PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	A protocol for a process evaluation of a randomised controlled trial of family-led rehabilitation post stroke (ATTEND) in India
AUTHORS	Liu, Hueiming; Lindley, Richard; Mohammed, Alim; Felix, Cynthia; Ghandi, Dorcas; Verma, Shweta; Tugnawat, Deepak; Syrigapu, Anuradha; Ramamurthy, Ramaprabhu; Pandian, Jeyaraj; Walker, Marion; Forster, Anne; Anderson, Craig; Langhorne, Peter; Murthy, GVS; BR, Shamanna; Hackett, Maree; Maulik, Pallab; Harvey, Lisa; Jan, Stephen

VERSION 1 - REVIEW

REVIEWER	Mertens, Vera-Christina, Postorctoral researcher Luxemburg University Research unit INSIDE Luxemburg
REVIEW RETURNED	12-Apr-2016

GENERAL COMMENTS	Thank you for giving me the opportunity to review your manuscript. The current manuscript describes the design of a process evaluation of the ATTEND trial which will be done before the effectiveness evaluation of the trial. It is a welcome and missing approach that the complementary design of process evaluations alongside clinical trials is published. In addition, the aim of this study is very important: to provide an overview of how to disseminate practical approaches in low and middle-income countries. This is a well written manuscript with a clear study design of a complex process evaluation. The methods of the process evaluation are state of the art and make me looking forward to the results of the process evaluation and the effectiveness evaluation. I have some fairly minor comments cq. suggestions which I outline below. Introduction Describe the primary and secondary outcome measures of the mother trial. Either in a small overview or in the text. (e.g. p. 7) Study design Could you elaborate on the setting of the location of the interviews with the patients and carers? (p. 12, Study Design) Evaluation of costs With the data you are collecting, you could even perform a Cost-Effectiveness Evaluation (CES) or a Cost-Utility Evaluation. Are there reasons not to do so? (p. 13) Additionally to the previous point: Which approach is chosen for the calculation of the costs due to the carer's additional responsibility.

	Please elaborate on this. (p. 13) Analysis plan for the process evaluation Could you give more insights in the process of triangulation of quantitative and qualitative data? More precisely, how will the findings of the current process evaluation weight in the outcomes of the effectiveness evaluation? (p. 14f) I am looking forward to you reply. Again, thank you for the opportunity to review.

REVIEWER	Barbara Lutz University of North Carolina-Wilmington Wilmington, NC United States
REVIEW RETURNED	05-May-2016

GENERAL COMMENTS	This is a very interesting description of the protocol for a process evaluation of a large randomized controlled clinical trial (RCT), the ATTEND trial, being conducted in India. Given the complexity of conducting intervention trials in the context of the community setting (and all the variation that can ensue), this is an important topic. • As described, the main study sounds like a pragmatic RCT trial, if so please include this in the description. A little more information about the main study would also be helpful, e.g. number of participants per site, how they are recruited, the consent process, length of the intervention, number of visits per patient/family, how they are randomized, etc. • It seems the focus of this process evaluation in on the intervention portion of the RCT. How is the usual care portion being evaluated? Please clarify. • In several places the authors refer to identifying “causal” mechanisms. Please provide evidence as to how a process evaluation can determine cause and effect. • What type of training/expertise do the team members have in qualitative research, data collection (interviewing) and data analysis? • Pg. 10, l. 3: How will the cost to families be measured? • Pg. 11, l. 34-53: Will this data be collected throughout the trial or after the trial has been completed. If collected during that trial, at what time points? • On pg. 13, l. 48: How will patients and caregivers be selected? How will they be consented? Please provide evidence as to the appropriateness of interviewing them together. What are the benefits and drawbacks of this approach? Since they will be interviewed together, what will happen if one of the dyad agrees to the interview and the other declines the interview? How are the assessor’s “blinded”? • Pg. 14, l. 12: Please explain the meaning of the following; “Thematic analysis will be conducted alongside the interviews…”. • Pg. 14, l. 18: Please indicate how many dyads will be interviewed from usual care vs intervention group • Pg. 15, l. 40: How will indirect costs be calculated from the electronic case record? What types of data will be used for this calculation? • Please provide more detail about the use of grounded theory (GT) and triangulation. Based on the description provided this study does

