

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

## Development of core outcome sets for effectiveness trials of interventions to prevent and/or treat delirium (Del-CORs): Study protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-016371
Article Type:	Protocol
Date Submitted by the Author:	09-Feb-2017
Complete List of Authors:	Rose, Louise; University of Toronto, Lawrence S. Bloomberg Faculty of Nursing Agar, Meera ; University of Technology Sydney, Centre of Cardiovascular and Chronic Care, Faculty of Health Burry, Lisa; Mount Sinai Hospital, Pharmacy Campbell, Noll; Indiana University Bloomington, Clarke, Mike; All-Ireland Hub for Trials Methodology Research, Centre for Public Health Lee, Jacques; University of Toronto, Clinical Epidemiology Unit Siddiqi, Najma; University of York, Psychiatry, Hull York Medical School, York and Bradford District Care NHS Foundation Trust, Bradford, UK Page, Valerie J.; West Hertfordshire Hospitals NHS Trust, Anaesthetics
<b>Primary Subject Heading</b>:	Mental health
Secondary Subject Heading:	Geriatric medicine, Intensive care, Palliative care
Keywords:	Delirium & cognitive disorders < PSYCHIATRY, core outcome set, systematic review, research methods

SCHOLARONE™  
Manuscripts

**TITLE**

Development of core outcome sets for effectiveness trials of interventions to prevent and/or treat delirium (Del-CORs): Study protocol

**CORRESPONDING AUTHOR**

Louise Rose

Department of Critical Care Medicine, Sunnybrook Health Sciences Centre;  
Lawrence S. Bloomberg Faculty of Nursing and Interdepartmental Division of Critical  
Care Medicine, University of Toronto

Postal Address: 155 College St. Rm 276 Toronto, Canada

Email: [louise.rose@utoronto.ca](mailto:louise.rose@utoronto.ca)

Phone: +1 416 978 3492

**CO-AUTHORS**

Meera Agar

Faculty of Health Sciences, University of Technology, Sydney, Australia

Lisa Burry

Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada

Noll Campbell

College of Pharmacy, Indiana University-Purdue University, Indianapolis, United States

Mike Clarke

School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast,  
Belfast, Northern Ireland

Jacques Lee

Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Toronto, Canada

Najma Siddiqi

School of Medicine, York University, York, England

Valerie Page

Watford General Hospital, Watford, England

For the Del-CORs group – Jennifer Ansell, Bronagh Blackwood; Rich Jones; Imogen  
Featherstone; Leslie Fornear; Annmarie Hosie; Miriam Johnson; Dale Needham; Nadine  
Schofield; Jo Taylor; Peter Lawlor

**KEYWORDS**

Delirium; core outcome set; systematic review; research methods

**WORD COUNT:** 3990 (Not including table and Figure).

## ABSTRACT

### Introduction

Delirium is a common, serious, and potentially preventable condition with devastating impact on quality of life prompting a proliferation of interventional trials. Core outcome sets aim to standardize outcome reporting by identifying outcomes perceived fundamental for measurement in trials of a specific interest area. Our aim is to develop international consensus on two core outcome sets for trials of interventions to prevent and/or treat delirium, irrespective of study population. We aim to identify additional core outcomes specific to the critically ill, acutely hospitalized patients, palliative care, and older adults.

### Methods and analysis

We will conduct a systematic review of published and ongoing delirium trials (1980 onwards) and one-on-one interviews of patients that have experienced delirium and family members. These data will inform Delphi round one of a two-stage consensus process. In round two we will provide participants their own response, summarized group responses, and those of patient/family participants for re-scoring. We will randomize participants to receive feedback as proportion scoring the outcome as critical, or as group mean responses. We will hold a consensus meeting using nominal group technique to finalize outcomes for inclusion. We will repeat the Delphi process and consensus meeting to select measures for each core outcome. We will recruit 240 Delphi participants giving us 80% power to detect a 1.0 to 1.5 point (9-point scale) difference by feedback method between rounds. We will analyze differences for subsequent scores, magnitude of opinion change, items retained, and level of agreement.

### Ethics and dissemination

We are obtaining research ethics approvals according to local governance. Participation will be voluntary and data deidentified. Support from three international delirium organizations will be instrumental in dissemination and core outcome set uptake. We will disseminate through peer-reviewed open access publications, and present at conferences selected to reach a wide range of knowledge users.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Word Count: 300

This Core Outcome Set is registered on the COMET website <http://www.comet-initiative.org/studies/details/796>.

The systematic review is registered on PROSPERO-ID: CRD42016052704  
[https://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42016052704](https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016052704)

For peer review only

## STRENGTHS and LIMITATIONS

### Strengths

- Rigorous systematic review and core outcome set development methods that adhere to Cochrane and COMET guidelines
- Engagement with survivors of delirium during development of the protocol
- Support of three international Delirium Societies (American, Australasian, European) will facilitate participant recruitment, dissemination, and uptake of our core outcome sets

### Potential Limitations

- Ability to recruit and retain participants, particularly delirium survivors and their family members. We are using multi-modal recruitment strategies and seeking advice from organizations experienced in recruitment and retention of patient/family participants.
- Ability to recruit participants with broad geographical representation.
- Inability to come to consensus on the core outcomes or the measures for these outcomes.

## INTRODUCTION

Delirium is a complex syndrome characterized by an acute confusional state with rapid onset, a fluctuating course, circadian disturbances, reduced or increased motor activity, as well as changes in cognition, notably in the domains of attention and higher-level thought processing.<sup>1 2</sup> Delirium is a common, serious, and potentially preventable source of morbidity, with devastating impacts on quality of life, and mortality. Delirium impacts all age groups, from infants to the very elderly. This includes patients, including those accessing primary care, resident in nursing homes,<sup>3</sup> those receiving palliative care services,<sup>4</sup> and a significant number of hospitalized patients, including the acute and critically ill. Prevalence rates in hospitalized patients range from 25% to 80%.<sup>5-8</sup>

Delirium is not a benign, self-limiting condition. As well as increased mortality, delirium is associated with prolonged length of stay (LOS); higher rates of unintentional device removal; falls and incontinence in the elderly; significant emotional distress for patients, families, caregivers, and healthcare professionals;<sup>9-12</sup> and escalating public healthcare costs.<sup>13-15</sup> Delirium also carries long term consequences including impaired physical functioning<sup>16 17</sup> and loss of independence resulting in long-term care placement;<sup>5</sup> caregiver burden;<sup>18 19</sup> decreased quality of life;<sup>20</sup> cognitive decline, and increased risk of dementia and Alzheimer's disease.<sup>11</sup>

With increased recognition of delirium as a common, costly, and potentially preventable condition associated with adverse outcomes, encouragingly studies examining interventions to prevent and/or treat delirium continue to proliferate. Currently, there is no systematic approach to the selection and reporting of outcomes and their measures in these studies resulting in reporting of numerous and varied study outcomes and measures for these outcomes. This hinders progress towards improvements in care, as to best inform the evidence base, outcomes must be selected, defined, and measured consistently across studies of similar interventions in similar populations. Core outcome sets (COS), developed using rigorous consensus processes involving key stakeholders including patients and carers, comprise outcomes perceived as fundamental to measure in all trials related to a specific and defined area of interest (such as a disease, condition, or intervention).<sup>21 22</sup> Although the importance and value of COS for standardizing outcomes

1  
2  
3 and measurement across trials is increasingly recognized, in general, they are still in their  
4 infancy and as yet have not been developed for trials of interventions to prevent or treat  
5 delirium. Therefore we aim to develop international consensus on two COS appropriate  
6 for trials of interventions designed to (1) prevent or (2) treat delirium, irrespective of  
7 study population. We also aim to identify additional core outcomes specific to four  
8 patient groups: the critically ill; patients requiring hospitalization in an acute care setting;  
9 palliative care; and older adults living in residential care or the community.  
10  
11  
12  
13  
14  
15  
16

### 17 Scope of Core Outcome Set Development

18 The scope of our COS will include our four patient populations of interest, considered at  
19 high risk of developing delirium.<sup>3 5 23 24</sup> These include (1) critically ill adults and children  
20 receiving care in high acuity settings, including intensive care and high dependency units;  
21 (2) non-critically ill adults and children hospitalized in acute care settings including  
22 postoperative surgical and medical patients, and patients presenting to an emergency  
23 department (ED); (3) adults and children receiving palliative care, either in a hospital,  
24 hospice, or community setting; and (4) older adults (65 and over) living in nursing or  
25 residential care homes or living in their own homes and defined as at risk of delirium by  
26 study authors. We recognize that certain subpopulations such as children and older adults  
27 with dementia spanning these patient populations may need a distinct COS or outcomes  
28 for substitution within a COS. This decision will be made following identification and  
29 mapping of outcomes during our systematic review and from interviews with  
30 patients/family.  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43

### 44 **METHODS**

45 We will use methods outlined in the OMERACT handbook<sup>25</sup> and those endorsed by the  
46 COMET initiative.<sup>26</sup> Our study steering group will comprise two experts with clinical  
47 and/or research expertise in delirium and a patient/family representative for each of our  
48 four patient populations. We will use the COMET Checklist for Public Research Partners  
49 and the COS Study Developers Involved in Designing a COS study checklist<sup>27</sup> to guide  
50 and optimize our engagement with patients/family around the COS design and conduct.  
51  
52  
53  
54  
55  
56  
57

### 58 **Information Sources**



1  
2  
3 We will conduct: (1) a systematic review of outcomes and measures reported in  
4 published and ongoing trials of interventions to prevent or treat delirium (1980 onwards);  
5 and (2) qualitative study comprising one-on-one interviews with patient survivors, family  
6 members, and patient advocacy groups to identify outcomes important to patients and  
7 families that have experienced delirium.  
8  
9  
10  
11

### 14 **Systematic Review**

15  
16 *Search Strategy and Data Sources:* We will develop an electronic search strategy through  
17 an iterative process informed by an experienced medical information specialist. We will  
18 search the following electronic databases, adjusting vocabulary and syntax for each, from  
19 1980 to present: Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed  
20 Citations, CINAHL, Embase Classic+Embase, PsychINFO, and Web of Science. To  
21 avoid limiting the scope of outcomes identified, we will not apply a study design filter.  
22 We will limit inclusion to studies published in English. A second librarian will review the  
23 search strategy prior to execution using the Peer Review for Electronic Search Strategies  
24 (PRESS) template.<sup>28 29</sup> We will search for relevant systematic reviews in the Cochrane  
25 Library, PROSPERO, and Joanna Briggs and unpublished studies and ongoing trials on  
26 the International Clinical Trials Registry Platform (<http://apps.who.int/trialsearch>).  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36

37 *Study Selection:* Two investigators will independently screen titles and abstracts for  
38 eligible studies. Inclusion criteria include: (1) one of the four patient groups of interest;  
39 (2) pharmacological and non-pharmacological intervention for delirium prevention,  
40 treatment, or both; (3) compared to usual care, other pharmacological agents, or other  
41 non-pharmacological interventions; and (4) randomized (individual, cluster, and cross  
42 over randomization), quasi-randomized, and non-randomized intervention studies. If we  
43 identify <5 intervention studies in any of the four patient groups, we will expand our  
44 inclusion criteria to include observational studies with a control group. We will examine  
45 full-text publications of potentially relevant articles for eligibility. We will screen the  
46 reference lists of eligible studies and systematic reviews for additional eligible studies for  
47 inclusion. We will resolve disagreements through discussion; if unable to achieve  
48 consensus, we will refer to an independent arbiter from among the study team.  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

*Data extraction:* Two investigators will independently extract data from eligible studies on publication date, design, participant characteristics, study objectives, intervention, comparator, outcomes, their definition, and measures used to document outcomes.

*Quality assessment:* Two investigators will assess independently risk of bias using the Cochrane Risk of Bias tool for randomized and quasi-randomized studies and the Cochrane Robin-I tool for non-randomized studies.<sup>30</sup> Two investigators will assess independently quality of describing and reporting outcomes using the six-point MOMENT scoring system with a score of  $\geq 4$  representing high quality outcome reporting.<sup>31</sup> The six elements (each scored as 1 point) include: (1) Was the primary outcome stated? (2) Was the primary outcome clearly defined so that another researcher would be able to reproduce its measurement? (3) Were the secondary outcomes clearly stated? (4) Were the secondary outcomes clearly defined? (5) Do the authors explain the choice of outcomes they have selected? (6) Were methods used to enhance quality of outcome measurement, if appropriate? We will resolve disagreements through discussion; if unable to achieve consensus, will refer to an independent arbiter.

