tan, B-K; Ge, Junbo; Maiorana, Andrew

VERSION 1 – REVIEW

REVIEWER	Hasnain Dalal University of Exeter Medical School ,UK
REVIEW RETURNED	15-Feb-2018

GENERAL COMMENTS	The sample size is not replicable without the authors stating their assumed standard deviation for the 6MWT The authors should consider regression methods for continuous outcomes such as the 6MWT to adjust for between group differences at follow up for baseline outcome scores. An example of a protocol that the may wish to look at in how to present a revised manuscript I suggest they refer to a recent one from our study group: Taylor RS, Hayward C, Eyre V, et al. Clinical effectiveness and cost-effectiveness of the Rehabilitation Enablement in Chronic Heart Failure (REACH-HF) facilitated selfcare rehabilitation intervention in heart failure patients and caregivers: rationale and protocol for a multicentre randomised controlled trial. BMJ Open 2015;5:e009994. doi:10.1136/bmjopen-2015-009994 The more up to date reference for CR in CHD by Anderson et al could be used emphasising that the latest evidence show an effect on cardiovascular mortality and not overall mortality Anderson L, Oldridge N, Thompson DR, et al. Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane systematic review and meta-analysis. J Am Coll Cardiol 2016;67:1-12. doi:10.1016/j.jacc.2015.10.044 pmid:26764059. The authors may also wish to consider using a disease specific health related quality of life measure such as the HeartQol Oldridge N, Hofer S, McGee H, et al. The HeartQoL: part II. Validation of a new core health-related quality of life questionnaire for patients with ischemic heart disease. Eur J Prev Cardiol 2014;21:98–106.

REVIEWER	Robert Jay Widmer Mayo Clinic, USA

REVIEW RETURNED	16-Feb-2018

GENERAL COMMENTS	In this well constructed protocol manuscript, Dorje et al lay out plans for what could be a pivotal trial in terms of both digital health and secondary cardiovascular prevention. The spirit of the trial, size of the population, metrics tracked, and length of follow up are to be commended. This reviewer has serious logistical and ethical concerns, however, that must be addressed before the trial's protocol paper can be considered. This trial essentially compares some secondary prevention measures vs none which has repeatedly been shown to be positive. The digital health angle is appealing, however, the ethics and logistics of withholding cardiac rehabilitation and digital health from a group of patients is a fatal flaw in the study. Major points: 1. It would appear that the authors are simply testing some cardiac rehabilitation vs no intervention, which is certain to be positive. Is there any intermediate arm (outpatient, traditional cardiac rehabilitation) that the authors can also use as a comparator? Without that frame of reference it is difficult to know if it is the digital health or simply some contact with the health system that has improved 6MWT in these patients. 2. This reviewer believes it unethical to withhold cardiac rehabilitation, a class 1A guideline recommendation from all major societies, from a group of patients for the purposes of a study. Although being approved by what would appear to be two ethics committees, the authors must address this substantial hurdle in this study. 3. Furthermore, the logistics of withholding such prevalent digital health tools and/or WeChat from a group of patients seems problematic. The authors provide no mention of unintentional cross overs or cross talk between patients which could affect the results in an unmeasurable way. Minor points: 1. There is very little mention of behavior change theory in the introduction or methods. It is unclear how a social media application will fundamentally alter lifestyle habits in such a high-risk population. The authors mention a "knowledge of the disease" questionnaire, however nothing that addresses readiness to change or awareness of progress. 2. The authors mention they will provide phones and software in the abstract, however in the methods state "All participants will be required to personally own an operational smartphone, have an active WeChat account, …". This discrepancy in patient selection – which could also introduce selection bias into the study – must be settled. 3. To that end, would all patients be given a smartphone and access to WeChat? Why not also track activity, diet, and potentially some of the questionnaire data from the control group through the app? 4. Lack of internet access is listed as an exclusion criteria. Could the authors simply have a cellular data plan on which the program could be delivered?

