PEER REVIEW HISTORY

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Research Priorities in Fragility Fractures of the Lower Limb and Pelvis: A UK Priority Setting Partnership with the James Lind Alliance
AUTHORS	Fernandez, Miguel Antonio; Arnel, Laura; Gould, Jenny; McGibbon, Alwin; Grant, Richard; Bell, Philip; White, Stuart; Baxter, Mark; Griffin, Xavier; Chesser, Tim; Keene, David; Kearney, R.S.; White, Catherine; Costa, Matthew L

VERSION 1 – REVIEW

REVIEWER	Santosh Rath Visiting Professor, Institute of Global Health Innovation, Imperial College, London
REVIEW RETURNED	30-Apr-2018

GENERAL COMMENTS	The manuscript reporting Top 10 UK research priorities in Fragility Fractures of the Lower Limb and Pelvis using JLA PSP process is an important addition to the repertoire of similar initiatives to identify societal and clinical priorities for research. This research is timely and important, given the burden and cost from fragility fractures of the lower extremity in the UK. The manuscript is well written and presents the JLA PSP process for top 10 research priorities. The following are my observations and comments. 1. Introduction: [line 15-20] The authors begin the introduction with global estimates of fragility fracture and hip fractures. They conclude the paragraph with estimates of cost to health care in the UK. It will be useful if they can add information on the UK burden of fragility fractures and estimates of Fragility Fractures of the Lower Limb and Pelvis. 2. Scoping survey and theme: Please detail the methodology for recruitment of respondents. It is not clear is this is an 'open' invitation for people to respond or if this was a 'purposive /selected ' sample. 3. It is not clear if the respondent in the second survey also participated in the earlier scoping survey. This information is important if the study has to be repeated elsewhere.

	4. Finally , how many of the participants in the final workshop were respondents to the previous surveys and 5. What was the role of the 'steering group' during the final workshop? Few lines to clarify the above in the methodology will improve clarity of the PSP process. Top 10 research questions: The JLA PSP process results in a Top 10. The aim of the Top 10 is to highlight important areas for research, but not necessarily to come up with the specific research questions. [Quote JLA guide-book] The authors should explain /justify why Questions 5, 13 and 19 should not be considered under a single research question i.e. the theme of 'weight bearing regime following treatment' or pain relief [combining Q 8 and 21]. At what stages of the PSP process that anatomical site i.e. weight bearing for ankle fracture gains priority over upper tibia or pelvis fracture. The authors mention in the discussion "broader less well defined questions receive higher ranking". It will be useful if the authors can elaborate in the discussion ways to retain the themes for research i.e. weight bearing and pain relief, rather than limiting the question to a target anatomical location. This will support their statement that "broader questions may have wider impact and cover multiple interventions [line 13 page 7]"

REVIEWER	Steven McPhail Queensland University of Technology and Metro South Health, Australia
REVIEW RETURNED	06-May-2018

GENERAL COMMENTS	The purpose of this study was to generate a prioritised list of research uncertainties / questions for fragility fractures affecting the lower limb and pelvis using a multi-phase methodology. It is always a pleasure to read research that has genuinely involved patients, family and friends in addition to clinicians and academics. For this alone the entire team (including patients, family and friends, as well as clinicians and researchers) are to be commended. Furthermore, publishing an ordered list of research priorities in this field will be very helpful for others working in the field. I enjoyed reading the manuscript which was easy to follow and applied an appropriate methodology to address the research aim. Therefore, my comments should be considered minor suggestions that are predominantly focused on requesting additional information related to methods in an effort to help the authors further improve the reporting of their research so that it could potentially be repeated by others. 1. Abstract methods – The phrase "…an established methodology…" is somewhat ambiguous and perhaps not particularly helpful for understanding what happened. In the context of a brief abstract, it may be better to start the abstract methods by framing what happened in terms of the study design (e.g., "a multi-phase methodology…" 2. Strengths and limitations text – Perhaps avoid abbreviation JLA in this section if possible? 3. Page 3, line 16 – "Nine million… presented in the year…" please clarify what is meant by "presented". (e.g., are you referring to patients that presented to hospital in a particular region or worldwide