*Data synthesis:* We will generate tables of outcomes, their descriptions, and measures. We will tabulate the proportion of included studies that report on each outcome and rank order the outcomes accordingly. We will calculate the frequency of the following scenarios: (1) outcomes reported with the same title and definition; (2) outcomes reported with the same title but different definition; and (3) outcomes reported with different titles but the same definition. We will then map outcomes to the OMERACT domains.<sup>25</sup> We will use the outcome matrix as recommended by the ORBIT project to organize outcomes.<sup>32</sup> Steering group members will review the outcome list to identify those with similar wording or meaning to be reduced to a single outcome for the purposes of the Delphi round one questionnaire.

### **Qualitative Study**

We will conduct patient and family member interviews as evidence indicates that they may hold different views about which outcomes are of relevance compared to healthcare professionals.<sup>33</sup>

1  
2  
3 *Study sample:* We will use purposive<sup>34</sup> and maximum variation sampling<sup>35</sup> to identify  
4 patient and family participants with the characteristics shown in Table 1 (minimum of 1  
5 representative of each characteristic) for each patient group. For pragmatic reasons  
6 related to resource availability, we will only be able to recruit participants fluent in  
7 English. We will recruit a sample of 15 to 20 participants for each patient group which  
8 should be sufficient to achieve saturation.<sup>36</sup> We will adjust our sample size using a  
9 stopping criterion of three consecutive interviews with no additional material to terminate  
10 data collection.  
11  
12  
13  
14  
15  
16  
17  
18  
19

20 **Table 1: Stakeholder Sampling Characteristics**

21 Stakeholder group	22 Characteristic
23 Patients/family members <sup>a</sup>	24 Age ( $\leq 65$ ; $> 65$ ) 25 Sex (male; female) 26 Partner status (has partner; no partner) 27 Country of residence (North America; Europe/UK; 28 Australasia; other)
29 Expert clinicians <sup>b</sup>	30 Profession (physician, nurse, allied health) 31 Years of relevant clinical experience ( $< 5$ ; 5 to 10; $> 10$ ), 32 Country of residence (North America; Europe/UK; 33 Australasia; other).
34 Trialists/researchers <sup>c</sup>	35 Stage of research career (early: $< 5$ years; mid: 5 to 15 36 years; senior $> 15$ years) 37 Country of residence (North America; Europe/UK; 38 Australasia; other).

39  
40  
41  
42  
43  
44  
45  
46 a Patients that survived delirium within the last 18 months and family members that  
47 had direct contact with patients while experiencing delirium within the last 18  
48 months irrespective of survival i.e., we will interview family members of patients  
49 that did and did not survive the ICU..

50  
51  
52 b Physicians, nurses, and allied health professionals that do not meet the criteria of  
53 a trialist.

54  
55 c Authors of published (over last 10 years) or ongoing clinical trials evaluating  
56 interventions aimed at preventing or treating delirium.  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

*Data Collection:* An experienced qualitative researcher will conduct semi-structured telephone interviews enabling representation across a wide geographic area. Following clarification of what a study outcome is and the importance of COS, patient/family members will be asked to suggest outcomes of relevance to them when considering their experience of delirium; why these outcomes are important; and to identify which outcomes they would consider core and why. All interviews will be audio-recorded and transcribed for analysis.

*Data Analysis:* The experienced qualitative researcher and study investigator will independently examine interview transcripts using content analysis methods.<sup>37</sup> Outcomes that do not duplicate those identified from the systematic review will be categorized into domains and noted as only being identified by patients/family. Discussion with another investigator and the patient/family representative on the steering committee will confirm outcomes are: of relevance, not duplicative; and are allocated to the appropriate domain.<sup>38</sup>

### **Delphi Consensus Building Exercise**

*Participants, Recruitment and Sample Size:* We will use the eligibility criteria and sampling strategy shown in Table 1 ensuring a minimum of two participants from each stakeholder group representing each of the demographic variables and categories within those variables. We will aim to maintain a minimum of 20 participants representing each stakeholder group (total 60 participants) for each patient population (total 240 participants) throughout Delphi rounds (R). Based on an estimated attrition of 30% across rounds, we will target recruitment of 310 participants. A sample size of 240 participants will give us 80% power with two sided test at  $\alpha=5\%$  to detect a difference of 1.0 to 1.5 points between rounds on the Grading of Recommendations Assessment, Development and Evaluations Scale<sup>39</sup> (range 1 to 9) by feedback groups when standard deviations for change vary between 1.4 and 4.1.

We will recruit expert clinicians using recruitment flyers sent through membership lists of the European, American, and Australasian Delirium Associations/Societies as well as professional societies of clinicians treating to our patient groups. We will continue to enrol participants until our sample size and maximum variation targets are met. We will

1  
2  
3 send personalized recruitment emails to all trialists/researchers identified via our  
4 systematic review. As patient/family recruitment may poses challenges, we will use a  
5 multi-modal strategy including contact with relevant patient/family support/advocacy  
6 groups/charities as well as generic organizations such as the James Lind Alliance and  
7 COMET, use of social media including twitter and patient-focused Facebook pages,  
8 advertisements placed on public and patient involvement websites, snowballing  
9 techniques, and personal contacts.  
10  
11

12  
13  
14  
15  
16  
17  
18 *Round One:* We will include all outcomes identified through our systematic review and  
19 patient/family interviews. We will describe outcomes in lay terms, with medical terms in  
20 brackets, to improve comprehensibility by all. We will seek advice from our  
21 patient/family steering group members for lay descriptions. To introduce the Delphi, we  
22 will provide plain language summaries developed by COMET. We will program the  
23 Delphi using the online e-management system such as the one developed by COMET.  
24 Prior to execution, we will pilot the questionnaire with 8 individuals (patients, family  
25 members, healthcare professionals and trialists) to assess face validity, understanding,  
26 and acceptability.  
27  
28  
29  
30  
31  
32  
33  
34

35 We will provide participants with outcomes identified through systematic review and  
36 interviews common to all four patient groups. Additionally, we will provide those  
37 outcomes specific to one of our four patient groups *only* to participant representatives of  
38 that group. We will ask participants to score each outcome using the GRADE Scale<sup>39</sup>  
39 which ranges from 1 to 9 (1 to 3 = not important for inclusion; 4 to 6 = important but not  
40 critical; 7 to 9 = critical for inclusion). We selected this scoring system to facilitate  
41 maximum discrimination between questionnaire items as noted by COMET,<sup>40 41</sup> and to  
42 enable testing of our methodological hypotheses. To avoid presentation bias, we will  
43 randomize outcome presentation for each participant. We will provide the opportunity to  
44 add additional outcomes. We will send three email completion reminders at two-week  
45 intervals. We will collect demographic information to describe our study sample; and to  
46 provide each respondent with a unique identifier, enabling personalized reminders for  
47 completion of subsequent rounds.  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 We will examine data distribution of importance scores attributed to each outcome and  
4 calculate the mean and standard deviation. We will determine the proportion of  
5 participants rating each outcome as 7 to 9, 4 to 6, and 1 to 3. To reduce participant  
6 burden, we will retain for R2 those items scored between 7 and 9 (critical importance) by  
7  $\geq 50\%$  and between 1 and 3 (not important) by  $< 15\%$  of respondents. We will apply  
8 these criteria separately for patient group.  
9

10  
11  
12  
13  
14  
15  
16 *Round Two:* The steering group will review any additional outcomes provided in R1 to  
17 determine if they represent new outcomes for inclusion and to ensure wording is  
18 understandable by all participants. We will provide participants with their own R1  
19 response, summarized responses according to their patient population group, and the  
20 summarized responses of patient/family member participants (also according to patient  
21 group), and ask them to re-score the importance of each outcome. We will provide any  
22 new outcomes from R1 for scoring on the 1 to 9 importance scale. As with R1, we will  
23 send 3 email completion reminders at two-week intervals.  
24  
25  
26  
27  
28  
29

30  
31  
32 If new outcomes are identified in R1, we will conduct a third round comprising *only* these  
33 items to enable two rounds of importance scoring. Items to be brought forward to the  
34 consensus meeting will be those scored between 7 and 9 by  $\geq 70\%$  of participants and  
35 between 1 and 3 by  $< 15\%$  of participants. We will identify items separately for (a)  
36 patients/family and (b) healthcare professionals and researchers combined.  
37  
38  
39

40  
41  
42 In the event of significant attrition (defined as loss of more than 30% of participants  
43 within a stakeholder group) between rounds 1 and 2 we will engage in additional  
44 recruitment for Round 2. A priori we anticipate this may be particularly problematic for  
45 patients in the palliative group.  
46  
47  
48

### 49 50 51 **Nested Methodological Studies**

52 We will conduct nested methodological studies to:

- 53 1. Determine if Delphi feedback provided as the proportion of participants scoring the  
54 outcome between 7 and 9 (indicating critical for inclusion) as opposed to mean  
55  
56  
57  
58  
59  
60

1  
2  
3 scores influences subsequent scores, magnitude of change, items retained, and level  
4 of agreement (overall and by patient population group).  
5

- 6  
7 2. Qualitatively explore the process of patient/family engagement and participation  
8 throughout COS development to determine barriers and facilitators as well as  
9 modification of our processes if needed; and  
10  
11 3. Determine if Delphi versus nominal group technique influences which measures are  
12 retained for outcomes included in the COS.  
13  
14  
15

### 16 17 18 **Delphi Feedback**

19 *Randomization and Allocation:* We will randomize (1:1 stratified by patient population  
20 group) using a computer-generated schedule developed by the study statistician. We will  
21 generate a questionnaire for each Delphi participant using this allocation schedule.  
22  
23 Participants will be randomized to receive feedback as either the proportion of  
24 participants scoring the outcome as critical (for their patient population group) or patient  
25 population group mean response (Figure 1).  
26  
27  
28  
29

30  
31 *Statistical Analysis:* We will analyze differences between feedback groups in terms of:  
32 (a) subsequent scores and magnitude of opinion change; (b) items retained at Delphi end;  
33 and (c) level of agreement between patient population groups. We will calculate the  
34 percentage of items for which a participant changed their score between rounds; and the  
35 mean absolute change in score (ignoring direction of change). We will compare results  
36 according to randomization group using an independent t test overall and by patient  
37 population group. For each outcome, we will use linear regression to compare R2 scores  
38 between feedback groups and among patient population groups, adjusting for R1 scores  
39 and testing for the interaction between feedback groups and patient populations.  
40  
41  
42  
43  
44  
45  
46  
47  
48

49 To ascertain feedback group differences for items retained, we will create contingency  
50 tables, for each feedback group, to categorize the number of items retained by (i) both  
51 feedback groups; (ii) critical response feedback group only; (iii) mean feedback group  
52 only; and (iv) neither. We will determine percentage of items for which there was  
53 agreement to retain and percentage of discordant items retained by only one feedback  
54 group. To ascertain differences between feedback groups in terms of the level of  
55  
56  
57  
58  
59  
60

1  
2  
3 agreement of items retained across patient population groups, we will generate  
4 contingency tables categorizing number of items retained by (i) all; (ii) 1 group only; (iii)  
5 2 groups only; (iv) 3 groups only; and (iv) none. We will calculate the percentage  
6 agreement and percentage of discordant items.  
7  
8  
9

10  
11  
12 To explore the impact of feedback on consensus between patient population groups, we  
13 will transform the unit of analysis to be the questionnaire item (outcome), with each  
14 observation an aggregate statistic. We will use linear regression to determine, for each  
15 outcome, and for each feedback group, the absolute difference (ignoring direction) in  
16 mean R2 scores, adjusting for the participant's R1 score. We will compare absolute mean  
17 differences between patient population groups across outcomes between the two feedback  
18 groups using a paired t test. Finally, we will compare responses irrespective of patient  
19 population groups within each randomization arm, calculate the standard deviation for  
20 each outcome separately for R1 and R2, and calculate the reduction in each outcome's  
21 variability between rounds. We will compare mean reductions in standard deviation  
22 across all outcomes between feedback groups using a paired t test.  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32

33 Given the anticipated number of statistical tests, we expect 5 % to result in a P value  $\leq$   
34 0.05 by chance; therefore we will examine the percentage of tests with  $P \leq 0.05$  in  
35 relation to this expected percentage.  
36  
37  
38  
39

### 40 **Outcome Consensus Meeting**

41 We will hold consensus meetings to determine the outcomes for inclusion in the two  
42 COS's; prevention and/or treatment of delirium irrespective of patient population. We  
43 will identify additional outcomes for inclusion in COS specific to our four patient  
44 populations. We will aim to be as representative of all stakeholders as possible<sup>42</sup> as we  
45 anticipate there may be differences between stakeholder groups in the priority given to  
46 outcomes. To ensure we have meaningful input across participant groups, we will invite  
47 Delphi participants to attend the meeting. Due to the large size of our Delphi panel, we  
48 will randomly select eight participants to represent each of the stakeholder groups; two  
49 representing each patient population group.  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3 We will provide the consensus panel with outcomes established as critical using either  
4 method of feedback for inclusion via the Delphi across all four patient groups. We will  
5 use a modified nominal group technique to work towards consensus that includes small  
6 and whole group discussion and ranking, Ranking will be discussed with the aim of  
7 agreeing upon the top four or five outcomes across all patients and the top one to two  
8 specific to each patient population. To ensure there is no duplication in the final proposed  
9 set, each outcome will be discussed to ensure it relates to a distinct construct. If required  
10 we may hold an additional or standalone consensus meeting for patients and family  
11 members to enable facilitation of their understanding and thus informed voting on  
12 outcomes for the COS.  
13  
14  
15  
16  
17  
18  
19  
20  
21

