PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Economic evaluation protocol for a multicentre randomised controlled trial to compare Smartphone Cardiac Rehabilitation, Assisted self-Management (SCRAM) versus usual care cardiac rehabilitation among people with coronary heart disease
AUTHORS	Gao, Lan; Maddison, R; Rawstorn, Jonathan; Ball, Kylie; Oldenburg, Brian; Chow, Clara; McNaughton, Sarah; Lamb, Karen; Amerena, John; Nadurata, Voltaire; Neil, Christopher; Cameron, Stuart; Moodie, Marj

VERSION 1 – REVIEW

REVIEWER	Rod Taylor University of Glasgow
REVIEW RETURNED	25-Mar-2020

GENERAL COMMENTS	This paper describes an economic evaluation alongside a randomised controlled trial designed to determine the effectiveness of a telebased rehab intervention (SCRAM) in comparison to usual care cardiac rehabilitation (UC) alone in people with CHD. The manuscript is well written and the proposed economic evaluation methods robust and in accord with accepted reporting guidelines. I had two questions for the authors 1. Value of cost-effectiveness analysis: I agree with the cost per QALY analysis but I am unconvinced of the CEA analysis and value the incremental cost per unit increase in benefits for both the primary and secondary outcomes will be calculated if significant between-group differences are observed, e.g. what does a incremental cost per increase in VO2 per ml/kg/min mean. 2. Publication of main trial protocol: I note the authors have published the protocol for RCT – I wasn't sure if the a parallel economic evaluation needs a further full publication. However, I don't feel strongly and will leave it to the journal editors to make a final decision.

REVIEWER	Lisa Gregersen Oestergaard DEFACTUM, Central Denmark Region & Institute of Public Health, Aarhus University
REVIEW RETURNED	08-Apr-2020

GENERAL COMMENTS	Thank you for the opportunity to review the study "Economic evaluation protocol for a multicenter randomized controlled trial to compare Smartphone Cardiac Rehabilitation, Assisted Sef-Management (SCRAM) versus usual cardiac rehabilitation among people with coronary heart diseases" for BMJ Open.

	I find the topic to be of significant relevance, and I acknowledge the importance of the study. The economic evaluation is performed alongside both a clinical evaluation and a process evaluation, following leading guidelines for evaluating complex interventions. I believe that this study will bring important knowledge of the economic aspects of Cardiac Rehabilitation. The abstract is clearly presented. The introduction is well-structured and includes relevant references. I have a few suggestions for improving the article. You clearly describe the importance of conducting this economic evaluation, and that this evaluation will provide important evidence for policy decision-making. However, I would suggest that you specify the aim of the planned economic evaluation. On page 9 you write “All participants retain access to usual care CR - regardless of treatment allocation - as it is unethical to withhold evidence-based treatment”. This gives the impression that the intervention group receives both SCRAM and usual care CR and is compared to usual care CR alone. If so, I would suggest that that the aim of your study is to evaluate the cost-effectiveness and cost-utility of the SCAM program as an add on to usual care CR compared to usual care CR alone. Overall, the article reads well. However, I find that the manuscript would benefit from an elaboration of the methodological descriptions, which I will address in the following: My main concern is the use of the AQoL-8D to calculate Quality Adjusted Life Years (QALYs). I recognize the AQoL-8D as a relevant instrument to measure quality of life. However, in order to calculate QALYs, two components are needed: 1) a component that classifies health status (i.e. the AQoL-8D) and 2) a component in the form of a scoring algorithm that assigns a preference value to health status. Do you plan to use preference weights in order to calculate QALYs? Do Australian preference weights exist for AQoL-8D, or will you be using preference weights from other countries? Please specify if you use preference weights and add the relevant references. It seems unclear, if you plan to perform the cost-utility analyse based on quality of life measurements, and not on calculated QALYs? If so, please delete the part about QALY and specify that this is what you will do. You describe that you perform a trial-based economic evaluation alongside an RCT, and overall you present a well-described plan for the costing and the plan for the analysis. On page 13, you also describe that a model-based evaluation using a Markov model will be performed. Is this a supplemental secondary analysis? Or do you perform both a trial-based and a model-based economic evaluation? If so, please describe this and give more detailed information regarding the methods used in the model-based evaluation and also include this in the abstract. A detailed and sufficient description of the costing is presented alongside a sufficient plan of the analysis of the cost-effectiveness and cost-utility analysis. However, I would suggest that you not only use the methods of bootstrapping to estimate the confidence intervals of the ICER, but also use this method to estimate the 95% CI of all costs in the two groups. You state that you intend to perform the analysis in accordance with the intention-to-treat principles. Please specify how you will handle possible missing data. In the discussion, relevant topics regarding the methods are discussed. However, I would suggest that you elaborate the discussion on the following topics; the timeframe for your trial-based evaluation and what the accompanying model-based

	evaluation will bring to your evaluation. Also, the planned handling of the missing data could be discussed. I hope that my comments are beneficial, and wish you the best of luck with the study.