	as it is a bit unclear as to whether the term ‘worldwide’ applies to the nine million figure or only the end of the sentence? 4. Page 3, line 26-27 – The comment about research in the field ‘usually’ being driven by academics and pharmaceutical companies sounds speculative without a reference or further information. If the authors have a reference to support this assertion it would strengthen the justification for the manuscript. 5. Page 4, first line of first paragraph on page 4 - Perhaps add a little background or brief description on how the steering group was formed, ideally with the authors considering how they could describe it in a way that could be replicated by others? 6. Page 4, line 6-8 – It is unclear how a neutral facilitator can ensure equal contributions from patients, carers and health professionals. Perhaps this could be clarified? 7. Page 4, first line of ‘scope’ paragraph – It seems there may be something missing from that sentence. E.g., you could add “…were considered in scope” at the end of the sentence? Perhaps also clarify whether the in-scope / out-of-scope decision(s) were initially being made by a single person or whether there were multiple people verifying against the scope criteria during the initial screening phase. 8. Page 4, line 28.29 – It is unclear what they did to “ensure acceptability to all stakeholders prior to launch”. Please clarify. 9. Page 4, line 34-39 – Was the thematic analysis completed by a single person, two people +/- 3rd person to adjudicate any unresolved differences of opinion? 10. Page 4, line 39-40 – I am unsure how the steering group can "advise" on a qualitative analysis that should be summarising themes emerging from the data (etc.)?. 11. Page 4, line 43-44 – Re: generating research questions from themes: Who did this? How was it done? 12. Perhaps add an ethics statement somewhere in the methods? 13. Page 4, line 46-47 – I am curious to know how the steering group knew whether they were representative of the original submissions? Did the steering committee each read all of the original submissions? 14. Page 6, 11-12 – This sounds like it is describing methods related to how questions were ranked from 1-76 and may be better integrated into the methods section. (Although the results of the ranking should remain in the results section). 15. Discussion – I (and perhaps other readers) would be interested to know how the final list compares to relevant research uncertainties mentioned in guidelines in the field (e.g., those from NICE or other international guidelines or recommendations)?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Santosh Rath
Institution and Country: Visiting Professor, Institute of Global Health Innovation, Imperial College, London
Competing Interests: None

See file attached. *We have copied the comments from the attachment into this document – see responses below.*

This is a well written manuscript detailing research priorities in fragility fractures of the lower limb in the UK. There are few issues in the methodology that needs clarification. I will appreciate your response/views for clubbing questions under the theme for weight bearing and pain.

Reviewer comments

The manuscript reporting Top 10 UK research priorities in Fragility Fractures of the Lower Limb and Pelvis using JLA PSP process is an important addition to the repertoire of similar initiatives to identify societal and clinical priorities for research. This research is timely and important, given the burden and cost from fragility fractures of the lower extremity in the UK.

The manuscript is well written and presents the JLA PSP process for top 10 research priorities. The following are my observations and comments.

1. Introduction: [line 15-20] The authors begin the introduction with global estimates of fragility fracture and hip fractures. They conclude the paragraph with estimates of cost to health care in the UK. It will be useful if they can add information on the UK burden of fragility fractures and estimates of Fragility Fractures of the Lower Limb and Pelvis.

We have modified this sentence to address the numbers of fragility fractures in the UK per year.

"In the UK over 300,000 patients present to hospital with fragility fractures[3] and the associated treatment costs are around 2% of the total healthcare burden in the UK – approximately £3billion per year.[4]"

2. Scoping survey and theme: Please detail the methodology for recruitment of respondents. It is not clear is this is an 'open' invitation for people to respond or if this was a 'purposive /selected ' sample.