### 22 **Process Evaluation of Patient/Family Participant Engagement**

23 We will conduct a process evaluation of patient/family participant engagement and  
24 participation throughout COS development.  
25  
26  
27  
28  
29

30 *Participants:* We will recruit participants to take part in semi-structured interviews to  
31 determine barriers and facilitators to participation as well as recommendations for  
32 improvement strategies to inform future COS development. We will recruit 15 to 20  
33 participants. Interviews will be audio recorded and transcribed verbatim.  
34  
35  
36  
37

38 *Analysis:* We will analyze interview transcripts using content analysis<sup>43-46</sup> employing an  
39 inductive, four-step content analysis process<sup>47</sup>. An experienced qualitative researcher and  
40 an investigator will independently identify, code, and categorize important meanings and  
41 predominant themes from the text. Following an immersive reading of the transcripts,  
42 initial patterns and recurring categories will be identified by relevant highlighting  
43 sections. The second step will seek similarities and differences between participant  
44 accounts. Third and fourth steps involve creation of codes and their application over the  
45 volume of interviews respectively. The larger team will be involved in in-depth reading  
46 of the coding to ensure credibility. NVivo 10 software will be used for all facets of the  
47 analysis.  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57

### 58 **Instruments to Measure Outcomes**

1  
2  
3 During our systematic review we will also extract measures for outcomes reported in  
4 studies meeting our inclusion criteria. We will assess the measurement and psychometric  
5 properties of measures of the outcomes selected for our two COS (prevention and  
6 treatment) using the COSMIN check list.<sup>48</sup>  
7  
8  
9

10  
11  
12 *Participants:* We will invite all Delphi participants involved in establishment of the  
13 COSs to participate in a second Delphi to establish measures for these outcomes. We will  
14 recruit additional participants if required due to attrition. We will recruit an additional 24  
15 participants to take part in a separate consensus building exercise using only a modified  
16 nominal group technique to address the following hypothesis: measures selected for the  
17 COS are influenced by the method used for consensus building (Delphi versus nominal  
18 group technique).  
19  
20  
21  
22  
23  
24  
25

26  
27 *Procedures:* We will use the same Delphi methods as described above to establish one set  
28 of measures each for the two COS (prevention and treatment) including the same nested  
29 study design of randomization to two feedback methods (Delphi group). We will provide  
30 ‘measure cards’ provided standardized descriptions of the measures, psychometric  
31 properties, and feasibility of use (i.e., time to complete, number of items) in language  
32 understandable to all participants. We will use the same nominal group technique  
33 methods as described for the COS consensus meetings to establish a second set of  
34 measures (nominal group technique group). We will provide to the same description of  
35 the measures and their psychometric properties as provided to the Delphi method group.  
36 Additionally, we will invite a psychometrician, clinicians and/or researchers with  
37 familiarity with the measures to the nominal group technique group thus enabling  
38 informed discussion.  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48

49  
50 *Statistical Analysis:* We will perform the same statistical analyses as described for the  
51 COS Delphi to determine differences related to consensus group method. To ascertain  
52 differences in terms of measures retained between consensus group methods, we will  
53 create contingency tables to categorize number of items retained on completion by (i)  
54 both Delphi and nominal group technique groups; (ii) Delphi group only; (iii) nominal  
55 group technique only; and (iv) neither. We will determine the percentage of items for  
56  
57  
58  
59  
60

1  
2  
3 which there was agreement along with the percentage of discordant items, retained by  
4 one consensus group method but not the other.  
5  
6  
7

### 8 9 **Final Consensus**

10 We will hold a final steering group meeting to review the findings of the consensus  
11 building exercises. Depending on the number of measures rated as critical to include we  
12 will hold a second consensus meeting using the methods described above to guide final  
13 decisions.  
14  
15  
16  
17

### 18 19 **ETHICS AND DISSEMINATION**

20 We are seeking research ethics board approvals as required by local governance. We will  
21 obtain written consent from participants in interviews and consensus meetings.  
22  
23 Participation in Delphi rounds will be considered indicative of consent. Consent will  
24 emphasize the voluntary nature of participation and anonymity.  
25  
26  
27  
28

29  
30 Knowledge users within our investigator team as well as the support of three international  
31 Delirium Societies (American, Australasian, European) will be instrumental in  
32 dissemination of the COS's and subsequent uptake. We will provide a one page summary  
33 (clinicians/researchers and in lay language for patients and families) to these Societies for  
34 distribution among their networks and engage with them to seek additional opportunities  
35 to present our findings (educational seminars/workshops). We will disseminate our  
36 findings through peer-reviewed and open access publications, and presentations at  
37 international conferences purposefully selected to reach a wide range of knowledge users  
38 taking into account geographic locations. We will engage with journal editors and  
39 funding agencies to promote awareness of our COS's.  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**REFERENCES**

1. American Psychiatric Association, . *Diagnostic and Statistical Manual (5th edition)*. Washington, DC: American Psychiatric Association, 2013.
2. Trzepacz P, Meagher D. *Oxford Textbook of Psychiatry (2nd edition)*. London, UK: Oxford University Press, 2009.
3. Siddiqi N, Young J, House A, et al. Stop Delirium! A complex intervention to prevent delirium in care homes: a mixed-methods feasibility study. *Age Ageing* 2011;**40**:90-98.
4. Hosie A, Davidson P, Agar M, et al. Delirium prevalence, incidence, and implications for screening in specialist palliative care inpatient settings: a systematic review. *Palliat Med* 2012;**27**:486-98.
5. Inouye S, Westendorp R, Saczynski J. Delirium in elderly people. *Lancet* 2014;**383**:911–22.
6. Mistraletti G, Carloni E, Cigada M, et al. Sleep and delirium in the intensive care unit. *Minerva Anestesiol* 2008;**74**(6):329-33.
7. Daoud A, Duff JP, Joffe AR, et al. Diagnostic accuracy of delirium diagnosis in pediatric intensive care: a systematic review. *Crit Care* 2014;**18**(5):489.
8. Bellapart J, Boots R. Potential use of melatonin in sleep and delirium in the critically ill. *Br J Anaesth* 2012;**108**(4):572-80.
9. Zaal IJ, Slooter AJ. Delirium in critically ill patients: epidemiology, pathophysiology, diagnosis and management. *Drugs* 2012;**72**(11):1457-71.
10. Bickel H, Gradinger R, Kochs E, et al. High risk of cognitive and functional decline after postoperative delirium. A three-year prospective study. . *Dement Geriatr Cogn Disord* 2008;**26**:26-31.
11. O'Malley G, Leonard M, Meagher D. The delirium experience: A review. *J Psychosomatics* 2008;**65**:223-28.
12. Corsinovi L, Bo M, Ricauda Aimonino N, et al. Predictors of falls and hospitalization outcomes in elderly patients admitted to an acute geriatric unit. *Arch Gerontol Geriatr* 2009;**49**:142-45.
13. Leslie D, Marcantonio E, Zhang Y, et al. One-year health care costs associated with delirium in the elderly population. *Arch Intern Med* 2008;**14**:27-32.

- 1  
2  
3 14. Barr J, Fraser G, Puntillo K, et al. American College of Critical Care Medicine:  
4  
5 Clinical practice guidelines for the management of pain, agitation, and delirium in  
6  
7 adult patients in the intensive care unit. . Crit Care Med 2013;**41**:278–80.
- 8  
9 15. Traube C, Mauer E, Gerber L, et al. Cost associated with pediatric delirium in the  
10  
11 ICU. Crit Care Med 2016.
- 12  
13 16. Buurman B, Hoogerduijn J, de Haan R, et al. Geriatric conditions in acutely  
14  
15 hospitalized older patients: prevalence and one-year survival and functional  
16  
17 decline. PLoS One 2011;**6**:e26951.
- 18  
19 17. Rudolph J, Inouye S, Jones R, et al. Delirium: an independent predictor of functional  
20  
21 decline after cardiac surgery. J Am Geriatr Soc 2010;**58**:643-49.
- 22  
23 18. Carbone M, Gugliucci M. Delirium and the family caregiver: the need for evidence-  
24  
25 based education interventions. Gerontologist 2015;**55**:345-52.
- 26  
27 19. Finucane A, Lugton J, Kennedy C, et al. The experiences of caregivers of patients  
28  
29 with delirium, and their role in its management in palliative care settings: an  
30  
31 integrative literature review. Psychooncology 2016.
- 32  
33 20. Crocker E, Beggs T, Hassan A, et al. Long-term effects of postoperative delirium in  
34  
35 patients undergoing cardiac operation: a systematic review. Ann Thorac Surg  
36  
37 2016;pii: S0003-4975(16)30402-7.
- 38  
39 21. Clarke M. Standardising outcomes for clinical trials and systematic reviews. Trials  
40  
41 2007;**8**:39.
- 42  
43 22. Sanderson T, Morris M, Calnan M, et al. What outcomes from pharmacologic  
44  
45 treatments are important to people with rheumatoid arthritis? Creating the basis of  
46  
47 a patient core set. Arthrit Care Res 2010;**62**:640–46.
- 48  
49 23. Gagnon P. Treatment of delirium in supportive and palliative care. Curr Opin Support  
50  
51 Palliat Care 2008;**2**:60-66.
- 52  
53 24. LaHue, SC, Liu V. Loud and clear: sensory impairment, delirium, and functional  
54  
55 recovery in critical illness. Am J Respir Crit Care Med 2016 **194**:252-3.
- 56  
57 25. Tugwell P, Boers M, Brooks P, et al. OMERACT: an international initiative to  
58  
59 improve outcome measurement in rheumatology. Trials 2007;**8**:38.
- 60  
26. Williamson P, Altman D, Blazeby J, et al. Developing core outcome sets for clinical  
trials: issues to consider. Trials 2012;**13**:132.

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
27. COMET PoPPIE group. Checklist for public research partners and core outcome set (COS) study developers involved in designing a COS study. Secondary Checklist for public research partners and core outcome set (COS) study developers involved in designing a COS study 2015. <http://www.comet-initiative.org/assets/downloads/COS%20study%20development%20-%20PPI%20checklist%2016-03-16.pdf>.
  28. McGowan J, Sampson M, Salzwedel DM, et al. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol* 2016;**75**:40-46.
  29. Sampson M, McGowan J, Cogo E, et al. An evidence-based practice guideline for the peer review of electronic search strategies. *J Clin Epidemiol* 2009;**62**(9):944-52.
  30. Sterne J, Hernán M, Reeves B, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;**355**:i4919.
  31. Harman N, IA B, P C, et al. MOMENT--Management of Otitis Media with Effusion in Cleft Palate: protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. *Trials* 2013;**14**:70.
  32. Kirkham J, Dwan K, Altman D, et al. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *BMJ* 2010;**340**:c365.
  33. Boers M, Kirwan J, Tugwell P, et al. The OMERACT handbook. Ottawa: OMERACT, 2014.
  34. Pope C, Mays N. Qualitative Research: Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. *BMJ* 1995;**311**(6996):42-45.
  35. Patton M. Purposeful sampling. *Qualitative evaluation and research methods*. Beverly Hills, CA: Sage, 1990:169-86.
  36. Francis J, Johnston M, Robertson C, et al. What is an adequate sample size? Operationalising data saturation for theory-based interview studies. *Psychol Health* 2010;**25**:1229-45.
  37. Elo S, Kyngäs H. The qualitative content analysis process. *J Adv Nurs* 2008;**62**:107-15.
  38. Macefield R, Jacobs M, Korfage I, et al. Developing core outcomes sets: methods for identifying and including patient-reported outcomes (PROs). *Trials* 2014;**15**:49.

