PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Early initiation of post-sternotomy cardiac rehabilitation exercise training (SCAR): study protocol for a randomised controlled trial and economic evaluation.
AUTHORS	Ennis, Stuart; Lobley, Grace; Worrall, Sandra; Powell, Richard; Kimani, Peter; Khan, Amir; Banerjee, Prithwish; Barker, Thomas; McGregor, Gordon

VERSION 1 – REVIEW

REVIEWER	Karen Chia UNSW Rural Clinical School, Coffs Harbour, NSW Australia
REVIEW RETURNED	19-Oct-2017

GENERAL COMMENTS	**BMJ Open: SCAR Protocol (Early CR versus usual CR)** I read your protocol with great interest- thank you for the opportunity to review. Your project addresses a relevant, worthwhile topic. The protocol is well written and I look forward to the outcomes. Just a few minor points for clarification: <u>1) Consent</u> In Australia, the recommend period between providing potential participants with information and then obtaining informed consent is one week, to give participants time to process the information without any time pressure. It appears that it may be as little as >24hrs in your study. Perhaps this is standard practice in the UK? I see that you have Ethics approval, so I understand that this may not be an issue in the UK.

	2) Intervention I would appreciate a little more detail here (for example, how much time is allocated to each component of CR), so that readers can see if their cardiac rehabilitation services are comparable, and also to allow reproducibility of your results. I note in Figure 1 page 36 or 61 overall, titled "Trial Flow Chart: Figure 1: Flow of participants through the study" it is mentioned that the intervention will be of 1 hour duration. This is not specified in the text, or in "Figure 1: Study flow chart", but would be useful to include in either the final flow chart or text. It would also be helpful to know if there are other differences in the exercise prescription between intervention and control group, for example in terms of supervision ratio. I note that the early CR group will have an individualized programme. Does this mean that there will be fewer patients in the group compared to the control group? Or will numbers be kept the same? If there is a difference in supervision ratio, this may be a confounder. 3) Statistical analysis *Non-inferiority trial:* Sample size calculation for non-inferiority trial noted. A SD of 112m is conservative, as noted by the authors. First sentence could be re-worded to minimize confusion- I suggest removing "allow a switch to a superiority test", as this may confuse readers. The test/analysis itself will not be switched, rather if the CI is >0 then early CR is concluded superior to usual care. *Clarify the statistical analyses:* There is, I presume, a typographical error that is confusing – "The

	non-inferiority margin has been set at 60m by the research team. Early CR will be concluded non-inferior to usual care CR if the lower bound of the 95% CI interval for the mean difference of changes at the end of CR is **above 60**". I assume this is meant to be: the lower bound CI for the mean difference of change between groups is **less than 60**/ or above **minus** 60 (less than 60 is a less confusing way to write). Please clarify. 4) Choice of non-inferiority margin This is the area of the study that I think needs the most revision. The authors are to be commended for clearly stating how they have set this margin. However, there are a few issues noted: a) Clinical relevance- the non-inferiority margin of 60m is too large. A mean difference between groups of 60m in clinical practice would be considered relevant and therefore, if the difference between groups was up to 60m, would not constitute non-inferiority. A more appropriate non-inferiority margin might be set at <35m (a conservative margin), based on mean clinically important distance (MCID) reported in several studies. The MCID in patients with coronary artery disease during cardiac rehabilitation has been noted to be 25m *(Gremeaux et al, Arch Phys Med Rehabil Vol 92, April 2011; 611-619).* Although the MCID is population specific, and Gremeaux's population may be slightly different (coronary artery disease after acute coronary syndrome) to the SCAR population, the magnitude of MCID is within that range. In chronic heart failure patients MCID was 32m (*Shoemaker et al, Cardiopulm Phys Ther J. 2013 Sep; 24(3): 21–29*). Across several disease groups, range was found to be between 14-35m (*Bohannon et al, Journal of Evaluation in Clinical Practice Volume 23, Issue 2, pages 377–381, April 2017).* b) Choice of non inferiority margin- references If the authors wish to keep the non-inferiority margin at 60m, this needs to be justified with more appropriate references. On page 18, in Statistical analysis, "The non-inferiority margin was informed by the fact that a 6MWT distance of 60m equates to an improvement of approximately 0.5 metabolic equivalents (METs) ***reference needed*** which leads to a 10% reduction in all-cause mortality (47). Cited reference 47 does not state any relationship between METs

	and mortality, rather measured peak oxygen consumption (Vo_2) and mortality. Any relationship between METs and mortality based on reference 47 is inferred. Perhaps this could be made clearer, or a different reference cited.