The following text has been added to the Scoping Survey and themes section to address this point.

'The survey was circulated via the steering group and their partner organisations as an open invitation. The survey was available in both paper and online formats (Bristol online survey tool)[10].'

3. It is not clear if the respondent in the second survey also participated in the earlier scoping survey. This information is important if the study has to be repeated elsewhere.

The following text has been added to the Interim Prioritisation Survey section.

'The second survey was again circulated as an open invitation and not restricted to respondents from the first survey.'

4. Finally, how many of the participants in the final workshop were

respondents to the previous surveys and

Some participants in the final workshop had submitted responses to the surveys but we did not record exactly how many.

5. What was the role of the 'steering group' during the final workshop? Few

lines to clarify the above in the methodology will improve clarity of the PSP

process.

The following text has been added to the Final Workshop section to clarify this.

'The role of the steering group at this stage was to ensure that patients and carers were well supported with information and with practical support on the day. As places in the final workshop were limited, the majority of the steering group did not participate in the final workshop.'

Top 10 research questions:

The JLA PSP process results in a Top 10. The aim of the Top 10 is to highlight

important areas for research, but not necessarily to come up with the

specific research questions. [Quote JLA guide-book]

The authors should explain /justify why Questions 5, 13 and 19 should not be

considered under a single research question i.e. the theme of 'weight bearing regime following treatment' or pain relief [combining Q 8 and 21]. At what stages of the PSP process that anatomical site i.e. weight bearing for ankle fracture gains priority over upper tibia or pelvis fracture.

This is a valid point and one which was the focus of much discussion during the stages of the PSP and at the final workshop.

In summary, these questions were kept as separate entities as the steering group felt, as did the respondents to the surveys, that the answers to these questions might be quite different. This is particularly so for the pain questions where the effectiveness of pain relief strategies may be quite different at different stages of the patient pathway.

The prioritisation of one anatomical region over another for the weight bearing questions was decided *at the final workshop and based on the incidence figures for these injuries – ankle fractures being much more common than tibial plateau or pelvic fractures.*

The steering group concluded that presenting the questions as we have done has struck the right balance between keeping the resolution in the original submissions whilst not overwhelming the respondents during the prioritisation process with too many questions on the same theme.

The authors mention in the discussion "broader less well defined questions receive higher ranking". It will be useful if the authors can elaborate in the discussion ways to retain the themes for research i.e. weight bearing and pain relief, rather than limiting the question to a target anatomical location. This will support their statement that "broader questions may have wider impact and cover multiple interventions [line 13 page 7]"

It is difficult describe "ways to retain the themes for research" as this will depend greatly of the subject matter, the original uncertainties submitted, and the views of the steering group. However, we acknowledge this important point, and the previous point, and have made reference to it by adding the following text.

"Nevertheless, we felt it was important to strike a balance between more general questions and questions about specific interventions such that the spectrum of the original submissions was accurately reflected. Future prioritisation partnerships will need to consider this aspect of the process and decide on the right balance between inclusion of specific versus general indicative questions."

Reviewer: 2
Reviewer Name: Steven McPhail
Institution and Country: Queensland University of Technology and Metro South Health, Australia
Competing Interests: None declared

The purpose of this study was to generate a prioritised list of research uncertainties / questions for fragility fractures affecting the lower limb and pelvis using a multi-phase methodology. It is always a pleasure to read research that has genuinely involved patients, family and friends in addition to clinicians and academics. For this alone the entire team (including patients, family and friends, as well as clinicians and researchers) are to be commended. Furthermore, publishing an ordered list of research priorities in this field will be very helpful for others working in the field. I enjoyed reading the manuscript which was easy to follow and applied an appropriate methodology to address the research aim. Therefore, my comments should be considered minor suggestions that are predominantly focused on requesting additional information related to methods in an effort to help the authors further improve the reporting of their research so that it could potentially be repeated by others.