	not fit the parameters of a grounded theory study. For example, there is no mention of theoretical sampling or building theory and the study is guided by 2 theoretical frameworks (which is not typical in a GT study). The paper needs a lot more detail about how grounded theory is being used with appropriate citations. Triangulation can be defined in many ways. Please be clear and specific about how triangulation is being used in this evaluation. Please provide relevant references for the qualitative methods and analysis. • Pg. 16, l. 18-21: The protocol indicates that any process issues that are discovered will be "fed back" to the usual management communication channels. What does this mean? And, if problems are identified and addressed how will this affect the ongoing trial? • This trial appears to rely significantly on family involvement, but there is no discussion about how the impact of this involvement is being measured, (i.e. caregiver burden, strain, depression, injury). Will this be assessed? If so how? If not why not (given the robust literature on this topic)? • What are the limitations of this type of process evaluation? How will they be addressed? Specific comments: • Pg. 8, lines 20-25: Consider using the word "can" instead of "will" in the following statement: "The context of each patient will…" – the word will is determinative and there is no supporting evidence of this. • Please review closely for grammatical errors throughtout, e.g. verb tenses, appropriate use of singular vs. plural. • Please be consistent with the term carer or caregiver. Figure 1: It's not clear how causal inferences will be made (or whether this is possible). The description of the ATTEND as a type of early supported discharge is not discussed in the manuscript text. Please revise the text to include this File 2: This interview guide is quite complex with many questions, and many which require "yes/no" responses. This is inconsistent with most qualitative research / interviewing. File 3: How will caregiver difficulties with providing care be assessed? File 3 & 4: Are these interview guides for patients and caregivers in both the usual care and intervention group? Since you are interviewing patients and caregivers together how will you ask the specific questions of each person? How will you prevent the responses of one person in the dyad from influencing the responses of the other? In File 4, pg. 33 specifically, how will you separate the patient's perspective from the caregiver's since they are being interviewed together? Overall, this is a very interesting and well written description of the protocol. The biggest issues are the lack of sufficient detail in some places and the likely inappropriate application of grounded theory and the lack of clarity about how data will be "triangulated".

VERSION 1 – AUTHOR RESPONSE

Reviewer One

Thank you for giving me the opportunity to review your manuscript.The current manuscript describes the design of a process evaluation of the ATTEND trial which will be done before the effectiveness evaluation of the trial. It is a welcome and missing approach that the complementary design of process evaluations alongside clinical trials is published. In addition, the aim of this study is very important: to provide an overview of how to disseminate practical approaches in low and middle-income countries. This is a well written manuscript with a clear study design of a complex process evaluation. The methods of the process evaluation are state of the art and make me looking forward to the results of the process evaluation and the effectiveness evaluation. I have some fairly minor comments cq. suggestions which I outline below.

1) Introduction- Describe the primary and secondary outcome measures of the mother trial. Either in a small overview or in the text. (e.g. p. 7)

Response: Thank you for this suggestion. The additional summary of the outcome measures of the ATTEND RCT is provided in Figure 1 which is a study flow chart from the published trial protocol. . Amendments made on: line 133, p. 7.

2) Study design- Could you elaborate on the setting of the location of the interviews with the patients and carers? (p. 12, Study Design)

Response: The interviews would be conducted in a private room in the hospitals or at the participant's homes. This is elaborated on line 269, p. 13.