VERSION 1 – AUTHOR RESPONSE

Comments	Response	Revision
Reviewer 1		
Value of cost-effectiveness analysis: I agree with the cost per QALY analysis but I am unconvinced of the CEA analysis and value the incremental cost per unit increase in benefits for both the primary and secondary outcomes will be calculated if significant between-group differences are observed, e.g. what does a incremental cost per increase in VO2 per ml/kg/min mean.	We acknowledge reviewer's concern. It is not straightforward to interpret such ICERs calculated based on other primary and secondary outcomes (and there is no threshold to determine the cost-effectiveness of these outcomes). However, this will give the policy-maker some indicative value of the cost to pay for the additional VO2 gain, and the ICERs based on non-QALY outcomes have been reported in existing economic analyses[1, 2].	No change has been made.
Publication of main trial protocol: I note the authors have published the protocol for RCT – I wasn't sure if a parallel economic evaluation is needed	No details for the economic evaluation were provided in the main trial protocol (doi: 10.2196/15022.). For the purpose of transparent reporting, an increasing number of separate protocols are being published for economic evaluations.	No change has been made.
Reviewer 2		
I find the topic to be of significant relevance, and I acknowledge the importance of the study. The economic evaluation is performed alongside both a clinical evaluation and a process evaluation, following leading guidelines for evaluating complex interventions. I believe that this study will bring important knowledge of the	Thank you.	No change has been made.

Comments	Response	Revision
economic aspects of Cardiac Rehabilitation.		
You clearly describe the importance of conducting this economic evaluation, and that this evaluation will provide important evidence for policy decision-making. However, I would suggest that you specify the aim of the planned economic evaluation.	Thanks for the suggestion. The aim of the planned economic evaluation has been now added to the revised manuscript.	Page 7 of the revised manuscript: *This planned economic evaluation aims to provide the evidence around the cost-effectiveness of cardiac tele rehabilitation, assessing its value-for-money in the Australian context.*
On page 9 you write "All participants retain access to usual care CR - regardless of treatment allocation - as it is unethical to withhold evidence-based treatment". This gives the impression that the intervention group receives both SCRAM and usual care CR and is compared to usual care CR alone. If so, I would suggest that that the aim of your study is to evaluate the cost-effectiveness and cost-utility of the SCRAM program as an add on to usual care CR compared to usual care CR alone	Thanks to the reviewer for pointing this out. However, only a small percentage (i.e. 20%[3]) of patients would accept the referral of the traditional CR in Australia, even though, it is considered unethical to not refer them for this evidence-based treatment. The aim of the SCRAM program is to offer an alternative option for treating clinicians when referring patients on for post-discharge CR – usual care CR or SCRAM. So SCRAM is not added on to usual care CR. We have added further clarification in the revised manuscript.	Pages 9 to 10 of the revised manuscript: *It is unclear how many participants will choose to access SCRAM and usual care CR; nevertheless, widespread low uptake of centre-based CR suggests very few patients randomised to SCRAM program will seek to complete both programs[4]. To explore impact on trial outcomes, self-reported usual care CR utilisation for patients assigned to SCRAM program will be assessed.*
My main concern is the use of the AQoL-8D to calculate Quality Adjusted Life Years (QALYs). I recognize the AQoL-8D as a relevant instrument to measure quality of life. However, in order to calculate QALYs, two components are needed: 1) a component that classifies health status (i.e. the AQoL-8D) and 2) a component in the form of a scoring algorithm that	Thanks for reviewer's comment. AQoL-8D was developed in Australia and has Australian preference weights (Richardson J., Sinha K., Iezzi A., & Khan M.A. 2014. Modelling utility weights for the Assessment of Quality of Life (AQoL) 8D. Quality of Life Research, vol 23, pp2395-2404. DOI:10.1007/s11136-014-0686-8.)	Page 11 of the revised manuscript: *The Australian tariff for AQoL-8D will be used to estimate the QALY gains for individual participants[3].*