1. Abstract methods – The phrase "…an established methodology…" is somewhat ambiguous and perhaps not particularly helpful for understanding what happened. In the context of a brief abstract, it may be better to start the abstract methods by framing what happened in terms of the study design (e.g., "a multi-phase methodology…"

The phrase ‘an established methodology” has been change to “a multi-phase methodology” as suggested.

2. Strengths and limitations text – Perhaps avoid abbreviation JLA in this section if possible?

JLA now reads James Lind Alliance.

3. Page 3, line 16 – “Nine million… presented in the year…” please clarify what is meant by “presented”. (e.g., are you referring to patients that presented to hospital in a particular region or worldwide as it is a bit unclear as to whether the term ‘worldwide’ applies to the nine million figure or only the end of the sentence?

We have changed the wording of this sentence to clarify.

“An estimated nine million fragility fractures occurred worldwide in the year 2000, with 50 million people suffering from the sequelae of these fractures.[1]”

4. Page 3, line 26-27 – The comment about research in the field ‘usually’ being driven by academics and pharmaceutical companies sounds speculative without a reference or further information. If the authors have a reference to support this assertion it would strengthen the justification for the manuscript.

Agree with this being speculative. We have removed this sentence. The paragraph now opens with the following:

“There is evidence of a mismatch between the research priorities of patients and healthcare professionals and the research which is actually undertaken and delivered.[4-6]”

5. Page 4, first line of first paragraph on page 4 - Perhaps add a little background or brief description on how the steering group was formed, ideally with the authors considering how they could describe it in a way that could be replicated by others?

The formation of the steering group is detailed in the Methods section ‘Steering group & Partner Organisations’ section.

“The steering group consisted of patient representatives, healthcare professionals, and carers with established links to relevant partner organisations (see Appendix 1) to ensure that a range of stakeholder groups were represented.”

The following text has been added to clarify the steering group participation.

“Steering group members did so on a voluntary basis and were expected to commit to the whole process where possible.”

6. Page 4, line 6-8 – It is unclear how a neutral facilitator can ensure equal contributions from patients, carers and health professionals. Perhaps this could be clarified?

The neutral facilitator did this by chairing the sessions in such a way that all voices were heard. The following text has been added to clarify and strengthen this point.

"This is an important aspect of the JLA process and ensures that all voices are heard and respected throughout the process."

7. Page 4, first line of 'scope' paragraph – It seems there may be something missing from that sentence. E.g., you could add "…were considered in scope" at the end of the sentence? Perhaps also clarify whether the in-scope / out-of-scope decision(s) were initially being made by a single person or whether there were multiple people verifying against the scope criteria during the initial screening phase.

The first line now reads "All research uncertainties related to fragility fractures of the lower limbs and pelvis for patients over 60 years of age were considered in scope."

In addition, the following sentence has been added to address the second point.

"The decisions about whether submissions were in or out-of-scope were made by the information specialist and subsequently verified by the steering group."

8. Page 4, line 28.29 – It is unclear what they did to "ensure acceptability to all stakeholders prior to launch". Please clarify.

This sentence has been changed to the following:

"A pilot phase was undertaken to ensure that the survey was clearly written, understandable to all groups, and easy to complete."

9. Page 4, line 34-39 – Was the thematic analysis completed by a single person, two people +/- 3rd person to adjudicate any unresolved differences of opinion?

The following has been added to clarify this.

"The thematic analysis was undertaken by the information specialist and decisions verified by the steering group."

10. Page 4, line 39-40 – I am unsure how the steering group can "advise" on a qualitative analysis that should be summarising themes emerging from the data (etc.)?.

The word 'advise' has been removed and the role of the steering group incorporated into the above sentence.

11. Page 4, line 43-44 – Re: generating research questions from themes: Who did this? How was it done?

The following text has been added to address this query

"These were derived from the original submissions and were designed to summarise the submissions within each subtheme/theme. The information specialist undertook this process. The indicative questions were then reviewed by the steering group to ensure that they were a true representation of

the original submissions, and to ensure that the language used was understandable to all stakeholder groups."