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
39. The GRADE working group. GRADE. Secondary GRADE 2016.  
<http://www.gradeworkinggroup.org/>.
40. Sinha I, Smyth R, Williamson P. Using the Delphi technique to determine which outcomes to measure in clinical trials: recommendations for the future based on a systematic review of existing studies. *PLoS Med* 2011;**8**: e1000393.
41. The COMET Initiative. The COMET Initiative. Secondary The COMET Initiative 2011. <http://www.comet-initiative.org>.
42. Simon L, Strand V, Bingham C, et al. OMERACT 11: international consensus conference on outcome measures. *J Rheumatol* 2014;**41**:145-49.
43. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse Educ Today* 2004;**24**(2):105-12.
44. Onwuegbuzie A, Dickinson W, Leech N, et al. A qualitative framework for collecting and analyzing data in focus group research. *Int J Qual Meth* 2009;**8**:1-21.
45. Carlsen B, Glenton C. What about N? A methodological study of sample-size reporting in focus group studies. *BMC Med Res Methodol* 2011;**11**:26.
46. Vaismoradi M, Turunen H, Bondas T. Content analysis and thematic analysis: Implications for conducting a qualitative descriptive study. *Nursing & health sciences* 2013;**15**(3):398-405.
47. Burnard F. Teaching the analysis of textual data: an experiential approach. *Nurse Educ Today* 1996;**16**:278–81.
48. Terwee CB, Mokkink LB, Knol DL, et al. Rating the methodological quality in systematic reviews of studies on measurement properties: a scoring system for the COSMIN checklist. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2012;**21**(4):651-7.

### **AUTHOR CONTRIBUTIONS**

LR and VP conceived of the study. LR, MA, NS, and VP developed the study protocol. MC advised on the design of the nested methodological studies as well as contributed to design of the protocol. All authors edited the manuscript, and read and approved the final version.

### **FUNDING STATEMENT**

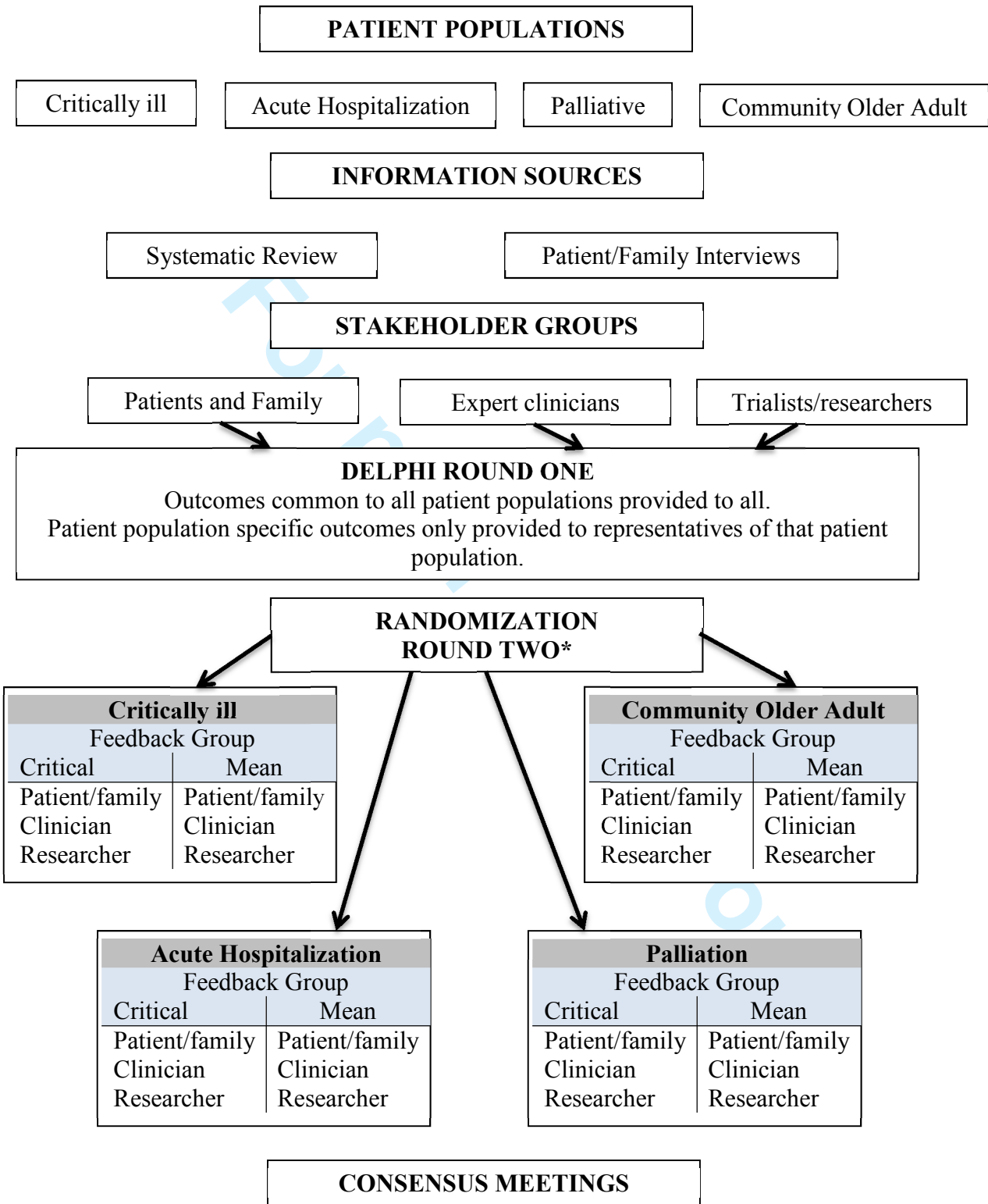
This study is not funded. Dr. Louise Rose holds a Canadian Institutes of Health Research New Investigator Award. Jennifer Ansell has received funding towards her PhD Studentship through the University of Toronto.

### **COMPETING INTERESTS STATEMENT**

The authors have no competing interests to declare.



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



**Figure 1: Flow of core outcome set development**  
\* We will conduct an third Delphi round if additional outcomes are identified in round one

# BMJ Open

## Development of core outcome sets for effectiveness trials of interventions to prevent and/or treat delirium (Del-COrS): Study protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-016371.R1
Article Type:	Protocol
Date Submitted by the Author:	25-May-2017
Complete List of Authors:	Rose, Louise; University of Toronto, Lawrence S. Bloomberg Faculty of Nursing Agar, Meera ; University of Technology Sydney, Centre of Cardiovascular and Chronic Care, Faculty of Health Burry, Lisa; Mount Sinai Hospital, Pharmacy Campbell, Noll; Indiana University Bloomington, Clarke, Mike; All-Ireland Hub for Trials Methodology Research, Centre for Public Health Lee, Jacques; University of Toronto, Clinical Epidemiology Unit Siddiqi, Najma; University of York, Psychiatry, Hull York Medical School, York and Bradford District Care NHS Foundation Trust, Bradford, UK Page, Valerie J.; West Hertfordshire Hospitals NHS Trust, Anaesthetics
<b>Primary Subject Heading</b>:	Mental health
Secondary Subject Heading:	Geriatric medicine, Intensive care, Palliative care
Keywords:	Delirium & cognitive disorders < PSYCHIATRY, core outcome set, systematic review, research methods

SCHOLARONE™  
Manuscripts

**TITLE**

Development of core outcome sets for effectiveness trials of interventions to prevent and/or treat delirium (Del-CORs): Study protocol

**CORRESPONDING AUTHOR**

Louise Rose

Department of Critical Care Medicine, Sunnybrook Health Sciences Centre;  
Lawrence S. Bloomberg Faculty of Nursing and Interdepartmental Division of Critical  
Care Medicine, University of Toronto

Postal Address: 155 College St. Rm 276 Toronto, Canada

Email: [louise.rose@utoronto.ca](mailto:louise.rose@utoronto.ca)

Phone: +1 416 978 3492

**CO-AUTHORS**

Meera Agar

Faculty of Health Sciences, University of Technology, Sydney, Australia

Lisa Burry

Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada

Noll Campbell

College of Pharmacy, Indiana University-Purdue University, Indianapolis, United States

Mike Clarke

School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast,  
Belfast, Northern Ireland

Jacques Lee

Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Toronto, Canada

Najma Siddiqi

School of Medicine, York University, York, England

Valerie Page

Watford General Hospital, Watford, England

For the Del-CORs group – Jennifer Ansell, Bronagh Blackwood; Rich Jones; Imogen  
Featherstone; Leslie Fornear; Annmarie Hosie; Miriam Johnson; Dale Needham; Nadine  
Schofield; Jo Taylor; Peter Lawlor

**KEYWORDS**

Delirium; core outcome set; systematic review; research methods

**WORD COUNT:** 3990 (Not including table and Figure).

## ABSTRACT

### Introduction

Delirium is a common, serious, and potentially preventable condition with devastating impact on quality of life prompting a proliferation of interventional trials. Core outcome sets aim to standardize outcome reporting by identifying outcomes perceived fundamental for measurement in trials of a specific interest area. Our aim is to develop international consensus on two core outcome sets for trials of interventions to prevent and/or treat delirium, irrespective of study population. We aim to identify additional core outcomes specific to the critically ill, acutely hospitalized patients, palliative care, and older adults.

### Methods and analysis

We will conduct a systematic review of published and ongoing delirium trials (1980 onwards) and one-on-one interviews of patients that have experienced delirium and family members. These data will inform Delphi round one of a two-stage consensus process. In round two we will provide participants their own response, summarized group responses, and those of patient/family participants for re-scoring. We will randomize participants to receive feedback as proportion scoring the outcome as critical, or as group mean responses. We will hold a consensus meeting using nominal group technique to finalize outcomes for inclusion. We will repeat the Delphi process and consensus meeting to select measures for each core outcome. We will recruit 240 Delphi participants giving us 80% power to detect a 1.0 to 1.5 point (9-point scale) difference by feedback method between rounds. We will analyze differences for subsequent scores, magnitude of opinion change, items retained, and level of agreement.

### Ethics and dissemination

We are obtaining research ethics approvals according to local governance. Participation will be voluntary and data deidentified. Support from three international delirium organizations will be instrumental in dissemination and core outcome set uptake. We will disseminate through peer-reviewed open access publications, and present at conferences selected to reach a wide range of knowledge users.

1  
2  
3 Word Count: 300  
4  
5  
6

7 This Core Outcome Set is registered on the COMET website [http://www.comet-](http://www.comet-initiative.org/studies/details/796)  
8 [initiative.org/studies/details/796](http://www.comet-initiative.org/studies/details/796).  
9

10  
11 The systematic review is registered on PROSPERO-ID: CRD42016052704  
12 [https://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42016052704](https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016052704)  
13  
14

15  
16  
17 The study is funded by the Canadian Institutes of Health Research  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## STRENGTHS and LIMITATIONS

### Strengths

- Rigorous systematic review and core outcome set development methods that adhere to Cochrane and COMET guidelines
- Engagement with survivors of delirium during development of the protocol
- Support of three international Delirium Societies (American, Australasian, European) will facilitate participant recruitment, dissemination, and uptake of our core outcome sets

### Potential Limitations

- Ability to recruit and retain participants, particularly delirium survivors and their family members. We are using multi-modal recruitment strategies and seeking advice from organizations experienced in recruitment and retention of patient/family participants.
- Ability to recruit participants with broad geographical representation.
- Inability to come to consensus on the core outcomes or the measures for these outcomes.
- Important outcomes are identified that are difficult to measure due to the absence of valid and reliable measures.

