PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Development of core outcome sets for effectiveness trials of interventions to prevent and/or treat delirium (Del-COrS): Study protocol
AUTHORS	Rose, Louise; Agar, Meera; Burry, Lisa; Campbell, Noll; Clarke, Mike; Lee, Jacques; Siddiqi, Najma; Page, Valerie J.

VERSION 1 - REVIEW

REVIEWER	Rakesh C. Arora University of Manitoba, Canada I do not have a direct relationship to this analysis, however, I serve on the American Delirium Society Board of Directors with a Co-Author of this manuscript (N. Campbell). However, I believe that I have been able to objectively assess the merit of this submission in keeping with SPIRIT guidelines.
REVIEW RETURNED	06-Mar-2017

GENERAL COMMENTS	Summary: This a protocol manuscript detailing the research plan for an SR and subsequent Delphi process to determine two core outcome sets for trials of interventions for delirium trials. Study Strengths: 1. This was a well-crafted manuscript and of adequate length. 2. Research Question Novelty: This is an important initiative that seeks to address a pressing issue in delirium research, the standardization of reporting outcomes. 3. The appropriate registration with COMET and PROSPERO has been undertaken. Comments/Concerns: The following few comments/questions are seeking clarification on a few issues (separated by section) to further strengthen the manuscript. METHODS: Will the use of conference proceeding or “grey” literature be used as part of the search strategy for the SR? METHODS: Are the Author planning for any internal audit or testing phase for the title and abstract phase and/or full-text screen to ensure adequate observed agreement and kappa of the screens? Minor Concerns: 1. It would be helpful for the Authors to include a completed SPIRIT checklist with their submission.

REVIEWER	James L. Rudolph Brown University, Providence RI, USA I am an unpaid board member of the American Delirium Society which is being used as a recruitment site for this study. I have no other interests
REVIEW RETURNED	17-Mar-2017

GENERAL COMMENTS	This is an exciting study and thank you for the broad international effort to pull this together. There are a couple concerns that relate to sampling bias from the experts. 1) Combining pediatric and adults into the same group will be challenging because the literature on pediatrics is just beginning to expand. As a result, there are few pediatric experts and their voice in the Delphi may be limited by a larger number of adult experts. Please consider modifying the Delphi to insure that pediatrics gets its time. 2) Recruiting from the three societies will bring you a cohort of delirium experts. The challenge will be relating this back to actual clinical practice, because the experts who attend these meetings tend to have a strong bias toward delirium. Please consider the representation on the panels has adequate clinical experience to make this a valuable clinical method 3) Thank you for including the qualitative interviews, they are an important piece of delirium. Please consider having representation from all groups (although palliative, dementia, and peds will be difficult)

REVIEWER	Dr Thomas Jackson Institute of Inflammation and Ageing, University of Birmingham, United Kingdom
REVIEW RETURNED	28-Apr-2017

GENERAL COMMENTS	Development of core outcome sets for effectiveness trials of interventions to prevent and/or treat delirium (Del-COrS): Study protocol This study protocol clearly outlines a number of studies planned to be undertaken to arrive at a set of core outcomes for future delirium trials. It's well written, and clearly written by the right people. The topic is extremely important. Currently interventions to treat or prevent delirium are. A main limitation of these studies has been the wide difference in outcomes used. It may well be that 'traditional' outcomes such as mortality may not be as important as the relieving of distress, shortening of duration of delirium, or amelioration of longer term cognitive decline. I have a few comments to make. The authors have selected four groups of people at risk of delirium. I do wonder if a fifth could be considered, that of older people undertaking elective surgery, especially cardiac surgery or joint arthroplasty. Delirium rates post cardiac surgery are high (approx.