12. Perhaps add an ethics statement somewhere in the methods?

The following text has been added to the Scoping Survey and Identification of themes section.

"This work did not require formal ethical approval. Respondents to the surveys gave written consent to the inclusion of their anonymised data in this process."

13. Page 4, line 46-47 – I am curious to know how the steering group knew whether they were representative of the original submissions? Did the steering committee each read all of the original submissions?

The following sentence has been altered to answer this query.

'The indicative questions were then reviewed by the steering group along with a selection of the original uncertainties to ensure that they were a true representation, and to ensure that the language used was understandable to all stakeholder groups.'

14. Page 6, 11-12 – This sounds like it is describing methods related to how questions were ranked from 1-76 and may be better integrated into the methods section. (Although the results of the ranking should remain in the results section).

This is already described in the methods section and is included here purely for the purpose of clarity. We suggest that this should remain unchanged.

15. Discussion – I (and perhaps other readers) would be interested to know how the final list compares to relevant research uncertainties mentioned in guidelines in the field (e.g., those from NICE or other international guidelines or recommendations)?

Agree. We have added the following which makes reference to the NICE hip fracture guidelines.

"These priorities compliment research priorities highlighted by national guidelines in this area which also highlight research uncertainties in rehabilitation and physiotherapy.[12]"

VERSION 2 – REVIEW

REVIEWER	Santosh Rath institute for Global Health Innovations Imperial College London UK
REVIEW RETURNED	14-Jul-2018

GENERAL COMMENTS	The authors have clarified and responded to the suggestions of both reviewers. The manuscript is much improved and easy to read and replicate by others.

REVIEWER	Steven McPhail Queensland University of Technology and Metro South Hospital and Health Service
REVIEW RETURNED	30-Jul-2018

GENERAL COMMENTS	Thanks to the authors for addressing most of my concerns. A few remain based on their responses: Comment 6: I disagree with the authors assertion that a neutral facilitator chairing a session in a way that ensures all voices are heard equates to ‘ensuring equal contributions from patients, carers and health professionals’. Equal contributions and provision of equal opportunity to make contributions are not the same thing. In case my earlier comment was not clear, the former relates to actual contributions to the task at hand, the latter relates to opportunity (regardless of actual contributions made). My concern is with the description “ensured equal contributions”, not with the way the sessions were chaired. Comment 9: Are you stating that the analysis was undertaken by one person (information specialist)? If so, please state this plainly. Second, if there was a verification procedure involving the steering group, could you clarify what that actually involved so the reader can understand how (or if) it strengthened the study? To get directly to my concern: I am unsure how a steering group can verify that decisions taken during the thematic analysis appropriately represented the views/ opinions emerging from the raw data when (at least based on my understanding of the current text) they have not actually seen / read all the raw data? Response to Comment 11 and 13: “The indicative questions were then reviewed by the steering group to ensure that they were a true representation of the original submissions” Similar to the above comment, I am not sure how the steering group can ensure the questions were “a true representation of the original submissions” without reading all of the original submissions? Again, my concern here is not so much about the process, but rather the description potentially giving the reader a false impression that a steering committee with information (potentially) ‘cherry picked’ by the person who prepared the questions could genuinely ensure the representativeness of the questions. I assume (probably like the steering committee) that the questions were appropriate, my concern is about the description and risk of ‘over-selling’ the rigour of the procedures. Comment 12: Wow, I wasn’t aware that ethical approval is not required in the UK for research programs that involve survey research (two national surveys including health professions, patients, carers, family & friends) + focus group-style workshop (patients, carers, health-professionals). I will not comment on this further other than to say that I sincerely hope this is acceptable to the publisher, as this is a useful contribution to the field and it would be a real shame if it weren’t exempt. I had / have no evidence or concern that the conduct of the research was in any way unethical when making the original comment, I just thought that the authors had forgotten to add their ethics statement.