## INTRODUCTION

Delirium is a complex syndrome characterized by an acute confusional state with rapid onset, a fluctuating course, circadian disturbances, reduced or increased motor activity, as well as changes in cognition, notably in the domains of attention and higher-level thought processing.<sup>1 2</sup> Delirium is a common, serious, and potentially preventable source of morbidity, with devastating impacts on quality of life, and mortality. Delirium impacts all age groups, from infants to the very elderly. This includes patients, including those accessing primary care, resident in nursing homes,<sup>3</sup> those receiving palliative care services,<sup>4</sup> and a significant number of hospitalized patients, including the acute and critically ill. Prevalence rates in hospitalized patients range from 25% to 80%.<sup>5-8</sup>

Delirium is not a benign, self-limiting condition. As well as increased mortality, delirium is associated with prolonged length of stay (LOS); higher rates of unintentional device removal; falls and incontinence in the elderly; significant emotional distress for patients, families, caregivers, and healthcare professionals;<sup>9-12</sup> and escalating public healthcare costs.<sup>13-15</sup> Delirium also carries long term consequences including impaired physical functioning<sup>16 17</sup> and loss of independence resulting in long-term care placement;<sup>5</sup> caregiver burden;<sup>18 19</sup> decreased quality of life;<sup>20</sup> cognitive decline, and increased risk of dementia and Alzheimer's disease.<sup>11</sup>

With increased recognition of delirium as a common, costly, and potentially preventable condition associated with adverse outcomes, encouragingly studies examining interventions to prevent and/or treat delirium continue to proliferate. Currently, there is no systematic approach to the selection and reporting of outcomes and their measures in these studies resulting in reporting of numerous and varied study outcomes and measures for these outcomes. This hinders progress towards improvements in care, as to best inform the evidence base, outcomes must be selected, defined, and measured consistently across studies of similar interventions in similar populations. Core outcome sets (COS), developed using rigorous consensus processes involving key stakeholders including patients and carers, comprise outcomes perceived as fundamental to measure in all trials related to a specific and defined area of interest (such as a disease, condition, or intervention).<sup>21 22</sup> Although the importance and value of COS for standardizing outcomes

1  
2  
3 and measurement across trials is increasingly recognized, in general, they are still in their  
4 infancy and as yet have not been developed for trials of interventions to prevent or treat  
5 delirium. Therefore we aim to develop international consensus on two COS appropriate  
6 for trials of interventions designed to (1) prevent or (2) treat delirium, irrespective of  
7 study population. We also aim to identify additional core outcomes specific to four  
8 patient groups: the critically ill; patients requiring hospitalization in an acute care setting;  
9 palliative care; and older adults living in residential care or the community.  
10  
11  
12  
13  
14  
15  
16

### 17 Scope of Core Outcome Set Development

18  
19 The scope of our COS will include our four patient populations of interest, considered at  
20 high risk of developing delirium.<sup>3 5 23 24</sup> These include (1) critically ill adults and children  
21 receiving care in high acuity settings, including intensive care and high dependency units;  
22 (2) non-critically ill adults and children hospitalized in acute care settings including  
23 postoperative surgical and medical patients, and patients presenting to an emergency  
24 department (ED); (3) adults and children receiving palliative care, either in a hospital,  
25 hospice, or community setting; and (4) older adults (65 and over) living in nursing or  
26 residential care homes or living in their own homes and defined as at risk of delirium by  
27 study authors. We recognize that certain subpopulations such as children and older adults  
28 with dementia spanning these patient populations may need a distinct COS or outcomes  
29 for substitution within a COS. This decision will be made following identification and  
30 mapping of outcomes during our systematic review and from interviews with  
31 patients/family.  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43

### 44 **METHODS**

45 We will use methods outlined in the OMERACT handbook<sup>25</sup> and those endorsed by the  
46 COMET initiative.<sup>26</sup> Our study steering group will comprise two experts with clinical  
47 and/or research expertise in delirium and a patient/family representative for each of our  
48 four patient populations. We will use the COMET Checklist for Public Research Partners  
49 and the COS Study Developers Involved in Designing a COS study checklist<sup>27</sup> to guide  
50 and optimize our engagement with patients/family around the COS design and conduct.  
51  
52  
53  
54  
55  
56  
57

### 58 **Information Sources**



1  
2  
3 We will conduct: (1) a systematic review of outcomes and measures reported in  
4 published and ongoing trials of interventions to prevent or treat delirium (1980 onwards);  
5 and (2) qualitative study comprising one-on-one interviews with patient survivors, family  
6 members, and patient advocacy groups to identify outcomes important to patients and  
7 families that have experienced delirium.  
8  
9  
10  
11

### 12 13 14 **Systematic Review**

15  
16 *Search Strategy and Data Sources:* We will develop an electronic search strategy through  
17 an iterative process informed by an experienced medical information specialist. We will  
18 search the following electronic databases, adjusting vocabulary and syntax for each, from  
19 1980 to present: Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed  
20 Citations, CINAHL, Embase Classic+Embase, PsychINFO, and Web of Science. To  
21 avoid limiting the scope of outcomes identified, we will not apply a study design filter.  
22 We will limit inclusion to studies published in English. A second librarian will review the  
23 search strategy prior to execution using the Peer Review for Electronic Search Strategies  
24 (PRESS) template.<sup>28 29</sup> We will search for relevant systematic reviews in the Cochrane  
25 Library, PROSPERO, and Joanna Briggs and unpublished studies and ongoing trials on  
26 the International Clinical Trials Registry Platform (<http://apps.who.int/trialsearch>).  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36

37  
38 *Study Selection:* Two investigators will independently screen titles and abstracts for  
39 eligible studies. Inclusion criteria include: (1) one of the four patient groups of interest;  
40 (2) pharmacological and non-pharmacological intervention for delirium prevention,  
41 treatment, or both; (3) compared to usual care, other pharmacological agents, or other  
42 non-pharmacological interventions; and (4) randomized (individual, cluster, and cross  
43 over randomization), quasi-randomized, and non-randomized intervention studies. If we  
44 identify <5 intervention studies in any of the four patient groups, we will expand our  
45 inclusion criteria to include observational studies with a control group. We will examine  
46 full-text publications of potentially relevant articles for eligibility. We will screen the  
47 reference lists of eligible studies and systematic reviews for additional eligible studies for  
48 inclusion. We will resolve disagreements through discussion; if unable to achieve  
49 consensus, we will refer to an independent arbiter from among the study team.  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

*Data extraction:* Two investigators will independently extract data from eligible studies on publication date, design, participant characteristics, study objectives, intervention, comparator, outcomes, their definition, and measures used to document outcomes.

*Quality assessment:* Two investigators will assess independently risk of bias using the Cochrane Risk of Bias tool for randomized and quasi-randomized studies and the Scottish Intercollegiate Guidelines Network (SIGN) checklists for non-randomized studies.<sup>30</sup> Two investigators will assess independently quality of describing and reporting outcomes using the six-point MOMENT scoring system with a score of  $\geq 4$  representing high quality outcome reporting.<sup>31</sup> The six elements (each scored as 1 point) include: (1) Was the primary outcome stated? (2) Was the primary outcome clearly defined so that another researcher would be able to reproduce its measurement? (3) Were the secondary outcomes clearly stated? (4) Were the secondary outcomes clearly defined? (5) Do the authors explain the choice of outcomes they have selected? (6) Were methods used to enhance quality of outcome measurement, if appropriate? We will resolve disagreements through discussion; if unable to achieve consensus, will refer to an independent arbiter.

*Data synthesis:* We will generate tables of outcomes, their descriptions, and measures. We will tabulate the proportion of included studies that report on each outcome and rank order the outcomes accordingly. We will calculate the frequency of the following scenarios: (1) outcomes reported with the same title and definition; (2) outcomes reported with the same title but different definition; and (3) outcomes reported with different titles but the same definition. We will then map outcomes to the OMERACT domains.<sup>25</sup> We will use the outcome matrix as recommended by the ORBIT project to organize outcomes.<sup>32</sup> Steering group members will review the outcome list to identify those with similar wording or meaning to be reduced to a single outcome for the purposes of the Delphi round one questionnaire.

### **Qualitative Study**

We will conduct patient and family member interviews as evidence indicates that they may hold different views about which outcomes are of relevance compared to healthcare professionals.<sup>33</sup>

1  
2  
3 *Study sample:* We will use purposive<sup>34</sup> and maximum variation sampling<sup>35</sup> to identify  
4 patient and family participants with the characteristics shown in Table 1 (minimum of 1  
5 representative of each characteristic) for each patient group. For the patient groups  
6 representing high acuity settings, acute care settings, and palliative care, we will also  
7 target parents and where possible children that have experienced delirium. For pragmatic  
8 reasons related to resource availability, we will only be able to recruit participants fluent  
9 in English. We will recruit a sample of 15 to 20 participants for each patient group which  
10 should to be sufficient to achieve saturation.<sup>36</sup> We will adjust our sample size using a  
11 stopping criterion of three consecutive interviews with no additional material to terminate  
12 data collection.  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22

23 **Table 1: Stakeholder Sampling Characteristics**

24 Stakeholder group	25 Characteristic
26 Patients/family members <sup>a</sup>	27 28 Age ( $\leq 65$ ; $>65$ ) 29 Sex (male; female) 30 Partner status (has partner; no partner) 31 Country of residence (North America; Europe/UK; 32 Australasia; other)
35 Expert clinicians <sup>b</sup>	36 37 Profession (physician, nurse, allied health) 38 Years of relevant clinical experience ( $<5$ ; 5 to 10; $>10$ ), 39 Country of residence (North America; Europe/UK; 40 Australasia; other).
42 Trialists/researchers <sup>c</sup>	43 44 Stage of research career (early: $<5$ years; mid: 5 to 15 45 years; senior $>15$ years) 46 Country of residence (North America; Europe/UK; 47 Australasia; other).

49  
50 a Patients that survived delirium within the last 18 months and family members that  
51 had direct contact with patients while experiencing delirium within the last 18  
52 months irrespective of survival i.e., we will interview family members of patients  
53 that did and did not survive the ICU.  
54

55 b Physicians, nurses, and allied health professionals that do not meet the criteria of  
56 a trialist.  
57  
58  
59  
60

- 1  
2  
3 c Authors of published (over last 10 years) or ongoing clinical trials evaluating  
4 interventions aimed at preventing or treating delirium.  
5  
6

7  
8 *Data Collection:* An experienced qualitative researcher will conduct semi-structured  
9 telephone interviews enabling representation across a wide geographic area. Following  
10 clarification of what a study outcome is and the importance of COS, patient/family  
11 members will be asked to suggest outcomes of relevance to them when considering their  
12 experience of delirium; why these outcomes are important; and to identify which  
13 outcomes they would consider core and why. All interviews will be audio-recorded and  
14 transcribed for analysis.  
15  
16  
17  
18  
19

20  
21  
22 *Data Analysis:* The experienced qualitative researcher and study investigator will  
23 independently examine interview transcripts using content analysis methods.<sup>37</sup> Outcomes  
24 that do not duplicate those identified from the systematic review will be categorized into  
25 domains and noted as only being identified by patients/family. Discussion with another  
26 investigator and the patient/family representative on the steering committee will confirm  
27 outcomes are: of relevance, not duplicative; and are allocated to the appropriate domain.<sup>38</sup>  
28  
29  
30  
31  
32  
33

### 34 **Delphi Consensus Building Exercise**

35  
36 *Participants, Recruitment and Sample Size:* We will use the eligibility criteria and  
37 sampling strategy shown in Table 1 ensuring a minimum of two participants from each  
38 stakeholder group representing each of the demographic variables and categories within  
39 those variables. For the patient groups representing high acuity settings, acute care  
40 settings, and palliative care, we will also aim to have a minimum of 5 participants  
41 representing paediatrics in each group if deemed appropriate to combine in the same COS  
42 development process following our systematic review work. We will aim to maintain a  
43 minimum of 20 participants representing each stakeholder group (total 60 participants)  
44 for each patient population (total 240 participants) throughout Delphi rounds (R). Based  
45 on an estimated attrition of 30% across rounds, we will target recruitment of 310  
46 participants. A sample size of 240 participants will give us 80% power with two sided  
47 test at  $\alpha=5\%$  to detect a difference of 1.0 to 1.5 points between rounds on the Grading of  
48 Recommendations Assessment, Development and Evaluations Scale<sup>39</sup> (range 1 to 9) by  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 feedback groups when standard deviations for change vary between 1.4 and 4.1. A priori  
4 we anticipate there may be differences in responses provided by patients and family  
5 members compared to those provided by clinicians and researchers. We will test for  
6 interaction and if significant examine each group separately.  
7  
8  
9

10  
11  
12 We will recruit expert clinicians using recruitment flyers sent through membership lists  
13 of the European, American, and Australasian Delirium Associations/Societies as well as  
14 professional societies of clinicians treating to our patient groups. We will continue to  
15 enrol participants until our sample size and maximum variation targets are met. We will  
16 send personalized recruitment emails to all trialists/researchers identified via our  
17 systematic review. As patient/family recruitment may poses challenges, we will use a  
18 multi-modal strategy including contact with relevant patient/family support/advocacy  
19 groups/charities as well as generic organizations such as the James Lind Alliance and  
20 COMET, use of social media including twitter and patient-focused Facebook pages,  
21 advertisements placed on public and patient involvement websites, snowballing  
22 techniques, and personal contacts.  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32

33 *Round One:* We will include all outcomes identified through our systematic review and  
34 patient/family interviews. We will describe outcomes in lay terms, with medical terms in  
35 brackets, to improve comprehensibility by all. We will seek advice from our  
36 patient/family steering group members for lay descriptions. To introduce the Delphi, we  
37 will provide plain language summaries developed by COMET. We will program the  
38 Delphi using the online e-management system such as the one developed by COMET.  
39 Prior to execution, we will pilot the questionnaire with 8 individuals (patients, family  
40 members, healthcare professionals and trialists) to assess face validity, understanding,  
41 and acceptability.  
42  
43  
44  
45  
46  
47  
48  
49

50  
51 We will provide participants with outcomes identified through systematic review and  
52 interviews common to all four patient groups. Additionally, we will provide those  
53 outcomes specific to one of our four patient groups *only* to participant representatives of  
54 that group. We will ask participants to score each outcome using the GRADE Scale<sup>39</sup>  
55 which ranges from 1 to 9 (1 to 3 = not important for inclusion; 4 to 6 = important but not  
56  
57  
58  
59  
60