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1
Reviewer Name: Hasnain Dalal
Institution and Country: University of Exeter Medical School, UK
Competing Interests: None

The sample size is not replicable without the authors stating their assumed standard deviation for the 6MWT
R: We thank the reviewer for his comment. We have included the SD in the description of the sample size calculation in the manuscript.
The authors should consider regression methods for continuous outcomes such as the 6MWT to adjust for between group differences at follow up for baseline outcome scores. An example of a protocol that they may wish to look at in how to present a revised manuscript I suggest they refer to a recent one from our study group: Taylor RS, Hayward C, Eyre V, et al. Clinical effectiveness and cost-effectiveness of the Rehabilitation Enablement in Chronic Heart Failure (REACH-HF) facilitated self-care rehabilitation intervention in heart failure patients and caregivers: rationale and protocol for a multicentre randomised controlled trial. BMJ Open 2015;5:e009994. doi:10.1136/bmjopen-2015-009994

R: We thank the reviewer for his suggestion regarding the outcome analyses. We have read the protocol paper recommended by the reviewer, and consulted with our statistician, and revised the data analysis plan in the manuscript accordingly.

The more up to date reference for CR in CHD by Anderson et al could be used emphasising that the latest evidence show an effect on cardiovascular mortality and not overall mortality

Anderson L, Oldridge N, Thompson DR, et al. Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane systematic review and meta-analysis. J Am Coll Cardiol 2016;67:1-12. doi:10.1016/j.jacc.2015.10.044 pmid:26764059.

R: We thank the reviewer for his advice. We have replaced the original reference with the updated version of the Cochrane review.
The authors may also wish to consider using a disease specific health related quality of life measure such as the HeartQol. Oldridge N, Hofer S, McGee H, et al. The HeartQoL: part II. Validation of a new core health-related quality of life questionnaire for patients with ischemic heart disease. Eur J Prev Cardiol 2014;21:98–106.

R: We thank the reviewer for the suggestion. We will consider the above outcome measurement tool in our future studies.

Reviewer: 2
Reviewer Name: Robert Jay Widmer
Institution and Country: Mayo Clinic, USA
Competing Interests: None declared.

In this well constructed protocol manuscript, Dorje et al lay out plans for what could be a pivotal trial in terms of both digital health and secondary cardiovascular prevention. The spirit of the trial, size of the population, metrics tracked, and length of follow up are to be commended. This reviewer has serious logistical and ethical concerns, however, that must be addressed before the trial's protocol paper can be considered. This trial essentially compares some secondary prevention measures vs none which has repeatedly been shown to be positive. The digital health angle is appealing, however, the ethics

and logistics of withholding cardiac rehabilitation and digital health from a group of patients is a fatal flaw in the study.
Major points:
1. It would appear that the authors are simply testing some cardiac rehabilitation vs no intervention, which is certain to be positive. Is there any intermediate arm (outpatient, traditional cardiac rehabilitation) that the authors can also use as a comparator? Without that frame of reference it is difficult to know if it is the digital health or simply some contact with the health system that has improved 6MWT in these patients.
R: We thank the reviewer for his comments, however, we respectfully disagree that the trial design will invariably produce positive results; without a trial, this would merely conjecture on our part, hence the need for a trial. Traditional CR/SP services (both outpatient and inpatient) are still underdeveloped and underutilised in mainland China. For example, prior to this project, there has been no cardiac rehabilitation program at the trial hospital, so the study will be comparing a novel intervention against usual care. We acknowledge the reviewer's concerns that have increased contact with the health system may have an effect on participants' behaviour and have added this as a limitation of the study

2. This reviewer believes it unethical to withhold cardiac rehabilitation, a class 1A guideline recommendation from all major societies, from a group of patients for the purposes of a study. Although being approved by what would appear to be two ethics committees, the authors must address this substantial hurdle in this study.
R: As mentioned in our response above, there is no cardiac rehabilitation program available to patients at the trial hospital so cardiac rehabilitation won't be withheld. We agree with the reviewer that cardiac rehabilitation is an important component of managing cardiovascular disease. The objective of this study is to evaluate a novel approach that may be well suited to the Chinese population and healthcare system. This has been informed by our preliminary surveys and focus groups with patients from the hospital. Unlike in many developed countries, patients with cardiovascular disease in mainland China have very limited access to modern CR/SP services. A recent national survey showed that only 30 of 124 (24%) large medical centres surveyed in China have operational CR programs, translating to approximately two programs per 100 million inhabitants (Zhang Z, et al. Availability and characteristics of cardiac rehabilitation programmes in China. Heart Asia 2016;8:9-12.). It is in this context that we have developed the current study. However, prior to providing this mHealth-based CR/SP to a large population, the feasibility and efficacy of this new model of care need to be investigated. It is the nature of an RCT that some of the participants will be randomly allocated to a control group. However, we will provide access to the WeChat-based educational materials developed for the study to participants from the control group at the end of the study, to provide secondary prevention support to them for their long-term disease management and risk factor modification.

