Author’s response to reviews

Title: A rehabilitation intervention to promote physical recovery following intensive care: A detailed description of construct development, rationale and content together with proposed taxonomy to capture processes in a randomised controlled trial.

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Version: 2 Date: 1 December 2013

Author’s response to reviews: see over
Dear Editors-in-Chief,

Re: Manuscript MS:2853591821020789. A rehabilitation intervention to promote physical recovery following intensive care: A detailed description of construct development, rationale and content together with proposed taxonomy to capture processes in a randomised controlled trial.

Thank you for the opportunity to respond to the reviewers comments regarding our manuscript. We are very keen for our paper to be in the published peer reviewed literature as it will form an important part of the context for our RCT, and we believe prove valuable when interpreting our trial results. Inevitably, the detail we will be able to include in our main trial report will be limited given the complexity of the trial design and numbers of outcomes, together with the inclusion of both quantitative and qualitative methods of evaluation.

We value the detailed comments made by two of the reviewers, which have resulted in a very substantial revision of the manuscript. We have completed this detailed revision quickly in the hope that an early decision may be possible given the first review process seemed rather protracted (we submitted the manuscript in June 2013).

We include a version with all changes shown in “track changes”, but given the extensive revision undertaken (largely in response to reviewer 3) we include a version with all track changes accepted, which may be easier to assess. We respond to each comment made by the reviewers below, and note where changes have been made using page numbers in the version with changes accepted where relevant (for ease of review). As reviewer 3 in particular made many comments in a lengthy narrative review we found it difficult to pick out a series of individual points to preface each of our responses below. We therefore provide context to each of our responses, which are intended to address the points raised. We also include a single eSupplement that includes the materials that are not published with the trial protocol paper. Some of these were referenced to the trial website, but to ensure longevity of the link to this piece of work we think it best to include them as a document directly associated with this paper.

Specific Responses to reviewers
Reviewer 1

No comments

Reviewer 2

Major revisions

My only major concern about this manuscript is that of overlapping publication with the Walsh et al (2012) publication of the RECOVER study protocol. This article is appropriately cited (#17). The ICMJE recommendations do not specify an approximate amount of allowable duplicate publication. However, there seems to me to be considerable overlap. Perhaps I have this impression because of looking at the supplements that were added to this submission, some of which were in the Walsh article. This may not require revision, but rather an explanation by the authors to the editors and a judgement by the editors as to whether the amount of overlap is acceptable to the journal. If it is considered excessive, major revisions would be required.

We acknowledge that there is overlap between this paper and the published protocol paper. Our intention is not for duplicate publication, but rather complementary pieces of work. We have therefore removed the reference and detail of outcomes, and all supplementary materials that are published with the protocol paper. The remaining content is fully focussed on development and full description of the intervention, and the taxonomy of description. We have included a single supplementary file with the important additional materials relevant to the intervention.

Minor revisions

1. Add ‘former’ prior to patients on p. 5 (my page numbering from 1st page of body of text), line 11. The word “former” has been added where relevant throughout the revised text.

2. Please clarify the statement p. 6, para 2 (This was . . . identified as an excess treatment cost for the purposes of the economic evaluation, and specific appointments (were) made . . . ). It is not clear why these two points are linked. Our meaning here was that we developed a specific job specification for the GRAs that delivered the complex intervention, and appointed them through interview through an interview process. The “excess” treatment cost meant an additional treatment cost above existing care, which was relevant to the economic evaluation. We have changed the wording of this section (which has been moved with the restructuring to page 10).

3. Please clarify the numbers given for expected ICU mortality rates of 20-25% (p. 6, para 3). This is exceptionally high for Western countries and higher than the rate cited in the Walsh article in which the main study protocol is published. Do you mean in-ICU mortality or that plus mortality within the 3-month followup period? Even then the rate would be high, and no reference is given to support the numbers given. The expected mortality was for combined ICU and hospital mortality for all ICU patients who require >48 hours of mechanical ventilation, not the intended study cohort for the trial in whom we predicted mortality of 12% between randomisation and 3...
month assessment (detailed in the protocol paper). These outcomes are typical of ICU populations in the UK, and most western countries, and equates to Standardised Mortality Ratios of around 0.8-0.9 against the APACHE II model. The point we make in the discussion was the issue of competing risk of death when mortality is high and the primary and most secondary outcomes require assessment of surviving patients. We have re-worded this section to increase clarity (page 9).