1  
2  
3 critical; 7 to 9 = critical for inclusion). We selected this scoring system to facilitate  
4 maximum discrimination between questionnaire items as noted by COMET,<sup>40 41</sup> and to  
5 enable testing of our methodological hypotheses. To avoid presentation bias, we will  
6 randomize outcome presentation for each participant. We will provide the opportunity to  
7 add additional outcomes. We will send three email completion reminders at two-week  
8 intervals. We will collect demographic information to describe our study sample; and to  
9 provide each respondent with a unique identifier, enabling personalized reminders for  
10 completion of subsequent rounds.  
11  
12

13  
14  
15  
16  
17  
18  
19 We will examine data distribution of importance scores attributed to each outcome and  
20 calculate the mean and standard deviation. We will determine the proportion of  
21 participants rating each outcome as 7 to 9, 4 to 6, and 1 to 3. To reduce participant  
22 burden, we will retain for R2 those items scored between 7 and 9 (critical importance) by  
23  $\geq 50\%$  and between 1 and 3 (not important) by  $< 15\%$  of respondents. We will apply  
24 these criteria separately for patient group.  
25  
26  
27  
28  
29  
30

31  
32 *Round Two:* The steering group will review any additional outcomes provided in R1 to  
33 determine if they represent new outcomes for inclusion and to ensure wording is  
34 understandable by all participants. We will provide participants with their own R1  
35 response, summarized responses according to their patient population group, and the  
36 summarized responses of patient/family member participants (also according to patient  
37 group), and ask them to re-score the importance of each outcome. We will provide any  
38 new outcomes from R1 for scoring on the 1 to 9 importance scale. As with R1, we will  
39 send 3 email completion reminders at two-week intervals.  
40  
41  
42  
43  
44  
45  
46  
47

48 If new outcomes are identified in R1, we will conduct a third round comprising *only* these  
49 items to enable two rounds of importance scoring. Items to be brought forward to the  
50 consensus meeting will be those scored between 7 and 9 by  $\geq 70\%$  of participants and  
51 between 1 and 3 by  $< 15\%$  of participants. We will identify items separately for (a)  
52 patients/family and (b) healthcare professionals and researchers combined.  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 In the event of significant attrition (defined as loss of more than 30% of participants  
4 within a stakeholder group) between rounds 1 and 2 we will engage in additional  
5 recruitment for Round 2. A priori we anticipate this may be particularly problematic for  
6 patients in the palliative group.  
7  
8  
9

### 10 11 12 **Nested Methodological Studies**

13 We will conduct nested methodological studies to:

- 14 1. Determine if Delphi feedback provided as the proportion of participants scoring the  
15 outcome between 7 and 9 (indicating critical for inclusion) as opposed to mean  
16 scores influences subsequent scores, magnitude of change, items retained, and level  
17 of agreement (overall and by patient population group).  
18
- 19 2. Qualitatively explore the process of patient/family engagement and participation  
20 throughout COS development to determine barriers and facilitators as well as  
21 modification of our processes if needed; and  
22
- 23 3. Determine if Delphi versus nominal group technique influences which measures are  
24 retained for outcomes included in the COS.  
25  
26  
27  
28  
29  
30  
31  
32

### 33 **Delphi Feedback**

34  
35 *Randomization and Allocation:* We will randomize (1:1 stratified by patient population  
36 group) using a computer-generated schedule developed by the study statistician. We will  
37 generate a questionnaire for each Delphi participant using this allocation schedule.  
38  
39 Participants will be randomized to receive feedback as either the proportion of  
40 participants scoring the outcome as critical (for their patient population group) or patient  
41 population group mean response (Figure 1).  
42  
43  
44  
45  
46  
47

48 *Statistical Analysis:* We will analyze differences between feedback groups in terms of:  
49 (a) subsequent scores and magnitude of opinion change; (b) items retained at Delphi end;  
50 and (c) level of agreement between patient population groups. We will calculate the  
51 percentage of items for which a participant changed their score between rounds; and the  
52 mean absolute change in score (ignoring direction of change). We will compare results  
53 according to randomization group using an independent t test overall and by patient  
54 population group. For each outcome, we will use linear regression to compare R2 scores  
55  
56  
57  
58  
59  
60

1  
2  
3 between feedback groups and among patient population groups, adjusting for R1 scores  
4 and testing for the interaction between feedback groups and patient populations.  
5  
6  
7

8  
9 To ascertain feedback group differences for items retained, we will create contingency  
10 tables, for each feedback group, to categorize the number of items retained by (i) both  
11 feedback groups; (ii) critical response feedback group only; (iii) mean feedback group  
12 only; and (iv) neither. We will determine percentage of items for which there was  
13 agreement to retain and percentage of discordant items retained by only one feedback  
14 group. To ascertain differences between feedback groups in terms of the level of  
15 agreement of items retained across patient population groups, we will generate  
16 contingency tables categorizing number of items retained by (i) all; (ii) 1 group only; (iii)  
17 2 groups only; (iv) 3 groups only; and (iv) none. We will calculate the percentage  
18 agreement and percentage of discordant items.  
19  
20  
21  
22  
23  
24  
25  
26  
27

28 To explore the impact of feedback on consensus between patient population groups, we  
29 will transform the unit of analysis to be the questionnaire item (outcome), with each  
30 observation an aggregate statistic. We will use linear regression to determine, for each  
31 outcome, and for each feedback group, the absolute difference (ignoring direction) in  
32 mean R2 scores, adjusting for the participant's R1 score. We will compare absolute mean  
33 differences between patient population groups across outcomes between the two feedback  
34 groups using a paired t test. Finally, we will compare responses irrespective of patient  
35 population groups within each randomization arm, calculate the standard deviation for  
36 each outcome separately for R1 and R2, and calculate the reduction in each outcome's  
37 variability between rounds. We will compare mean reductions in standard deviation  
38 across all outcomes between feedback groups using a paired t test.  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48

49 Given the anticipated number of statistical tests, we expect 5 % to result in a P value  $\leq$   
50 0.05 by chance; therefore we will examine the percentage of tests with  $P \leq 0.05$  in  
51 relation to this expected percentage.  
52  
53  
54  
55

### 56 **Outcome Consensus Meeting**

57  
58  
59  
60



1  
2  
3 We will hold consensus meetings to determine the outcomes for inclusion in the two  
4 COS's; prevention and/or treatment of delirium irrespective of patient population. We  
5 will identify additional outcomes for inclusion in COS specific to our four patient  
6 populations. We will aim to be as representative of all stakeholders as possible<sup>42</sup> as we  
7 anticipate there may be differences between stakeholder groups in the priority given to  
8 outcomes. To ensure we have meaningful input across participant groups, we will invite  
9 Delphi participants to attend the meeting. Due to the large size of our Delphi panel, we  
10 will randomly select eight participants to represent each of the stakeholder groups; two  
11 representing each patient population group.  
12  
13  
14  
15  
16  
17  
18  
19

20  
21 We will provide the consensus panel with outcomes established as critical using either  
22 method of feedback for inclusion via the Delphi across all four patient groups. We will  
23 use a modified nominal group technique to work towards consensus that includes small  
24 and whole group discussion and ranking. Ranking will be discussed with the aim of  
25 agreeing upon the top four or five outcomes across all patients and the top one to two  
26 specific to each patient population. To ensure there is no duplication in the final proposed  
27 set, each outcome will be discussed to ensure it relates to a distinct construct. If required  
28 we may hold an additional or standalone consensus meeting for patients and family  
29 members to enable facilitation of their understanding and thus informed voting on  
30 outcomes for the COS.  
31  
32  
33  
34  
35  
36  
37  
38  
39

#### 40 **Process Evaluation of Patient/Family Participant Engagement**

41 We will conduct a process evaluation of patient/family participant engagement and  
42 participation throughout COS development.  
43  
44  
45

46  
47 *Participants:* We will recruit participants to take part in semi-structured interviews to  
48 determine barriers and facilitators to participation as well as recommendations for  
49 improvement strategies to inform future COS development. We will recruit 15 to 20  
50 participants. Interviews will be audio recorded and transcribed verbatim.  
51  
52  
53  
54

55  
56 *Analysis:* We will analyze interview transcripts using content analysis<sup>43-46</sup> employing an  
57 inductive, four-step content analysis process<sup>47</sup>. An experienced qualitative researcher and  
58  
59  
60

1  
2  
3 an investigator will independently identify, code, and categorize important meanings and  
4 predominant themes from the text. Following an immersive reading of the transcripts,  
5 initial patterns and recurring categories will be identified by relevant highlighting  
6 sections. The second step will seek similarities and differences between participant  
7 accounts. Third and fourth steps involve creation of codes and their application over the  
8 volume of interviews respectively. The larger team will be involved in in-depth reading  
9 of the coding to ensure credibility. NVivo 10 software will be used for all facets of the  
10 analysis.  
11  
12  
13  
14  
15  
16  
17  
18  
19

### 20 **Instruments to Measure Outcomes**

21 During our systematic review we will also extract measures for outcomes reported in  
22 studies meeting our inclusion criteria. We will assess the measurement and psychometric  
23 properties of measures of the outcomes selected for our two COS (prevention and  
24 treatment) using the COSMIN check list.<sup>48</sup>  
25  
26  
27  
28  
29

30 *Participants:* We will invite all Delphi participants involved in establishment of the  
31 COSs to participate in a second Delphi to establish measures for these outcomes. We will  
32 recruit additional participants if required due to attrition. We will recruit an additional 24  
33 participants to take part in a separate consensus building exercise using only a modified  
34 nominal group technique to address the following hypothesis: measures selected for the  
35 COS are influenced by the method used for consensus building (Delphi versus nominal  
36 group technique).  
37  
38  
39  
40  
41  
42  
43

44 *Procedures:* We will use the same Delphi methods as described above to establish one set  
45 of measures each for the two COS (prevention and treatment) including the same nested  
46 study design of randomization to two feedback methods (Delphi group). We will provide  
47 ‘measure cards’ provided standardized descriptions of the measures, psychometric  
48 properties, and feasibility of use (i.e., time to complete, number of items) in language  
49 understandable to all participants. We will use the same nominal group technique  
50 methods as described for the COS consensus meetings to establish a second set of  
51 measures (nominal group technique group). We will provide to the same description of  
52 the measures and their psychometric properties as provided to the Delphi method group.  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 Additionally, we will invite a psychometrician, clinicians and/or researchers with  
4 familiarity with the measures to the nominal group technique group thus enabling  
5 informed discussion.  
6  
7

8  
9  
10 *Statistical Analysis:* We will perform the same statistical analyses as described for the  
11 COS Delphi to determine differences related to consensus group method. To ascertain  
12 differences in terms of measures retained between consensus group methods, we will  
13 create contingency tables to categorize number of items retained on completion by (i)  
14 both Delphi and nominal group technique groups; (ii) Delphi group only; (iii) nominal  
15 group technique only; and (iv) neither. We will determine the percentage of items for  
16 which there was agreement along with the percentage of discordant items, retained by  
17 one consensus group method but not the other.  
18  
19  
20  
21  
22  
23  
24

### 25 26 **Final Consensus**

27 We will hold a final steering group meeting to review the findings of the consensus  
28 building exercises. Depending on the number of measures rated as critical to include we  
29 will hold a second consensus meeting using the methods described above to guide final  
30 decisions.  
31  
32  
33  
34  
35  
36

37 **Table 2: Study Timeline**

38 <b>Key Project Milestones</b>	39 <b>Start Date</b>	40 <b>End date</b>
41 Systematic review	42 May 2017	43 Feb 2018
44 Patient and family member interviews	45 Oct 2017	46 Feb 2018
47 Delphi consensus and nested methodological 48 study	49 April 2018	50 Mar 2019
51 Consensus meeting	52 Jun 2019	53 Jun 2019
54 Process evaluation patient/family interviews	55 Feb 2018	56 Mar 2020
57 Consensus on measures	58 Sept 2019	59 Mar 2020
60 Knowledge translation/dissemination	Jun 2019 onwards	

## ETHICS AND DISSEMINATION

We are seeking research ethics board approvals as required by local governance. We will obtain written consent from participants in interviews and consensus meetings.

Participation in Delphi rounds will be considered indicative of consent. Consent will emphasize the voluntary nature of participation and anonymity.

Knowledge users within our investigator team as well as the support of three international Delirium Societies (American, Australasian, European) will be instrumental in dissemination of the COS's and subsequent uptake. We will provide a one page summary (clinicians/researchers and in lay language for patients and families) to these Societies for distribution among their networks and engage with them to seek additional opportunities to present our findings (educational seminars/workshops). We will disseminate our findings through peer-reviewed and open access publications, and presentations at international conferences purposefully selected to reach a wide range of knowledge users taking into account geographic locations. We will engage with journal editors and funding agencies to promote awareness of our COS's.