3) Evaluation of costs - With the data you are collecting, you could even perform a Cost-Effectiveness Evaluation (CES) or a Cost-Utility Evaluation. Are there reasons not to do so? (p. 13) Additionally to the previous point: Which approach is chosen for the calculation of the costs due to the carer's additional responsibility. Please elaborate on this. (p. 13)

Response: This trial was designed with the intention of conducting an economic evaluation from a health system and societial perspective. As such relevant questions were asked by the blinded assessor regarding loss of family income (e.g number of hours of work taken off) due to carer's additional responsibility; and estimation of the such costs will be done using the average wage. There is a separate economic evaluation protocol outlining these details and assumptions, and proposed sensitivity analysis.

Amendments have been made on line 302-315 pg 14-15 to highlight the separate cost-effectiveness evaluation, and to provide further detail about the costs data used as part of the process evaluation.

4) Analysis plan for the process evaluation- Could you give more insights in the process of triangulation of quantitative and qualitative data? More precisely, how will the findings of the current process evaluation weight in the outcomes of the effectiveness evaluation? (p. 14f)

Response: Thank you for the query. The overall process evaluation frameworkwill aid in the analysis by triangulating the process quantitative data with the qualitative data addressing the questions within its subheadings.

For example, under the heading 'Implemention- Fidelity and dose'; a specific question would be whether usual care is provided equally in both arms of the intervention and thus the quantitative process data would be the time spent by the usual care physiotherapist and should be roughly

equivalent in both arms documented in the logs (or not), and the qualitative data would include, for example, the usual care physiotherapists' responses as to whether they did treat all the patients equally, or the neurologist's description of what happens to the study participants.

In regards to the weight of the outcomes of the effectiveness evaluation- this will most likely be a post-hoc examination of the process evaluation findings, in the light of the of the main results of the trial. For example, if there is a non-significant result of the trial; could this be because of contamination between usual care and stroke coordinators of aspects of the trial intervention and is this evident from the process evaluation?; or if it is positive result, how much could this be attributed to particular aspects of the trial intervention e.g. the repetitive gait exercises, as compared to usual care etc.

Amendments have been made on lines 336-344 p. 16 and lines 362- 381, pg 17-18 to elaborate on this.

Reviewer 2

1) As described, the main study sounds like a pragmatic RCT trial, if so please include this in the description. A little more information about the main study would also be helpful, e.g. number of participants per site, how they are recruited, the consent process, length of the intervention, number of visits per patient/family, how they are randomized, etc.

Response: Thank you for this suggestion. The main study protocol has been published and is references in the text. In addition, a study flow chart (from the published protocol) summarising the RCT's study visits and the outcome measures is provided. . Amendments made on line 133 pg 7.

In regards to describing it as a pragmatic RCT (1) ; while this trial does have many pragmatic features such as participant eligibility criteria, comparison to usual care and selecting and analysing primary outcomes which are relevant to clinical practice; we do not meet the criteria of "intervention flexibility and expertise" as we have recruited and trained physiotherapists specifically for the study rather than training the currently available hospital staff; and kept the details of the intervention blinded to the principal investigators, blinded assessors and the rest of the hospital staff, in addition there is a strong emphasis by the clinical coordinating team that the stroke coordinators follow the intervention protocol. For these reasons, it was decided during a steering committee meeting not to describe ATTEND trial as a pragmatic RCT.

2) It seems the focus of this process evaluation in on the intervention portion of the RCT. How is the usual care portion being evaluated? Please clarify.

Response: The usual care is being evaluated through the log forms which include the time spent by the usual care physotherapists in both arms of the trial; and through the interviews with the usual care physiotherapists, patients and carers in the usual care arm. Amendments have been made on lines 209-210 pg 10, lines 287 pg 14 to clarify this.

3) In several places the authors refer to identifying "causal" mechanisms. Please provide evidence as to how a process evaluation can determine cause and effect.