4. In the discussion (p. 9, line 4) it is stated that this is a new area of research. While this may have been somewhat correct at the time of development of the study protocol, there has been more research in the area published in recent years. This further research would obviously be cited and discussed in relation to the results of the RECOVER study, but the authors may wish to consider whether more recent findings should be included in the Discussion in the present manuscript. In particular, the lack of assessment of sleep and its relationship to recovery, a finding that is reported in one of the current references, Orwelius et al (2010) (ref #24) and others, might be mentioned as a limitation of the study. We agree that it is relevant to include reference to more recently published trials, and include these in the discussion (Page 13) in a clearer section on potential weaknesses of our design. We also discuss the compromise required between including many intervention components (but risking inadequate development of each element, reduced protocol compliance and inadequate process description) and a potentially less “comprehensive” intervention (but with fuller justification and description).

5. On p. 10, line 2, it would assist the reader if the authors expanded on the main points stated as the ‘. . . information we have provided’. We have re-structured this part of the paper.

Discretionary revisions

6. The 90-day followup is relatively short but probably appropriate for the primary outcome of physical recovery, with other studies showing minimal change after this time. Whether it is long enough for study of mental health outcomes is not clear at present, but it may be a limitation that should be acknowledged, at least in the publication of the results. Our choice of 3 months for the primary outcome is justified in the text (page 9-10). We also follow up patients at 6 and 12 months. We agree with the reviewer that the optimum timing for outcomes is uncertain, but believe that 3 months is relevant because it is close to the time of maximum intervention (the acute hospital stay) and also is likely to have discriminatory value based on our pilot work, and observational studies (especially in relation to physical function components of HRQoL measures). The risk of ceiling effects in these measures is low at this time point. We have not added a detailed further discussion of these issues as we have removed the description of outcomes, which are included in the protocol paper.

7. The use of the HADS, a widely used instrument, has recently been questioned. It was the subject of an editorial on ‘time to abandon the HADS’ (Coyne JC, van Sonderen E. No further research needed: abandoning the Hospital Anxiety Depression Scale (HADS) J Psychosom Res. 2012 Mar;72(3):173-4), notwithstanding its widespread use. This is
possibly another limitation that should be acknowledged, at least in the publication of the results. We accept the limitations of HADS, but this is a secondary outcome and not central to the study hypothesis of altering physical recovery. We have not therefore included specific mention of this issue in the paper.

Reviewer 3

General comments

The reviewer suggests that our process is not repeatable in its current form. We have not set out to describe a generic method of developing a complex intervention. Rather, we have adhered to the MRC guidance which emphasises a cyclical iterative process responding to the data that emerge. The point of this manuscript is to describe our experience in detail. We believe this may help others undertaking similar complex intervention development, either through the approaches we used or the specific data we included. We have re-structured the manuscript substantially to present the process more like a framework, namely sections addressing “development of content”, “defining the timing of the intervention”, “the method for delivering the intervention”, and “final construct and taxonomy for describing the intervention”. We have not included the ideal framework as requested by the reviewer as this was not our aim. The point of our paper is to contribute to the literature that might develop or define the ideal structure in the future. We also think the MRC framework implies that there is unlikely to be a “one size fits all” for this type of research, and therefore implying our method was ideal could be misleading.

We have re-structured the paper to reduce any repetition, use the revised framework described above, and present the development of content in a more logical sequential manner. We believe this makes it easier to understand how we chose the different intervention components and their justification, and links referencing closely to the selection of elements especially for those originating from the local pre-trial work.

We have included specific reference to weaknesses in the discussion in a revised section (page 13), including potential sources of bias and effect modification in the revised discussion.

Major revisions

1. Restructure manuscript into generalizable framework as suggested in general comments. We have re-structured the manuscript (see above responses to general comments)

2. Was the literature review systematic? Whilst the details might be beyond the scope the authors are suggesting their method is repeatable and so some key information should be provided. We have clarified that we did not undertake a systematic review at the start of the development process (we did undertake a detailed literature review but not a formal systematic review; page 6-7), but that the NICE systematic review became highly relevant during the intervention development (page 7). As we developed the intervention iteratively over 5 years, the NICE SR became an important part of the process which was our rationale for the GDG chair joining the team in an advisory capacity prior to the trial (and including him as an acknowledged co-author for this important contribution). We have specifically mentioned this as a possible weakness on page 13.
3. **Summarize key points in each of the sub-sections of the Results section and reference previously conducted work with key points rather than restating significant text of the results/findings.** We have re-structured the manuscript to account for the repetition alluded to by the referee, and create a clearer flow through the description of the development process.