## REFERENCES

1. American Psychiatric Association, . *Diagnostic and Statistical Manual (5th edition)*. Washington, DC: American Psychiatric Association, 2013.
2. Trzepacz P, Meagher D. *Oxford Textbook of Psychiatry (2nd edition)*. London, UK: Oxford University Press, 2009.
3. Siddiqi N, Young J, House A, et al. Stop Delirium! A complex intervention to prevent delirium in care homes: a mixed-methods feasibility study. *Age Ageing* 2011;**40**:90-98.
4. Hosie A, Davidson P, Agar M, et al. Delirium prevalence, incidence, and implications for screening in specialist palliative care inpatient settings: a systematic review. *Palliat Med* 2012;**27**:486-98.
5. Inouye S, Westendorp R, Saczynski J. Delirium in elderly people. *Lancet* 2014;**383**:911–22.
6. Mistraletti G, Carloni E, Cigada M, et al. Sleep and delirium in the intensive care unit. *Minerva Anestesiol* 2008;**74**(6):329-33.
7. Daoud A, Duff JP, Joffe AR, et al. Diagnostic accuracy of delirium diagnosis in pediatric intensive care: a systematic review. *Crit Care* 2014;**18**(5):489.
8. Bellapart J, Boots R. Potential use of melatonin in sleep and delirium in the critically ill. *Br J Anaesth* 2012;**108**(4):572-80.
9. Zaal IJ, Slooter AJ. Delirium in critically ill patients: epidemiology, pathophysiology, diagnosis and management. *Drugs* 2012;**72**(11):1457-71.
10. Bickel H, Gradinger R, Kochs E, et al. High risk of cognitive and functional decline after postoperative delirium. A three-year prospective study. . *Dement Geriatr Cogn Disord* 2008;**26**:26-31.
11. O'Malley G, Leonard M, Meagher D. The delirium experience: A review. *J Psychosomatics* 2008;**65**:223-28.
12. Corsinovi L, Bo M, Ricauda Aimonino N, et al. Predictors of falls and hospitalization outcomes in elderly patients admitted to an acute geriatric unit. *Arch Gerontol Geriatr* 2009;**49**:142-45.
13. Leslie D, Marcantonio E, Zhang Y, et al. One-year health care costs associated with delirium in the elderly population. *Arch Intern Med* 2008;**14**:27-32.

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
14. Barr J, Fraser G, Puntillo K, et al. American College of Critical Care Medicine: Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013;**41**:278–80.
15. Traube C, Mauer E, Gerber L, et al. Cost associated with pediatric delirium in the ICU. *Crit Care Med* 2016.
16. Buurman B, Hoogerduijn J, de Haan R, et al. Geriatric conditions in acutely hospitalized older patients: prevalence and one-year survival and functional decline. *PLoS One* 2011;**6**:e26951.
17. Rudolph J, Inouye S, Jones R, et al. Delirium: an independent predictor of functional decline after cardiac surgery. *J Am Geriatr Soc* 2010;**58**:643-49.
18. Carbone M, Gugliucci M. Delirium and the family caregiver: the need for evidence-based education interventions. *Gerontologist* 2015;**55**:345-52.
19. Finucane A, Lugton J, Kennedy C, et al. The experiences of caregivers of patients with delirium, and their role in its management in palliative care settings: an integrative literature review. *Psychooncology* 2016.
20. Crocker E, Beggs T, Hassan A, et al. Long-term effects of postoperative delirium in patients undergoing cardiac operation: a systematic review. *Ann Thorac Surg* 2016;pii: S0003-4975(16)30402-7.
21. Clarke M. Standardising outcomes for clinical trials and systematic reviews. *Trials* 2007;**8**:39.
22. Sanderson T, Morris M, Calnan M, et al. What outcomes from pharmacologic treatments are important to people with rheumatoid arthritis? Creating the basis of a patient core set. *Arthrit Care Res* 2010;**62**:640–46.
23. Gagnon P. Treatment of delirium in supportive and palliative care. *Curr Opin Support Palliat Care* 2008;**2**:60-66.
24. LaHue, SC, Liu V. Loud and clear: sensory impairment, delirium, and functional recovery in critical illness. *Am J Respir Crit Care Med* 2016 **194**:252-3.
25. Tugwell P, Boers M, Brooks P, et al. OMERACT: an international initiative to improve outcome measurement in rheumatology. *Trials* 2007;**8**:38.
26. Williamson P, Altman D, Blazeby J, et al. Developing core outcome sets for clinical trials: issues to consider. *Trials* 2012;**13**:132.

- 1  
2  
3  
4 27. COMET PoPPIE group. Checklist for public research partners and core outcome set  
5 (COS) study developers involved in designing a COS study. Secondary Checklist  
6 for public research partners and core outcome set (COS) study developers  
7 involved in designing a COS study. 2015. [http://www.comet-](http://www.comet-initiative.org/assets/downloads/COS%20study%20development%20-%20PPI%20checklist%2016-03-16.pdf)  
8 [initiative.org/assets/downloads/COS%20study%20development%20-](http://www.comet-initiative.org/assets/downloads/COS%20study%20development%20-%20PPI%20checklist%2016-03-16.pdf)  
9 [%20PPI%20checklist%2016-03-16.pdf](http://www.comet-initiative.org/assets/downloads/COS%20study%20development%20-%20PPI%20checklist%2016-03-16.pdf).  
10  
11  
12  
13  
14 28. McGowan J, Sampson M, Salzwedel DM, et al. PRESS Peer Review of Electronic  
15 Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol* 2016;**75**:40-46.  
16  
17 29. Sampson M, McGowan J, Cogo E, et al. An evidence-based practice guideline for the  
18 peer review of electronic search strategies. *J Clin Epidemiol* 2009;**62**(9):944-52.  
19  
20 30. Scottish Intercollegiate Guidelines Network. Methodology Checklists. 2015.  
21 [www.sign.ac.uk/methodology/checklists.html](http://www.sign.ac.uk/methodology/checklists.html)  
22  
23  
24  
25  
26  
27 31. Harman N, IA B, P C, et al. MOMENT--Management of Otitis Media with Effusion  
28 in Cleft Palate: protocol for a systematic review of the literature and identification  
29 of a core outcome set using a Delphi survey. *Trials* 2013;**14**:70.  
30  
31 32. Kirkham J, Dwan K, Altman D, et al. The impact of outcome reporting bias in  
32 randomised controlled trials on a cohort of systematic reviews. *BMJ*  
33 **2010**;**340**:c365.  
34  
35  
36 33. Boers M, Kirwan J, Tugwell P, et al. The OMERACT handbook. Ottawa:  
37 OMERACT, 2014.  
38  
39  
40 34. Pope C, Mays N. Qualitative Research: Reaching the parts other methods cannot  
41 reach: an introduction to qualitative methods in health and health services  
42 research. *BMJ* 1995;**311**(6996):42-45.  
43  
44  
45 35. Patton M. Purposeful sampling. *Qualitative evaluation and research methods*. Beverly  
46 Hills, CA: Sage, 1990:169-86.  
47  
48 36. Francis J, Johnston M, Robertson C, et al. What is an adequate sample size?  
49 Operationalising data saturation for theory-based interview studies. *Psychol*  
50 *Health* 2010;**25**:1229-45.  
51  
52  
53 37. Elo S, Kyngäs H. The qualitative content analysis process. *J Adv Nurs* 2008;**62**:107-  
54 15.  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
38. Macefield R, Jacobs M, Korfage I, et al. Developing core outcomes sets: methods for identifying and including patient-reported outcomes (PROs). *Trials* 2014; **15**:49.
  39. The GRADE working group. GRADE. Secondary GRADE 2016.  
<http://www.gradeworkinggroup.org/>.
  40. Sinha I, Smyth R, Williamson P. Using the Delphi technique to determine which outcomes to measure in clinical trials: recommendations for the future based on a systematic review of existing studies. *PLoS Med* 2011; **8**: e1000393.
  41. The COMET Initiative. The COMET Initiative. Secondary The COMET Initiative 2011. <http://www.comet-initiative.org>.
  42. Simon L, Strand V, Bingham C, et al. OMERACT 11: international consensus conference on outcome measures. *J Rheumatol* 2014; **41**:145-49.
  43. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse Educ Today* 2004; **24**(2):105-12.
  44. Onwuegbuzie A, Dickinson W, Leech N, et al. A qualitative framework for collecting and analyzing data in focus group research. *Int J Qual Meth* 2009; **8**:1-21.
  45. Carlsen B, Glenton C. What about N? A methodological study of sample-size reporting in focus group studies. *BMC Med Res Methodol* 2011; **11**:26.
  46. Vaismoradi M, Turunen H, Bondas T. Content analysis and thematic analysis: Implications for conducting a qualitative descriptive study. *Nursing & health sciences* 2013; **15**(3):398-405.
  47. Burnard F. Teaching the analysis of textual data: an experiential approach. *Nurse Educ Today* 1996; **16**:278–81.
  48. Terwee CB, Mokkink LB, Knol DL, et al. Rating the methodological quality in systematic reviews of studies on measurement properties: a scoring system for the COSMIN checklist. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2012; **21**(4):651-7.



### **AUTHOR CONTRIBUTIONS**

LR and VP conceived of the study. LR, MA, LB, NC, JL, NS, and VP developed the study protocol and funding applications to support conduct of the study. Additionally, MC advised on the design of the nested methodological studies as well as contributed to design of the protocol. All authors contributed to drafting and editing of the manuscript, as well as read and approved the final version.

### **FUNDING STATEMENT**

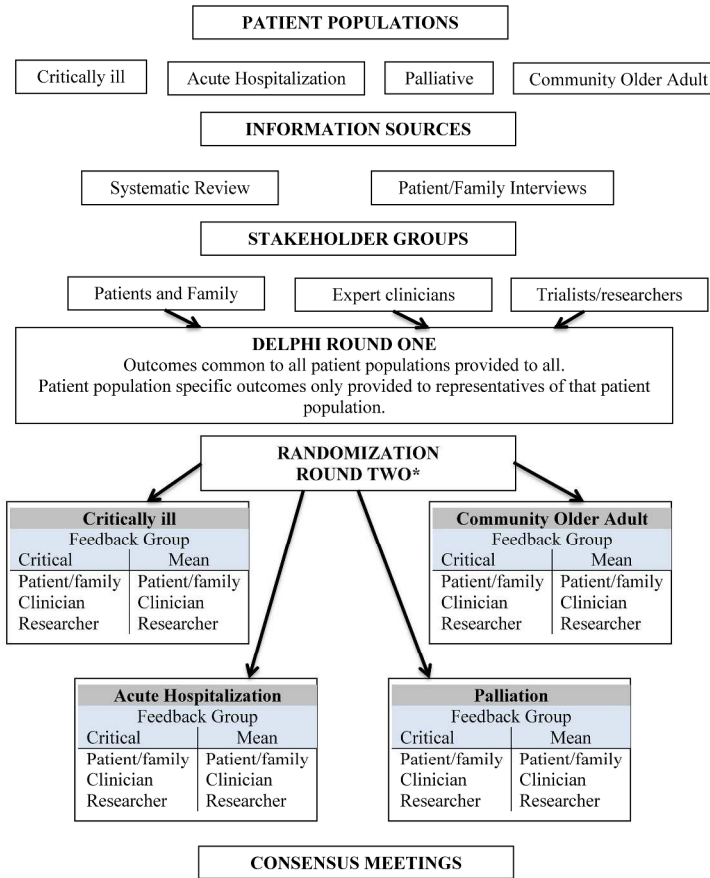
This study is not funded. Dr. Louise Rose holds a Canadian Institutes of Health Research New Investigator Award. Jennifer Ansell has received funding towards her PhD Studentship through the University of Toronto.

### **COMPETING INTERESTS STATEMENT**

The authors have no competing interests to declare.

Figure 1: Flow of Core Outcome Set Development

For peer review only



**Figure 1: Flow of core outcome set development**  
\* We will conduct an third Delphi round if additional outcomes are identified in round one

## Appendix: Search Strategy: Medline

Patient Group 1: critically ill adults and children receiving care in high acuity settings, including intensive care and high dependency units

1 ((postoperati\* or post-operati\* or postsurg\* or post-surg\*) adj1 ("cognitive dysfunction" or "brain dysfunction")).tw,kw,kf.

2 Delirium/

3 deliri\*.tw,kw,kf.

4 Psychoses, Substance-Induced/

5 (psychos\* adj3 (toxic\* or exogenous\* or chemical\* or drug or drugs or medication\* or substance\*)).tw,kw,kf.

6 (acute brain adj (dysfunction\* or failure\* or syndrome\*)).tw,kw,kf.