Response: Thank you. The term 'causal' mechanisms was described in the MRC guidance in the conduct of process evaluations, as a recommendation that trialists of complex interventions specify their hypothesized mechanisms of complex interventions, and the process evaluation aims to unpack whether in practice, these 'mechanisms' had its intended effect. For example, in our experience, our assumption is that early supported discharge as part of the intervention will decrease costs to the system and family; enable early patient rehabilitation which may improve patient recovery (primary

outcome) and result in shorter hospital stays in the intervention arm. However, in piloting our observation template at one site, we discovered that there was a bed shortage at this government hospital that patients were discharged at the earliest possibility when they were medically stable. This may perhaps be different to developed settings such as UK where rehabilitation trials showing positive results of early supported discharge. (2) This finding thus leads us to hypothesize that when the trial effectiveness outcomes are analysed, the secondary outcome of differences in length of stay in hospital may not be significant between intervention and usual care arm depending on the context of the hospital. Depending on the effectiveness results, we could then explore reasons why our hypothesis was met or not. Thus, this is an example of how we could gain a deeper understanding of the assumed causal mechanisms of the ATTEND intervention (as depicted in the logic model in the overall framework) were relevant. Such insights will help inform the final logic model of how the intervention truly impacted the trial effectiveness outcomes, and hopefully inform the generalizability the intervention.

This is elaborated on lines 362-381 pg. 18.

4) What type of training/expertise do the team members have in qualitative research, data collection (interviewing) and data analysis?

Response: Thank you for this clarification. This has been added into the methods section lines 233-236 pg 11-12.

5) On pg. 13, l. 48: How will patients and caregivers be selected? How will they be consented? Please provide evidence as to the appropriateness of interviewing them together. What are the benefits and drawbacks of this approach? Since they will be interviewed together, what will happen if one of the dyad agrees to the interview and the other declines the interview? How are the assessor's "blinded"?

Response: Thank you. A list of patients and caregivers who match our sampling critera will be generated. They will be contacted by the local site staff i.e either the stroke coordinator or the assessor (who is blinded to intervention details and also to the patient allocation to intervention or usual care) and reasons for not participating will be elicted where possible. They will be formally consented by the interviewer face to face, whereby it would be encouraged to conduct the interviews separatedly if feasible (e.g time constraints). The benefits of interviewing the patient and carer separately would be to gather perspectives which otherwise may not be shared should the other be present. Possible drawbacks of interviewing them separately include the missed opportunity to clarify their perspectives about the same issue (for example access to hospital) during the interview.
Amendments have been made on lines 262- 273 pg. 13 to elaborate on these details.

6) Pg. 14, l. 12: Please explain the meaning of the following; "Thematic analysis will be conducted alongside the interviews…".

Response: As per qualitative research methods, analysis will be iterative and thus the interviewer will do preliminary thematic data analysis at the end of each interview and discuss any highlights with the rest of the interview team. For example, the findings from the pilot interviews were discussed during the qualitative workship; in order for the team of interviewers to explore emerging themes in the data in the following interviews.
Amendments made on lines 273-283 pg 13-14 to include this description.

7) Pg. 14, l. 18: Please indicate how many dyads will be interviewed from usual care vs intervention group
Response: According to the sampling matrix, we would like to interview equal numbers from both

usual care vs intervention arm; and also include sampling for gender. For example, at each site, 2 usual care dyads and 2 intervention group dyads would be invited to participate. Amendments made on lines 286-289 pg 14.

8) Data collection- Pg. 10, l. 3: How will the cost to families be measured? Pg. 11, l. 34-53: Will this data be collected throughout the trial or after the trial has been completed. If collected during that trial, at what time points? Pg. 15, l. 40: How will indirect costs be calculated from the electronic case record? What types of data will be used for this calculation?