4. **The paragraph about why the ICU stay was excluded from the intervention should be moved up to the end of Paragraph 1. This is a critically important decision that has been made by the authors, as the literature acknowledges that early intervention is critical given patients lose muscle mass in the ICU stay (Poulsen et al., 2011 CCM 39:456-61). Many papers have demonstrated the feasibility at least if not always the benefit of commencing rehabilitation within the ICU (Schweickert et al., 2009 Lancet (as referenced by the authors); Pohlman et al., 2010 CCM: 38(11):2089-94; Berney et al., 2012 Physical Therapy 92(12):1524-1535; Denehy et al., 2013 Crit Care 17(4): R156; Zanni et al., 2010 J Crit Care 25(2):254-262; Skinner et al., 2009 Critical Care and Resuscitation 11(2): 110-115; and this will be one of the most significant criticisms of the completed RECOVER trial. This is the authors’ opportunity to make a watertight case as to their reasons for the ICU stay exclusion and they need to expand on the current text pertaining to this, particularly as the current text is not necessarily verifiable with data or published resources (and no references are given).**

We agree with the reviewer that the issue of mobilisation during ICU will be important to understanding our trial. We also agree that it may be a criticism of the design. We have expanded the reasons and justification for not including this period in the controlled part of the trial on both practical and methodological grounds (page 9). We also include consideration of this issue in the discussion in the new section considering weaknesses of our study (page 13).

5. **As per Point 3, the authors need to provide stronger justification as to why the intervention period was ceased at 3 months and provide relevant data/references to justify the assumption that this would cover up to a period of living at home or other placement for most patients.** We have included specific additional consideration of why the intervention duration was chosen as 3 months in the “timing” section within the re-structuring (pages 9-10). We also discuss this in the potential weaknesses section (page 13). Specifically, in the section on the “final construct and taxonomy” (pages 10-11) we highlight that we have designed our intervention for 3 of the 5 key stages set out in the NICE guideline, namely “ICU discharge”, “during ward-based care”, and “at discharge home” (excluding “during intensive care stay” and formal “follow up at 2-3 months following hospital discharge”).

6. **More justification should be given as to why the intervention was focused primarily on physical rehabilitation; in particular with referencing.** We include specific justification for why we chose to focus on physical recovery rather than psychological or cognitive issues throughout the sections on development (pages 6-10) and specifically explain why we decided not to include formal psychological intervention on page 9. We would highlight to the editors and reviewer that we believe this is the most comprehensive attempt yet undertaken to provide and describe in detail a multifaceted rehabilitation during the early post-ICU period.

7. **Discuss the implications of using 5 years to develop the intervention. Is this feasible? Should we recommend this for all intervention development? How was the constant...**
updating of referencing/literature undertaken/incorporated? How relevant is this process if it takes 5 years? The issue of development over 5 years is a potential strength and weakness. We consider this in the revised discussion (page 13), where we are clear that the final end to the iterative process was when development and trial design reached a point where external independent peer review, and the decision of the grant funder, considered the study should be funded. Again we stress that our intention in this paper was not to define the optimum framework or structure for a complex intervention development, rather to describe our experience of this process in detail in a manner that will be useful to others generally, and specifically to understanding the RECOVER trial. As stated above we believe this iterative “loose” process is entirely consistent with the recommendations of the MRC revised framework, and in fact is what is recommended.

8. Why did the authors choose to provide intervention after discharge home as a key point in the study given the results of the PRACTICAL trial (a negative trial, cited as one of the influential studies affecting the development of the intervention)? The PRACTICAL trial utilised a self-help physiotherapy intervention, with self-monitoring and outpatient follow up at 3 and 9 months at an outpatient clinic. As the reviewer notes this showed no demonstrable benefit (discussed on page 10). Our intervention therefore used supervised multidisciplinary intervention in hospital, with programmed follow up by telephone to provide advice and support in the early post-discharge period. The support post hospital discharge we include was in response to perceived patient need, as noted from the qualitative work that contributed to our intervention development (see page 7 “work with patients and families” and table 3). We did not include the formal follow up element at 2-3 months after hospital discharge or later because the PRACTICAL study was negative (see page 13). We were clear that we were intervening for 3 of the key stages identified in the NICE guideline (see above) for which research is lacking, but excluding stage 5 (“follow up at 2-3 months following hospital discharge”) because the PRACTICAL study RCT had showed no clinical or cost-effectiveness in the UK setting.

9. Why were the multiple other studies that would have come to the authors attention during their literature review (e.g. Burtin et al 2009 CCM; Morris et al 2008 CCM; Bailey et al., 2007 CCM; Martin et al., 2005 CCM; Chiang et al 2006 Physical Therapy; Zanotti et al., 2003 Chest) not included in the rehabilitation trials that influenced intervention development? We were aware of the other trials and evidence that emerged during the intervention development, including those noted by the reviewer. We cite those that strongly influenced development and were of highest methodological quality. It was beyond the scope of this article to include a description of all the published studies, and we re-state that this paper is intended to describe the process we went through in developing the intervention to be used in the RECOVER trial.