	50%) and I appreciate a number of these may be covered by the group on ITU, however elective joint arthroplasty (rates 10-15%) would be missed by this. I would add to the limitations the possibility that important outcomes identified may not be easy to ascertain in trials. It is possible that duration of delirium, or limitation of distress is important. Rigorous ascertainment of these would be difficult at present, and it may be that this would lead to work deriving methods to do this.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
1. Will the use of conference proceeding or "grey" literature be used as part of the search strategy for the SR?
Response: We do not intend to search conference proceedings or grey literature beyond Prospero and the Joanna Briggs library as we feel a comprehensive database search will provide sufficient breadth of scope in terms of study outcomes and measures.

2. Are the Author planning for any internal audit or testing phase for the title and abstract phase and/or full-text screen to ensure adequate observed agreement and kappa of the screens?
Response: We do not intend to assess agreement as the objective according to Cochrane guidelines is to resolve any disagreement through discussion between the two screeners and to defer to a third if required.

3. It would be helpful for the Authors to include a completed SPIRIT checklist with their submission.
Response: We are not sure why this reviewer has requested a SPIRIT checklist. We are not conducting a clinical trial and there are no interventions associated with the study. Therefore we have not completed as most elements are not applicable but are happy to be advised by the editor regarding this.

Reviewer: 2
1. Combining pediatric and adults into the same group will be challenging because the literature on pediatrics is just beginning to expand. As a result, there are few pediatric experts and their voice in the Delphi may be limited by a larger number of adult experts. Please consider modifying the Delphi to insure that pediatrics gets its time.
We agree with the reviewer that it will be important to ensure paediatric representation. We have included the following with respect to our interview stage….. 'For the patient groups representing high acuity settings, acute care settings, and palliative care, we will also target parents and where possible children that have experienced delirium'.

Once we have completed the systematic review work we will have a clearer idea as to whether we need to separate paediatrics completely for the Delphi and nominal group technique process. Therefore we have added the following in the Delphi section: 'For the patient groups representing high acuity settings, acute care settings, and palliative care, we will also aim to have a minimum of 5 participants representing paediatrics in each group if deemed appropriate to combine in the same COS development process following our systematic review work'.

2. Recruiting from the three societies will bring you a cohort of delirium experts. The challenge will be relating this back to actual clinical practice, because the experts who attend these meetings tend to

have a strong bias toward delirium. Please consider the representation on the panels has adequate clinical experience to make this a valuable clinical method.
Response: We believe that having a distinct cohort of clinicians that do not meet the criteria of trailist/researcher i.e. are not authors of published (over last 10 years) or ongoing clinical trials evaluating interventions aimed at preventing or treating delirium as we have outlined in our sampling strategy should address this concern.

3. Thank you for including the qualitative interviews, they are an important piece of delirium. Please consider having representation from all groups (although palliative, dementia, and peds will be difficult)
Response: again this is our intention, we will be seeking family and previous patients if practicable representative of each of our 4 patient groups and as above have clarified that we will be seeking input from parents and children.

Reviewer: 3
1. The authors have selected four groups of people at risk of delirium. I do wonder if a fifth could be considered, that of older people undertaking elective surgery, especially cardiac surgery or joint arthroplasty. Delirium rates post cardiac surgery are high (approx. 50%) and I appreciate a number of these may be covered by the group on ITU, however elective joint arthroplasty (rates 10-15%) would be missed by this.
Response: We debated out groups over many months. Older people receiving elective surgery will be included either in the patient groups representing high acuity settings or acute care settings and therefore we do not feel warrants a separate group.

2. I would add to the limitations the possibility that important outcomes identified may not be easy to ascertain in trials. It is possible that duration of delirium, or limitation of distress is important. Rigorous ascertainment of these would be difficult at present, and it may be that this would lead to work deriving methods to do this.
Response: We agree that there is the potential that patient/family interviews as well as additional outcomes suggested by Delphi participants may introduce outcomes that currently don't have measures. We have added the following: Important outcomes are identified that are difficult to measure due to the absence of valid and reliable measures.