REVIEWER	Andrew Hirschhorn MQ Health Physiotherapy, Australia
REVIEW RETURNED	05-Dec-2017

GENERAL COMMENTS	2. No abstract was included 4. There is no description of the cardiac rehabilitation interventions to be used in the trial 5. While it is stated that ethics review will be sought for the trial, it seems that this is yet to be obtained. There is not enough detail on how informed consent will be obtained from participants. 6. No discussion of how cost-benefit/safety aspects will be defined or analysed. 7. Not comprehensively described. No discussion about how the economic analysis is to be performed. The manuscript as reviewed reads as a within-institution research planning document, rather than a publication-ready study protocol. The manuscript needs significant editing particularly in regards to the introduction, and sections 8 through 11. It is undoubtedly a research project of worth, and I commend the authors for planning its undertaking.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Karen Chia
Institution and Country: UNSW Rural Clinical School, Coffs Harbour, NSW, Australia
Please state any competing interests: None declared

Please leave your comments for the authors below

This protocol aims to answer a highly relevant clinical question. Patient and public involvement in development of the protocol is very commendable. A few points require clarification. Please see attached file.

I read your protocol with great interest- thank you for the opportunity to review. Your project addresses a relevant, worthwhile topic. The protocol is well written and I look forward to the outcomes. Just a few minor points for clarification:

1) Consent

In Australia, the recommend period between providing potential participants with information and then obtaining informed consent is one week, to give participants time to process the information without any time pressure. It appears that it may be as little as >24hrs in your study. Perhaps this is standard

practice in the UK? I see that you have Ethics approval, so I understand that this may not be an issue in the UK.

Normally in the UK, a minimum of 48 hrs is specified in trial protocols. Due to the potential for a limited recruitment window in this trial, the ethics committee were happy to approve our request for 24hrs.

2) Intervention

I would appreciate a little more detail here (for example, how much time is allocated to each component of CR), so that readers can see if their cardiac rehabilitation services are comparable, and also to allow reproducibility of your results.

We appreciate this suggestion – we have added more detail as to what constitutes usual care in the UK. Attributing potential times to the early CR group exercises is a little difficult as it will be very variable depending on the ability of the participant. The key parameter for all CR in the UK is individualisation – we have made every effort to maxmise this rather than assigning set times to each component of the exercise programme, thus avoiding a 'one size fits all approach'. We hope this is an acceptable rationale. Also, we are recording the actual amount of exercise undertaken and will report this when writing up the completed trial.

I note in Figure 1 page 36 or 61 overall, titled "Trial Flow Chart: Figure 1: Flow of participants through the study" it is mentioned that the intervention will be of 1 hour duration. This is not specified in the text, or in "Figure 1: Study flow chart", but would be useful to include in either the final flow chart or text.

We have added this to both figure 1 and the manuscript text.

It would also be helpful to know if there are other differences in the exercise prescription between intervention and control group, for example in terms of supervision ratio. I note that the early CR group will have an individualized programme. Does this mean that there will be fewer patients in the group compared to the control group? Or will numbers be kept the same? If there is a difference in supervision ratio, this may be a confounder.

Thank you for the comment. We have now made this clearer in the manuscript. Both groups will undertake their exercise session in the same gym, at the same time, with the same level of supervision. For clarity, by 'individualised' we refer to the exercise prescription rather than the level of supervision. Both trial groups will have individualised prescriptions.

3) Statistical analysis

Non-inferiority trial:
Sample size calculation for non-inferiority trial noted. A SD of 112m is conservative, as noted by the authors. First sentence could be re-worded to minimize confusion- I suggest removing "allow a switch to a superiority test", as this may confuse readers. The test/analysis itself will not be switched, rather if the CI is >0 then early CR is concluded superior to usual care.