10. Some of the text around the GRAs (Lines 4 to 5 in particular) lacks clarity and is difficult to understand. Please rephrase. We have re-worded the section about the GRAs, which is now included in the section termed “method for delivering the intervention” (page 10). We have added more detail around GRA competency and training to this section.

11. Tables 4 and 5 are the most useful part of the Results section (indeed the crux) and should be given higher emphasis and moved up in the text. More detail could be provided in Table 4 (not in text but in succinctness) – for example – the component of the intervention “Meeting with ICU consultant” – is this the GRA, or the patient, or both? Obviously these
probably all relate to the patient, but this could be stated explicitly, either in the Table
header/footer or specific e.g. patient meeting with ICU consultant. The theory/rationale
aspect of Table 4 in particular should be referenced so that the reasons for the
decisions/inclusion are transparent and the reader can examine how evidence-based the
theory/rationale was. In addition, the intervention would not be repeatable by following
the Table. For example on the ward, regular assessment by GRA is noted as a component
of the intervention – what is “regular” assessment? Daily? Twice daily (as described by
others (Berney et al., 2012 PTJ)? Weekly? Using words such as regular, frequent etc are not
specific enough. What was the frequency of therapy sessions provided or aimed to be
provided? Was there a standard minimum? The authors have nominated that physical
recovery was a focus – was physiotherapy prioritized over dietetic or occupational
therapy? In the re-structured manuscript we include the section about taxonomy as the final
part of the description of the intervention (pages 10-11), with table 4 identified as the
method of fully describing what we planned to do, and how we intend to describe these
processes. We have omitted table 5 and 6, because these are included in the protocol paper
and trial analysis plan which are referenced appropriately. We have made some
modifications to some elements of table 4 as suggested by the reviewer. Most of the
information around timing and frequency requested by the reviewer was present in the
original table under the sections headed “flexibility” and “timing”. The theory/rationale
referencing suggested by the reviewer would be a repetition of the description of the
intervention development, as this table is intended to summarise this section in the form of
a taxonomy. We are unsure what the reviewer means in relation to our table not enabling
repetition of the intervention. Table 4 together with the text of the paper provide a fuller
description of a post-ICU rehabilitation intervention than has been included with any
previously published work. This is a major aim of this manuscript. The absence of exact
frequencies is intentional, because the intervention is tailored to the individual. This is the
reason for including the column describing “flexibility to individual patient” for each
component and rating this as low, moderate, or high. As the reviewer notes, physical
recovery was the main objective of our intervention. This requires coordinated provision of
physiotherapy, dietetics, occupational therapy, and sometimes speech/language therapy.
This was the rationale for the GRA role providing all aspects of care in a coordinated manner.
This approach distinguishes our study from other trials that focussed primarily of physical
therapy interventions. The description of the intervention development highlights these
issues, and our rationale for integrating all into the GRA role.

12. Given the aim of the manuscript is to describe the intervention, less text is required for the
trial outcome measures/qualitative data measurement/analysis (all of this information
should be located in the trial protocol manuscript). Re: outcome measures, it is sufficient to
say that the detailed description is available in the trial protocol paper, to cover this area
off for the reader who might be interested as to how these were selected. In my opinion,
the authors could almost reproduce this manuscript in the context of selection of outcome
measures as that is almost if not more important than the description of the intervention
given the sparse literature on the best measures (i.e. the ones with the strongest
psychometric properties) in the population of patients with and following critical illness).
Remove also the text at the end of paragraph five in the final construct section which
pertains to outcome measures; and remove Table 7. Remove the text at the end of the
13. **Does the text in the first paragraph of the Taxonomy section in the Results “pilot data indicated that these measures can be collected on a weekly basis from patient case notes for both intervention and usual care groups by research staff independent from clinical teams treating patients” mean that the intervention data will be extracted from the medical record retrospectively?** The text goes on to say that GRAs will be recording their treatment prospectively using a dedicated proforma – does this mean usual care won’t be documented in this manner and be subject only to retrospective audit? There are significant implications to the validity of the data should this be recorded retrospectively rather than prospectively. The data will be collected prospectively using a tool to extract process data from the patient record. We have removed this section because it relates to details of protocol that are included in the trial protocol paper.