VERSION 2 – REVIEW

REVIEWER	Rakesh C. Arora University of Manitoba, Canada I serve on the Board of Directors for the American Delirium Society with Dr. Noll Campbell. I have been aware of the development of this protocol, however I have not been directly involved with its creation.
REVIEW RETURNED	09-Jun-2017

GENERAL COMMENTS	This is an important international collaboration describing a protocol for the development of a core outcomes dataset for research purposes. The process described, once completed, will have significant impact in delirium research and ultimately delirium clinical management. This is a well-written and comprehensive protocol manuscript Comments/Concerns: The following comments are seeking clarification/further details to

	further strengthen this manuscript: 1. Can the Authors clarify if they intend on include a family member or previous patient with delirium as part of the Delphi process, or will their involvement be in primarily Delphi question development? 2. Please provide additional information on the "multi-modal recruitment strategies" for delirium survivors. 3. Can the Authors clarify the types of post-operative patients that will be represented in the study. 4. Will there be a testing/audit comp in abstract and full text abstract phase to ensure appropriate kappa between reviewers? 5. Can the Authors provide further details on how they will achieve adequate patient/caregiver representation from different age categories and different countries/languages?

REVIEWER	Dr Thomas Jackson Institute of Inflammation and Ageing, University of Birmingham, UK
REVIEW RETURNED	07-Jun-2017

GENERAL COMMENTS	Many thanks for taking the time to respond to the comments. I have no further concerns

VERSION 2 – AUTHOR RESPONSE

Response Tor Reviewer's comments

1. Can the Authors clarify if they intend on include a family member or previous patient with delirium as part of the Delphi process, or will their involvement be in primarily Delphi question development?
Response: we will include delirium survivors and family members in all stages of the COS development.
To emphasize this further we have added the following into the sentence describing the consensus building participants: We will use the eligibility criteria and sampling strategy shown in Table 1 ensuring a minimum of two participants from each stakeholder group (patients/family members; expert clinicians; trialists/researchers) representing each of the demographic variables and categories within those variables.

2. Please provide additional information on the "multi-modal recruitment strategies" for delirium survivors.
Response: We have already described this in detail as follows: contact with relevant patient/family support/advocacy groups/charities as well as generic organizations such as the James Lind Alliance and COMET, use of social media including twitter and patient-focused Facebook pages, advertisements placed on public and patient involvement websites, snowballing techniques, and personal contacts. We have added the following: hospital patient engagement and patient and public involvement groups

3. Can the Authors clarify the types of post-operative patients that will be represented in the study.
Response: All post-operative patients will be included as these will be incorporated into either the critical care or acute hospitalization populations. We have clarified in the text as follows: These include (1) critically ill adults and children (medical, surgical, and trauma) receiving care in high acuity

settings, including intensive care and high dependency units; (2) non-critically ill adults and children hospitalized in acute care settings including surgical (all surgeries) and medical patients,

4. Will there be a testing/audit comp in abstract and full text abstract phase to ensure appropriate kappa between reviewers?
Response: We addressed this in the previous round of reviewer comments. As per Cochrane guidance we will not be determining kappa ratings for screeners as the objective is to come to consensus.

5. Can the Authors provide further details on how they will achieve adequate patient/caregiver representation from different age categories and different countries/languages?
Response: We have described our methods of recruitment as purposeful and maximal variation (and the criteria for the variation sought and targets in detail) and cited references for these methods. These are standard qualitative methods for determining diversity in perspectives that may arise from demographic characteristics. We have added the following sentence to further clarify our recruitment methods to meet these targets: If required we will modify our recruitment advertising to target individuals meeting our demographic targets.

VERSION 3 - REVIEW

REVIEWER	Rakesh C. Arora University of Manitoba None that have not been previously disclosed
REVIEW RETURNED	18-Jun-2017

GENERAL COMMENTS	The Authors have responded/clarified all remaining questions. I have no further concerns.