We have amended this as suggested

Clarify the statistical analyses:
There is, I presume, a typographical error that is confusing – "The non- inferiority margin has been set at 60m by the research team. Early CR will be concluded non-inferior to usual care CR if the lower bound of the 95% CI interval for the mean difference of changes at the end of CR is above 60". I assume this is meant to be: the lower bound CI for the mean difference of change between groups is less than 60/ or above minus 60 (less than 60 is a less confusing way to write). Please clarify.

Thank you for spotting this – we have amended this in the manuscript to 'less than 60'

4) Choice of non-inferiority margin

This is the area of the study that I think needs the most revision.
The authors are to be commended for clearly stating how they have set this margin. However, there are a few issues noted:

Thank for this comment. It is a very important issue that we felt necessary to address in detail. We have amended this section to reflect your comments, and hopefully it is now clearer, more accurate and justified.

a) Clinical relevance- the non-inferiority margin of 60m is too large.

A mean difference between groups of 60m in clinical practice would be considered relevant and therefore, if the difference between groups was up to 60m, would not constitute non-inferiority. A more appropriate non-inferiority margin might be set at <35m (a conservative margin), based on mean clinically important distance (MCID) reported in several studies. The MCID in patients with coronary artery disease during cardiac rehabilitation has been noted to be 25m (Gremeaux et al, Arch Phys Med Rehabil Vol 92, April 2011; 611-619). Although the MCID is population specific, and Gremeaux's population may be slightly different (coronary artery disease after acute coronary syndrome) to the SCAR population, the magnitude of MCID is within that range. In chronic heart failure patients MCID was 32m (Shoemaker et al, Cardiopulm Phys Ther J. 2013 Sep; 24(3): 21–29). Across several disease groups, range was found to be between 14-35m (Bohannon et al, Journal of Evaluation in Clinical Practice Volume 23, Issue 2, pages 377–381, April 2017).

b) Choice of non inferiority margin- references

If the authors wish to keep the non-inferiority margin at 60m, this needs to be justified with more appropriate references.

On page 18, in Statistical analysis, "The non-inferiority margin was informed by the fact that a 6MWT distance of 60m equates to an improvement of approximately 0.5 metabolic equivalents (METs) reference needed which leads to a 10% reduction in all-cause mortality (47).

Cited reference 47 does not state any relationship between METs and mortality, rather measured peak oxygen consumption (Vo2) and mortality. Any relationship between METs and mortality based on reference 47 is inferred.
Perhaps this could be made clearer, or a different reference cited.

We have chosen to continue with 60 m as the non-inferiority margin for this trial. We hope we have now justified this clearly, with appropriate references, in the manuscript. According to the literature, an

improvement of 1.0 ml/kg/min in cardiorespiratory fitness equates to approx. 10-15% reduction in mortality (ref 47). We believe this is clinically relevant and would expect it to be an achievable goal of CR (early or usual care). Therefore, if the early CR group achieve an improvement that is within 1.0 ml/kg/min of that achieved by the usual care group, we can conclude that early CR is not inferior to usual care CR i.e. the early CR group achieve a reduction in mortality that differs less than 10-15 % from that achieved by the usual CR group. We further justify this on the basis that the 6MWT is an accurate estimator of mean peak VO2 within a clinical population (although not for individuals) (ref 30). Using the equation proposed by Ross et al (ref 30), an improvement of 60 m in 6MWT distance, in a population with a mean baseline distance walked of 250m, would equate to a mean estimated improvement of 1.0 ml/kg/min.

Reviewer: 2
Reviewer Name: Andrew Hirschhorn
Institution and Country: MQ Health Physiotherapy, Australia
Please state any competing interests: None declared

Please leave your comments for the authors below

Comments 1 and 3 do not appear to be listed

2. No abstract was included

The abstract is included in both the manuscript (page 2) and scholar one submission system. Perhaps there was a technical problem?. We have made every effort to ensure it is included in the resubmission (page 2).