VERSION 2 – AUTHOR RESPONSE

Comment 6:
I disagree with the authors assertion that a neutral facilitator chairing a session in a way that ensures all voices are heard equates to ‘ensuring equal contributions from patients, carers and health professionals’. Equal contributions and provision of equal opportunity to make contributions are not the same thing. In case my earlier comment was not clear, the former relates to actual contributions to the task at hand, the latter relates to opportunity (regardless of actual contributions made). My concern is with the description “ensured equal contributions”, not with the way the sessions were chaired.

Response to Comment 6:
Thank you. I have altered this sentence to reflect the opportunity for equal contributions rather than ensuring it. It now reads as follows:
"A JLA Adviser (CW) supported and guided the PSP as a neutral facilitator to ensure that it was undertaken in a fair and transparent way encouraging equal contributions from patients, carers and healthcare professionals."

Comment 9:
Are you stating that the analysis was undertaken by one person (information specialist)? If so, please state this plainly. Second, if there was a verification procedure involving the steering group, could you clarify what that actually involved so the reader can understand how (or if) it strengthened the study? To get directly to my concern: I am unsure how a steering group can verify that decisions taken during the thematic analysis appropriately represented the views/ opinions emerging from the raw data when (at least based on my understanding of the current text) they have not actually seen / read all the raw data?

Response to Comment 9:
The text already states that the thematic analysis was undertaken by the information specialist as follows:
"The thematic analysis was undertaken by the information specialist and decisions verified by the steering group."
I have added the following to clarify the steering group verification process:
"In order to do this the steering group were given to the opportunity to review all of the original submissions under each theme/subtheme. These were then referred to during the verification process."

Comment 11 and 13: “The indicative questions were then reviewed by the steering group to ensure that they were a true representation of the original submissions”
Similar to the above comment, I am not sure how the steering group can ensure the questions were “a true representation of the original submissions” without reading all of the original submissions? Again, my concern here is not so much about the process, but rather the description potentially giving the reader a false impression that a steering committee with information (potentially) ‘cherry picked’ by the person who prepared the questions could genuinely ensure the representativeness of the questions. I assume (probably like the steering committee) that the questions were appropriate, my concern is about the description and risk of ‘over-selling’ the rigour of the procedures.

Response to comment 11 and 13:
I believe this is now addressed by the answer to the above comment. The steering group were able to review all original uncertainties under each theme (this has been clarified above). They then reviewed a selection of original uncertainties for each indicative question - this is already stated in the manuscript.

Comment 12:
Wow, I wasn't aware that ethical approval is not required in the UK for research programs that involve survey research (two national surveys including health professions, patients, carers, family & friends) + focus group-style workshop (patients, carers, health-professionals). I will not comment on this further other than to say that I sincerely hope this is acceptable to the publisher, as this is a useful contribution to the field and it would be a real shame if it weren't exempt. I had / have no evidence or concern that the conduct of the research was in any way unethical when making the original comment, I just thought that the authors had forgotten to add their ethics statement.

Response to Comment 12:
The JLA is clear about not requiring ethics approval for priority setting exercises. This is consistent with other priority exercises published in the BMJ Open (https://bmjopen.bmj.com/content/7/9/e016540) and is reinforced by the guidance published by INVOLVE.
We have now included a separate ethics statement to clarify this as follows:
Ethics Statement
This work did not require ethics approval as per the JLA guidance[11] and guidance published by the NHS National Patient Safety Agency National Research Ethics Service.[12] Respondents to the surveys provided written consent to the inclusion of their anonymised data in this process.

VERSION 3 – REVIEW

REVIEWER	Steven McPhail Queensland University of Technology, Australia
REVIEW RETURNED	09-Aug-2018

GENERAL COMMENTS	I thank the authors for addressing these minor remaining concerns and I believe this manuscript is making a very useful contribution to the field.