Response: Thank you for this clarification. Costs will be measured at baseline, (ie. when patients are first recruited into the trial) and also at their 3 and 6 month follow up visits. In regards to the indirect cost and types of data- this trial was designed with the intention of conducting an economic evaluation from a health system and societial perspective. As such relevant questions were asked by the blinded assessor regarding loss of family income (e.g number of hours of work taken off) due to carer's additional responsibility; and estimation of the such costs will be done using the average wage. Amendments have been made on line 302-315 pg 14-15 to highlight the separate cost-effectiveness evaluation, and to provide further detail about the costs data used as part of the process evaluation.

9) Please provide more detail about the use of grounded theory (GT) and triangulation. Based on the description provided this study does not fit the parameters of a grounded theory study. For example, there is no mention of theoretical sampling or building theory and the study is guided by 2 theoretical frameworks (which is not typical in a GT study). The paper needs a lot more detail about how grounded theory is being used with appropriate citations. Triangulation can be defined in many ways. Please be clear and specific about how triangulation is being used in this evaluation. Please provide relevant references for the qualitative methods and analysis.

Response: Thank you for your suggestions and clarifications. When first drafting the protocol, we had aimed to explore the qualitative data using inductive and iterative analyisis in a 'ground up' manner; in order to code closely to the data and establish themes through constant comparison between sources e.g patient, carer, health provider. However, as you have highlighted, the use of the theorectical frameworks for the overall process evaluation study; has superimposed a framework upon the analysis and triangulation of the data types (e.g process data and qualitative data.) As such, the use of framework analysis of the qualitative data is more appropriate for our study.
The specific types of triangulation for our study have also been elaborated upon. There will be triangulation of data sources (e.g are the process data and in the qualitative interviews congruent and if not, why?); triangulation through the sampling of different perpsectives ie. patient, carer, neurologists, stroke coordinators as to for example what about the intervention created the greatest impact), and also through the triangulation of different analysts in the team who bring their own cultural backgrounds, academic experiences (e.g rehabilitation medicine, pharmacy, physiotherapy) and knowledge about different aspects of the trial into the analysis.

Amendments have been made on lines 325-349 pg.16 to indicate this.

10) Pg. 16, l. 18-21: The protocol indicates that any process issues that are discovered will be "fed back" to the usual management communication channels. What does this mean? And, if problems are identified and addressed how will this affect the ongoing trial?

Response: Thank you for this important question. While we were mindful for the process evaluation not to impact upon the results of the trial, some of the issues uncovered during the process evaluation were important to be addressed to maintain the rigour of the trial and this would be achieved through the usual communication channels. For example, we discovered during a observation visit, that there was inadvertent 'unblinding' of the assessor during the followup visit to the patient, as the driver talked

about how he had driven to the home several times (i.e intervention patient). However, the assessor was reticient to report this in the 'unblinding form' as trained as he thought it was a 'failure' of his. This was discussed with the project manager who then clarified the importance of reporting incidents of 'unblinding' and strategies to reduce these incidences with the assessors. Amendment was made on lines 354-356 pg. 17 to highlight this.

11) This trial appears to rely significantly on family involvement, but there is no discussion about how the impact of this involvement is being measured, (i.e. caregiver burden, strain, depression, injury). Will this be assessed? If so how? If not why not (given the robust literature on this topic)?

Response: The impact of this family involvement is measured as part of the secondary outcomes of the trial now depicted through the addition of the study flow chart (Figure 1). The trial protocol has been published in an open access journal, and this is referenced in the manuscript. We are collecting data on caregiver burden, depression and any carer injuries. Amendments made on line 133 pg 7 to highlight the addition of Figure 1.

12) What are the limitations of this type of process evaluation? How will they be addressed?

Response: A limitation to our current approach include the overlap between the trial coordinating team and the process evaluation team. While a strength of that is the team members have an in-depth knowledge of the trial and its implementation, a challenge for the process evaluation is for team members to be reflexive of their own biases in the conduct of the interviews for positive findings towards the trial. Our sampling approach for the interviews has been designed to maximise variation which should increase our understanding of the differing contextual factors. Pragmatically this is only a small sample (about 100 participants) of a 1200 patient trial. However, this is a large sample for qualitative research, and other data sources such as observations, administratively collected data, and relevant policies would be reviewed to provide additional context.