Comments	Response	Revision
assigns a preference value to health status. Do you plan to use preference weights in order to calculate QALYs? Do Australian preference weights exist for AQoL-8D, or will you be using preference weights from other countries? Please specify if you use preference weights and add the relevant references. It seems unclear, if you plan to perform the cost-utility analyse based on quality of life measurements, and not on calculated QALYs? If so, please delete the part about QALY and specify that this is what you will do.	It will be used in the proposed economic evaluation to calculate the QALYs. This now has been clarified in the revised manuscript.	
You describe that you perform a trial-based economic evaluation alongside an RCT, and overall you present a well-described plan for the costing and the plan for the analysis. On page 13, you also describe that a model-based evaluation using a Markov model will be performed. Is this a supplemental secondary analysis? Or do you perform both a trial-based and a model-based economic evaluation? If so, please describe this and give more detailed information regarding the methods used in the model-based evaluation and also include this in the abstract.	We will perform both a trial-based cost-efficacy analysis and a longer-term model-based economic evaluation (provided that the primary outcome from the trial is significant). We will convert the VO2 max (i.e. primary outcome of the RCT) to the reduction in the mortality (i.e. odds ratio in mortality for one unit improvement in VO2 max (reference: High Exercise Capacity Attenuates the Risk of Early Mortality After a First Myocardial Infarction: The Henry Ford Exercise Testing (FIT) Project), and combine it with the potential reduction in recurrent cardiovascular events to model the long-term health and cost outcomes for patients who receive SCRAM versus those received usual care CR in Australia. This has now been added to the revised manuscript.	Page 13 of the revised manuscript: *Model-based long-term cost-effectiveness analysis of SCRAM versus usual care CR will be undertaken if the primary outcome (VO2 max) from the RCT is proven to significantly increase. The VO2 max will be converted to the reduction in overall mortality (i.e. odds ratio in mortality for 1 MET increase). The difference (if any, observed from the RCT) in the incidence of recurrent CVD post the index MI will also be used to model the long-term health and cost outcomes associated with the application of the two modes of CR.*
A detailed and sufficient description of the costing is presented alongside a sufficient plan of the analysis	We have revised the manuscript in response to reviewer's comment.	Page 13 of the revised manuscript:

Comments	Response	Revision
of the cost-effectiveness and cost-utility analysis. However, I would suggest that you not only use the methods of bootstrapping to estimate the confidence intervals of the ICER, but also use this method to estimate the 95% CI of all costs in the two groups.		*Bootstrap simulation of the costs and ICER will be used to simulate the study results over 2,000 iterations.*
You state that you intend to perform the analysis in accordance with the intention-to-treat principles. Please specify how you will handle possible missing data.	We will undertake the analysis based on both completers (base case) and imputed data (sensitivity analysis). Multiple missing data imputation will be adopted to handle missingness in costs and QALYs with the assumption that missing is at random. We have now added this to the revised manuscript.	Page 12 of the revised manuscript: *In particular, completers data will be used for the base case analysis, whereas the imputed data analysis (using multiple missing data imputation approach, with the assumption that missingness is at random) will be undertaken to examine the robustness of base case results.*
In the discussion, relevant topics regarding the methods are discussed. However, I would suggest that you elaborate the discussion on the following topics; the timeframe for your trial-based evaluation and what the accompanying model-based evaluation will bring to your evaluation. Also, the planned handling of the missing data could be discussed.	We have added these topics in the discussion of the revised manuscript.	Page 15 of the revised manuscript: *Further, undertaking both completers and imputed data analyses for the trial-based economic evaluation will increased the validity of the results given the potential significant proportion of missingness in follow up cost and QALY data.* *The trial-based economic evaluation only has a short 24 week timeframe and was based on the trial under strictly controlled*

Comments	Response	Revision
		research conditions. It cannot answer the long term cost-effectiveness of SCRAM program which is pivotal for the reimbursement decision-making. The model-based economic evaluation that extrapolates the short-term trial outcome to the lifetime horizon and a real-world setting will inform the cost-effectiveness of the proposed program in the Australian context.

References

1. Deidda M, Coll-Planas L, Gine-Garriga M, Guerra-Balic M, Roque IFM, Tully MA, et al. Cost-effectiveness of exercise referral schemes enhanced by self-management strategies to battle sedentary behaviour in older adults: Protocol for an economic evaluation alongside the sitless three-armed pragmatic randomised controlled trial. BMJ Open. 2018;8:e022266
2. Haghparast-Bidgoli H, Shaha SK, Kuddus A, Chowdhury MAR, Jennings H, Ahmed N, et al. Protocol of economic evaluation and equity impact analysis of mhealth and community groups for prevention and control of diabetes in rural bangladesh in a three-arm cluster randomised controlled trial. BMJ Open. 2018;8:e022035
3. Richardson J, Sinha K, Iezzi A, Khan MA. Modelling utility weights for the assessment of quality of life (aqol)-8d. Qual Life Res. 2014;23:2395-2404
4. Worringham C, Rojek A, Stewart I. Development and feasibility of a smartphone, ecg and gps based system for remotely monitoring exercise in cardiac rehabilitation. PLoS One. 2011;6:e14669

VERSION 2 – REVIEW

REVIEWER	Rod Taylor University of Glasgow, UK
REVIEW RETURNED	14-May-2020

GENERAL COMMENTS	the authors have updated the paper according to review comments

REVIEWER	Lisa Gregersen Oestergaard DEFACTUM, Central Denmark Region, Denmark Institute of Public Health, Aarhus University, Denmark
REVIEW RETURNED	22-May-2020

GENERAL COMMENTS	Thank you for this revised manuscript. You have addressed all of my comments sufficiently. Good luck with the study.

VERSION 2 – AUTHOR RESPONSE

Thank you very much for your further comments. We have edited the manuscript accordingly.