3. Furthermore, the logistics of withholding such prevalent digital health tools and/or WeChat from a group of patients seems problematic. The authors provide no mention of unintentional cross overs or cross talk between patients which could affect the results in an unmeasurable way.
R: While the potential for information crossover exists in a trial of this nature, we believe the likelihood of this occurring is minimal for several reasons. The intervention will involve an individualized one-on-one CR/SP coaching program conducted in real-time via WeChat, so it is unlikely that participants will be able to share the live audio and video information provided. The educational cartoons will also be delivered on a one-on-one basis and participants will be informed not to share the material with other patients. Finally, the broad geographical distribution and cultural diversity of participants will mean they are very unlikely to come in contact with one another, further minimizing any potential for information crossover between participants in the two groups.

Minor points:

1. There is very little mention of behaviour change theory in the introduction or methods. It is unclear how a social media application will fundamentally alter lifestyle habits in such a high-risk population. The authors mention a “knowledge of the disease” questionnaire, however nothing that addresses readiness to change or awareness of progress.
R: We thank the reviewer for his comments and acknowledge the significance of behaviour change theory in risk factor modification. It is our hypothesis that the social media-based intervention, which involves cardiac health information, individualized CR/SP coaching, physical activity tracking, blood pressure monitoring and management and cardiac medication management, will provide the necessary education and support to invoke behaviour change. However, this is yet to be determined, hence the reason we are undertaking this trial. As with any trial which has a behaviour change component, some participants will be at a more advanced stage of readiness to change, however, we have not used readiness to change as an exclusion for enrolment to ensure we recruit a sample that is representative of the typical cardiac rehabilitation population. The assessment burden is already quite substantial for the study so we do not plan to use a questionnaire to address readiness to change, or awareness of progress, in the current study. We thank the reviewer for his suggestion and will consider including a questionnaire of this nature in future studies.
2. The authors mention they will provide phones and software in the abstract, however in the methods state “All participants will be required to personally own an operational smartphone, have an active WeChat account, …”. This discrepancy in patient selection – which could also introduce selection bias into the study – must be settled.
R: We apologize that our statement in the abstract was misleading and have amended this to more clearly describe the intent of the trial. The statement in the abstract now reads “The intervention group will receive a smartphone-based and WeChat-based CR/SP program providing education and support for risk factor monitoring and modification”. That is, participants will be provided with a “smartphone-based” CR/SP program, not a smartphone per se. We accept that this may introduce bias during the participant selection process and have added this as a delimitation to the study. However, given the high use of social media and good internet access in China, we believe the risk is relatively low. For instance, recently published data shows that currently there are over 900 million active WeChat users in Mainland China.
3. To that end, would all patients be given a smartphone and access to WeChat? Why not also track activity, diet, and potentially some of the questionnaire data from the control group through the app?
R. Further to our point of clarification above, participants in neither the experimental or control groups will be provided with a smartphone, however, it will be a requirement for both groups to have a smartphone and WeChat account, consistent with the study’s inclusion criteria. Physical activity will be tracked for both groups by using the step tracking function in WeChat. We are not planning to track diet throughout the intervention, however, it will be assessed in both groups at baseline and each follow-up.
4. Lack of internet access is listed as an exclusion criteria. Could the authors simply have a cellular data plan on which the program could be delivered?
R: During the early design phase of the trial, we considered the need to provide a cellular plan to participants. However, during preliminary surveys and focus groups with a representative cohort of patients, that were undertaken to guide the study design, we learnt that internet access was very high in this group of urban Chinese so decided that providing a cellular data plan wasn’t necessary. For instance, internet penetration rate has already reached 54.3% in China in 2017. However, cellular data support may be necessary if this new model of care is going be adopted in more remote areas, such as Western China, in the future.

VERSION 2 – REVIEW

REVIEWER	Robert Jay Widmer Mayo Clinic, USA
REVIEW RETURNED	14-Apr-2018

GENERAL COMMENTS	While there are still some theoretical concerns regarding selection bias and appropriateness of the allocation to intervention vs no-intervention. The authors have attempted to answer many of the reviewers' concerns. The authors will have some information regarding how this intervention did/did not affect behavior change and should report this in their outcomes paper. Finally, the fourth bullet point "delimited" should be changed to "limited".