14. **The discussion focuses on addressing whether the questions set out in the MRC complex intervention guidance have been addressed. This method is fine for the Discussion however the answers to the questions are wordy and general. They should be succinct and specific. Please revise. In particular the first and third answers say a lot (of words) without actually saying very much. I also don’t agree with some of the authors conclusions (e.g whether the intervention has a coherent theoretical basis) based on the gaps in specificity and inability to replicate the author steps based on what is currently presented. I encourage the authors to revise in the context that the theoretical basis for the intervention is much clearer). In addition, the authors are advised to compare their intervention with the interventions delivered by others in randomized controlled trials (referenced throughout the reviewer comments and in the manuscript) and discuss the differences, similarities and why these exist (or may exist). I think based on the detail presented, the answer to the third question is no. I encourage the authors to consider gaining external review of the manuscript by somebody uninvolved in the development of the trial (aside from the reviewers!) to gain an additional understanding of whether that individual could replicate the intervention based on the detail provided in the manuscript. All I feel I could do would be to provide a GRA, provide them some general training (and be unsure when they achieved the standard) and provide specific assessments/information at specific time points. This could result in an incredibly different intervention than that received in the RECOVER trial. The answer to the question regarding effectiveness and cost-effectiveness is an excellent example of the authors answering the question specifically and well (although the efficacy section is a bit wordy).** We have substantially revised the discussion section to address the issues raised by the reviewer. Specifically, we have removed the questions posed in the MRC complex intervention framework that were set out in the introduction and integrated the discussion text to improve flow. We believe the re-structured paper does allow the structure and content of our intervention to be replicated, but the actual frequency of the different therapies delivered to the intervention (and control) groups will be a key part of the process evaluation in the trial itself. This is inevitable as the intention is to provide individually tailored rehabilitation according to ability and need. We include comparison with the interventions in recently published trials in the section considering possible weaknesses of our intervention design.
We have not included all the reviewer text here but respond to the points made as follows:

For the protocol paper the supplemental documents reference the trial website within the Edinburgh Clinical Trials Unit website. This site will likely highlight active trials going forward, so to ensure the documents remain accessible to readers and are easily linked to this manuscript, we have prepared a single eSupplement of all the relevant materials. This is now cited throughout the manuscript to a single resource. For the James Lind report, we now cite the weblink to this resource. We think this is the best way to ensure the documents, which are important to provide reproducibility to the intervention, are accessible with this paper. In relation to further detail around the assessment of competency during training of the GRAs this detail has now been added to the supplementary file. An example lay summary has also been included based on the proforma developed for the trial. We have also edited the text to ensure clear referencing to the supplementary trial documents.

Minor essential revisions

1. Avoid the use of the personal voice (“we have provided”) and use the scientific “a detailed account has been provided”). We appreciate the reviewer’s personal preference for the avoidance of the personal voice approach, although this is widely used in medical writing as it provides a clear, easy to understand narrative. We think this approach is particularly suited to this manuscript, which is why we chose it, and therefore have retained it. If the editors feel strongly it should be changed we can make these alterations.

2. Discussion opening sentence implies that the intervention is designed to improve disability at three months following ICU discharge, however the trial has longer coverage. Please reword or delete this text. We have re-worded the opening line of the discussion.

3. The introduction should be bolstered by including references for some of the statements (e.g. the trajectories of recovery vary – how do we know this? Where does the terminology come from? Rehab interventions evaluated should be ref’d (first para last sentence). Suggest including some more recent references in the Introduction, particularly Denehy et al., 2013 Crit Care. In addition, there was a recent reference that did report on usual care in the context of a clinical trial (Berney et al 2012 PTJ) which should be included in paragraph four of the introduction and used by the authors in the Discussion. We have revised the introduction and included some additional references and relevant text.

4. State the intervention evolved (para 2 of methods) in response to the review process rather than developed. The text of the methods has changed substantially, but we have used the word “evolved” in preference to “developed” as suggested. We agree this is a better term.

5. Specify details of the interviews accessed at Healthtalkonline. Were they all used? Some used? Which ones? Healthtalkonline includes a wide range of patient experiences. Many are relevant to the intervention we developed. It is impractical to reference specific content, but we feel it important to acknowledge this important patient-centred resource as it influenced our work.

6. Rephrase the manuscript especially method/results in the past tense. We have undertaken a substantial redrafting in response to the comments from reviewer 3. We
believe this has improved the flow and structure without losing the sense of the "journey" we wished to share from our research.

Editorial Request

Please state clearly whether or not you have funding in the acknowledgement section. If there is no funding, please state this.

The funding body (Chief Scientist Office, Scotland) has now been included in the acknowledgements section.

We hope these extensive revisions are satisfactory.

Yours sincerely

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