The two limitations stated above are included in the submission as part of the description of the strengths and limitations as per the journal's requirements. However, these points are currently not part of the main text of the manuscript.

13) Pg. 8, lines 20-25: Consider using the word "can" instead of "will" in the following statement: "The context of each patient will…" – the word will is determinative and there is no supporting evidence of this. Please review closely for grammatical errors throughtout, e.g. verb tenses, appropriate use of singular vs. plural. Please be consistent with the term carer or caregiver.

Response: Thank you for your suggestion, amendments have been made in the manuscript line 130 pg 7.

14) Figure 1: It's not clear how causal inferences will be made (or whether this is possible). The description of the ATTEND as a type of early supported discharge is not discussed in the manuscript text. Please revise the text to include this.

Response: Please refer to response to qn 3 above in regards to causal inferences. The description of the early supported discharge is now included in the manuscript text on line 123 pg.7.

15) File 2: This interview guide is quite complex with many questions, and many which require "yes/no" responses. This is inconsistent with most qualitative research / interviewing.

Response: Thank you. The interview guide includes both initial broad descriptive questions (which are more open-ended) and suggested probing questions. Indeed as you noted, when this interview guide was piloted by AM, we realised that some of the probing questions were eliciting 'yes/ no ' responses and as such during our qualitative workshop as a group, it was emphasised that the open-ended questions addressing similar topic area would be more appropriate for the interviews.

16) How will caregiver difficulties with providing care be assessed?
Response: Please see response above to q. 11. in regards to assessing caregiver burden.

17) File 3 & 4: Are these interview guides for patients and caregivers in both the usual care and intervention group? Since you are interviewing patients and caregivers together how will you ask the specific questions of each person? How will you prevent the responses of one person in the dyad from influencing the responses of the other? In File 4, pg. 33 specifically, how will you separate the patient's perspective from the caregiver's since they are being interviewed together?

Response: Thank you for your insight. Yes, these interview guides are for both groups. As mentioned above, we encouraged interviewing caregivers and patients separately. It was stressed during the workshop that it would be useful to conduct the interview as a 'patient journey' and to incorporate both sets of questions in that manner during the interview. The perspectives can be separated during analysis as they will be labelled by the transcriber, and the audio files will be reviewed during the analysis.

References:
1. Thorpe KE, Zwarenstein M, Oxman AD, Treweek S, Furberg CD, Altman DG, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. J Clin Epidemiol. 2009 May;62(5):464-75. PubMed PMID: 19348971.
2. Fearon P, Langhorne P, Early Supported Discharge T. Services for reducing duration of hospital care for acute stroke patients. Cochrane Database Syst Rev. 2012 (9):CD000443. PubMed PMID: 22972045.

VERSION 2 – REVIEW

REVIEWER	Barbara Lutz University of North Carolina-Wilmington, Wilmington, NC USA
REVIEW RETURNED	09-Aug-2016

GENERAL COMMENTS	Thank your for the edits to this important manuscript. The added descriptions about the methods are very helpful. One suggestion, please include additional citation(s) for Framework Analysis as this is not a ubiquitous form of qualitative analysis/ methods. Based on the description, your analysis sounds like it is general thematic analysis and it's not clear how framework analysis differs from the more commonly used method of thematic analyses. If you choose to keep the term Framework analysis please include some additional citations -- here is one that might be helpful: "Using the framework method for the analysis of qualitative data in multi-disciplinary health research", Nicola K Gale; Gemma Heath, Elaine Cameron, Sabina Rashid and Sabi Redwood BMC Medical Research Methodology201313:117; DOI: 10.1186/1471-2288-13-117