4. There is no description of the cardiac rehabilitation interventions to be used in the trial

The 'intervention' section (lines 10-36) of the manuscript provides detail and appropriate references to the CR interventions to be used in the trial. Also table 2 provides more detail on the early CR intervention. To expand, we have added the specific CV exercise equipment that will be used, and examples of the muscular strengthening exercises.

5. While it is stated that ethics review will be sought for the trial, it seems that this is yet to be obtained. There is not enough detail on how informed consent will be obtained from participants.

Thank you. Full Research Ethics Committee, HRA and R&D approval have been obtained for this trial (UK approvals). Lines 26-50 of the 'study procedure' section give a relatively detailed description of how informed consent will be obtained. We hope that this satisfies this query.

6. No discussion of how cost-benefit/safety aspects will be defined or analysed.

There is a description of the economic analysis on p.17 lines 14-32, safety on p.17 lines 36-50 and cost effectiveness analysis on p.19 (line 34) to page 20 (line 50), and table 4 (pg.20). We hope this is sufficient detail – we have based the level of detail on previously published protocols in BMJ Open (including one of our own papers)

7. Not comprehensively described. No discussion about how the economic analysis is to be performed.

As above

The manuscript as reviewed reads as a within-institution research planning document, rather than a publication-ready study protocol. The manuscript needs significant editing particularly in regards to the introduction, and sections 8 through 11. It is undoubtedly a research project of worth, and I commend the authors for planning its undertaking.

We appreciate your support for the conduct of this trial. We request clarity as to your reference to the introduction, and sections 8-11. If this concerns pages 42 and 54-57 (which it seems to) then it is indeed 'a within-institution research planning document' – it is the trial protocol that was submitted to ethics. The actual manuscript introduction is on page 4.

VERSION 2 – REVIEW

REVIEWER	Karen Chia UNSW, Australia
REVIEW RETURNED	14-Jan-2018

GENERAL COMMENTS	*Early initiation of post-sternotomy cardiac rehabilitation exercise training (SCAR): study protocol for a randomized controlled trial and economic evaluation* Reviewer's response to revision 1: Dear authors, Thank you for your comments and revision. My only outstanding comment is with regard to the choice of non-inferiority margin. I appreciate your further clarification of your decision to keep the non-inferiority margin for the 6MWT at 60m. However, I still do not agree with keeping the non-inferiority margin at 60m (the link between 6MWT and mortality based on an inferred variable (peak oxygen consumption, which is not being directly measured) is too tenuous a justification), and I am concerned that others reading your papers may also view a non inferiority margin of 60m as too large. However, I see that you have allowed for a very generous standard deviation of change (112m) post CR in your power calculation. I would have kept the non-inferiority margin at 35m (based on published minimal clinical important difference in 6MWD as noted in my previous comments) and used a SD of 57m, based on your citation in your text. Even though this is the lower limit of the 6MWD SDs you mentioned, clinically it's reasonable to use this. (Please note that unfortunately, as reference 46 was incorrect I was unable to locate the correct citation that you referenced as 46, so have not been able read this reference. Please review reference 46 and correct this). Using these numbers, sample size required is slightly less than your calculations (see below). Therefore although we may not agree on the

	calculations, the outcomes for sample size are similar.  **Technical note** Calculation based on the formula: $n = f(\alpha, \beta) \times 2 \times \sigma^2 / d^2$ where σ is the standard deviation, and $f(\alpha, \beta) = [\Phi^{-1}(\alpha) + \Phi^{-1}(\beta)]^2$ Φ^{-1} is the cumulative distribution function of a standardised normal deviate. Thank you for the opportunity to review your protocol and best wishes for the trial. Sealed Envelope Ltd. 2012. Power calculator for continuous outcome non-inferiority trial. [Online] Available from: https://www.sealedenvelope.com/power/continuous-noninferior/ [Accessed Fri Jan 12 2018].

VERSION 2 – AUTHOR RESPONSE

Dear Reviewer

We have included the first participant enrolment date in the manuscript as requested.

We thank you for your detailed and considered review of the 2nd draft of this manuscript. After much deliberation, we have amended the MCID to 35 m in accordance with your recommendation and the published literature. Thank you again for your thorough appraisal and the time you have spent in review.

Gordon McGregor