7 (cloud\* adj3 consciousness\*).tw,kw,kf.

8 clouded state\*.tw,kw,kf.

9 ((psycho-organic syndrome\* or psychoorganic syndrome\* or organic psychosyndrome\* or organic psycho-syndrome\*) adj3 acute).tw,kw,kf.

10 exp Confusion/ci

11 Hallucinations/

12 hallucinat\*.tw,kw,kf.

13 or/1-12 [DELIRIUM]

14 exp Animals/ not (exp Animals/ and Humans/)

15 13 not 14 [ANIMAL-ONLY REMOVED]

16 Intensive Care Units/

17 Burn Units/

18 Coronary Care Units/

19 Respiratory Care Units/

20 exp Intensive Care Units, Pediatric/

21 exp Critical Care/

22 ((intensive or critical or acute) adj3 care).tw,kw,kf.

23 (ICU or ICUs or SICU or SICUs or CCU or CCUs).tw,kw,kf.

24 (PICU or PICUs or NICU or NICUs).tw,kw,kf.

25 (burn? adj3 (unit? or centre? or center?)).tw,kw,kf.

26 ((cardiac or coronary or heart) adj3 (unit? or centre? or center?)).tw,kw,kf.

27 (respiratory adj3 (unit? or centre? or center?)).tw,kw,kf.

28 ((surgical or surger\*) adj3 (unit? or centre? or center?)).tw,kw,kf.

29 (high dependency adj3 (unit? or centre? or center?)).tw,kw,kf.

30 ((stepdown or step-down) adj3 (unit? or centre? or center?)).tw,kw,kf.

31 (HDU or HDUs or SDU or SDUs or EDSDU or EDSDUs).tw,kw,kf.

32 ((special\* or dedicated or intens\*) adj weaning adj3 (unit? or centre? or center? or program\* or ward?)).tw,kw,kf.

33 Critical Illness/

34 (critical\* adj (ill or illness\*)).tw,kw,kf.

35 or/16-34

36 15 and 35 [DELIRIUM IN THE ICU]

37 limit 36 to yr="1980-current"

38 limit 37 to english language

2. Non-critically ill adults and children hospitalized in acute care settings including postoperative surgical and medical patients, those presenting to ED

1 ((postoperati\* or post-operati\* or postsurg\* or post-surg\*) adj1 ("cognitive dysfunction" or "brain dysfunction")).tw,kw,kf.

2 Delirium/

3 deliri\*.tw,kw,kf.

4 Psychoses, Substance-Induced/

5 (psychos\* adj3 (toxic\* or exogenous\* or chemical\* or drug or drugs or medication\* or substance\*)).tw,kw,kf.

6 (acute brain adj (dysfunction\* or failure\* or syndrome\*)).tw,kw,kf.

7 (cloud\* adj3 consciousness\*).tw,kw,kf.

8 clouded state\*.tw,kw,kf.

9 ((psycho-organic syndrome\* or psychoorganic syndrome\* or organic psychosyndrome\* or organic psycho-syndrome\*) adj3 acute).tw,kw,kf.

10 exp Confusion/ci

11 Hallucinations/

12 hallucinat\*.tw,kw,kf.

13 or/1-12 [DELIRIUM]

14 exp Animals/ not (exp Animals/ and Humans/)

15 13 not 14 [ANIMAL-ONLY REMOVED]

16 Inpatients/

17 inpatient\*.tw,kw,kf.

18 Adolescent, Hospitalized/

19 Child, Hospitalized/

20 exp Hospitalization/

21 Emergency Service, Hospital/

22 (emergency adj2 (care or center? or centre? or department? or dept? or room? or service? or unit or units or ward?)).tw,kw,kf.

23 (("A and E" or "A & E") adj2 (care or center? or centre? or department? or dept? or room? or service? or unit or units or ward?)).tw,kw,kf.

24 hospital\*.tw,kw,kf.

25 ((emergency or medical\* or surg\*) adj3 patient?).tw,kw,kf.

26 Postoperative Care/

27 ((postoperati\* or post-operati\* or postsurg\* or post-surg\*) adj3 (care or patient?)).tw,kw,kf.

28 or/16-27

29 15 and 28 [DELIRIUM IN INPATIENTS/HOSPITALIZED CARE]

30 limit 29 to yr="1980-CURRENT"

31 limit 30 to english language

1  
2  
3 3. Adults and children receiving palliative care, either in a hospital, hospice, or community setting  
4 1 ((postoperati\* or post-operati\* or postsurg\* or post-surg\*) adj1 ("cognitive dysfunction" or "brain  
5 dysfunction")).tw,kw,kf.  
6  
7 2 Delirium/  
8 3 deliri\*.tw,kw,kf.  
9 4 Psychoses, Substance-Induced/  
10 5 (psychos\* adj3 (toxic\* or exogenous\* or chemical\* or drug or drugs or medication\* or  
11 substance\*)).tw,kw,kf.  
12 6 (acute brain adj (dysfunction\* or failure\* or syndrome\*)).tw,kw,kf.  
13 7 (cloud\* adj3 consciousness\*).tw,kw,kf.  
14 8 clouded state\*.tw,kw,kf.  
15 9 ((psycho-organic syndrome\* or psychoorganic syndrome\* or organic psychosyndrome\* or organic  
16 psycho-syndrome\*) adj3 acute).tw,kw,kf.  
17 10 exp Confusion/ci  
18 11 Hallucinations/  
19 12 hallucinat\*.tw,kw,kf.  
20 13 or/1-12 [DELIRIUM]  
21 14 exp Animals/ not (exp Animals/ and Humans/  
22 15 13 not 14 [ANIMAL-ONLY REMOVED]  
23 16 Inpatients/  
24 17 inpatient\*.tw,kw,kf.  
25 18 Adolescent, Hospitalized/  
26 19 Child, Hospitalized/  
27 20 exp Hospitalization/  
28 21 Emergency Service, Hospital/  
29 22 (emergency adj2 (care or center? or centre? or department? or dept? or room? or service? or unit  
30 or units or ward?)).tw,kw,kf.  
31 23 (("A and E" or "A & E") adj2 (care or center? or centre? or department? or dept? or room? or  
32 service? or unit or units or ward?)).tw,kw,kf.  
33 24 hospital\*.tw,kw,kf.  
34 25 ((emergency or medical\* or surg\*) adj3 patient?).tw,kw,kf.  
35 26 Postoperative Care/  
36 27 ((postoperati\* or post-operati\* or postsurg\* or post-surg\*) adj3 (care or patient?)).tw,kw,kf.  
37 28 or/16-27  
38 29 15 and 28 [DELIRIUM IN INPATIENTS/HOSPITALIZED CARE]  
39 30 limit 29 to yr="1980-CURRENT"  
40 31 limit 30 to english language  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

4. Older adults (65 and over) living in nursing or residential care homes or living in their own homes and defined as at risk of delirium by study authors.

1 ((postoperati\* or post-operati\* or postsurg\* or post-surg\*) adj1 ("cognitive dysfunction" or "brain dysfunction")).tw,kw,kf.

2 Delirium/

3 deliri\*.tw,kw,kf.

4 Psychoses, Substance-Induced/

5 (psychos\* adj3 (toxic\* or exogenous\* or chemical\* or drug or drugs or medication\* or substance\*)).tw,kw,kf.

6 (acute brain adj (dysfunction\* or failure\* or syndrome\*)).tw,kw,kf.

7 (cloud\* adj3 consciousness\*).tw,kw,kf.

8 clouded state\*.tw,kw,kf.

9 ((psycho-organic syndrome\* or psychoorganic syndrome\* or organic psychosyndrome\* or organic psycho-syndrome\*) adj3 acute).tw,kw,kf.

10 exp Confusion/ci

11 Hallucinations/

12 hallucinat\*.tw,kw,kf.

13 or/1-12 [DELIRIUM]

14 exp Animals/ not (exp Animals/ and Humans/)

15 13 not 14 [ANIMAL-ONLY REMOVED]

16 exp Aged/

17 Health Services for the Aged/

18 (geriatric\* or psychogeriatric\* or psycho-geriatric\* or gerontolog\* or elder\$2 or old-age? or senior\*).tw,kw,kf.

19 (older adj2 (adult? or age? or female? or male? or man or men or patient? or person? or people? or population? or resident? or woman\* or women\*)).tw,kw,kf.

20 Homes for the Aged/

21 ((facility or facilities or home or homes) adj "for the aged").tw,kw,kf.

22 exp Nursing homes/

23 nursing home?.tw,kw,kf.

24 (nursing facility or nursing facilities).tw,kw,kf.

25 care home?.tw,kw,kf.

26 (care facility or care facilities).tw,kw,kf.

27 (residen\* adj1 (care or health care or healthcare)).tw,kw,kf.

28 ((care or healthcare or service?) adj "for the aged").tw,kw,kf.

29 (aged care or aged healthcare or aged health care or aged service?).tw,kw,kf.

30 or/16-29

31 15 and 30 [DELIRIUM IN THE ELDERLY]

32 limit 31 to yr="1980-CURRENT"

33 limit 32 to english language

# BMJ Open

## Development of core outcome sets for effectiveness trials of interventions to prevent and/or treat delirium (Del-COrS): Study protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-016371.R2
Article Type:	Protocol
Date Submitted by the Author:	14-Jun-2017
Complete List of Authors:	Rose, Louise; University of Toronto, Lawrence S. Bloomberg Faculty of Nursing Agar, Meera ; University of Technology Sydney, Centre of Cardiovascular and Chronic Care, Faculty of Health Burry, Lisa; Mount Sinai Hospital, Pharmacy Campbell, Noll; Indiana University Bloomington, Clarke, Mike; All-Ireland Hub for Trials Methodology Research, Centre for Public Health Lee, Jacques; University of Toronto, Clinical Epidemiology Unit Siddiqi, Najma; University of York, Psychiatry, Hull York Medical School, York and Bradford District Care NHS Foundation Trust, Bradford, UK Page, Valerie J.; West Hertfordshire Hospitals NHS Trust, Anaesthetics
<b>Primary Subject Heading</b>:	Mental health
Secondary Subject Heading:	Geriatric medicine, Intensive care, Palliative care
Keywords:	Delirium & cognitive disorders < PSYCHIATRY, core outcome set, systematic review, research methods

SCHOLARONE™  
Manuscripts



**TITLE**

Development of core outcome sets for effectiveness trials of interventions to prevent and/or treat delirium (Del-CORs): Study protocol

**CORRESPONDING AUTHOR**

Louise Rose

Department of Critical Care Medicine, Sunnybrook Health Sciences Centre;  
Lawrence S. Bloomberg Faculty of Nursing and Interdepartmental Division of Critical  
Care Medicine, University of Toronto

Postal Address: 155 College St. Rm 276 Toronto, Canada

Email: [louise.rose@utoronto.ca](mailto:louise.rose@utoronto.ca)

Phone: +1 416 978 3492

**CO-AUTHORS**

Meera Agar

Faculty of Health Sciences, University of Technology, Sydney, Australia

Lisa Burry

Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada

Noll Campbell

College of Pharmacy, Indiana University-Purdue University, Indianapolis, United States

Mike Clarke

School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast,  
Belfast, Northern Ireland

Jacques Lee

Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Toronto, Canada

Najma Siddiqi

School of Medicine, York University, York, England

Valerie Page

Watford General Hospital, Watford, England

For the Del-CORs group – Jennifer Ansell, Bronagh Blackwood; Rich Jones; Imogen  
Featherstone; Leslie Fornear; Annmarie Hosie; Miriam Johnson; Dale Needham; Nadine  
Schofield; Jo Taylor; Peter Lawlor

**KEYWORDS**

Delirium; core outcome set; systematic review; research methods

**WORD COUNT:** 3990 (Not including table and Figure).

## ABSTRACT

### Introduction

Delirium is a common, serious, and potentially preventable condition with devastating impact on quality of life prompting a proliferation of interventional trials. Core outcome sets aim to standardize outcome reporting by identifying outcomes perceived fundamental for measurement in trials of a specific interest area. Our aim is to develop international consensus on two core outcome sets for trials of interventions to prevent and/or treat delirium, irrespective of study population. We aim to identify additional core outcomes specific to the critically ill, acutely hospitalized patients, palliative care, and older adults.

### Methods and analysis

We will conduct a systematic review of published and ongoing delirium trials (1980 onwards) and one-on-one interviews of patients that have experienced delirium and family members. These data will inform Delphi round one of a two-stage consensus process. In round two we will provide participants their own response, summarized group responses, and those of patient/family participants for re-scoring. We will randomize participants to receive feedback as proportion scoring the outcome as critical, or as group mean responses. We will hold a consensus meeting using nominal group technique to finalize outcomes for inclusion. We will repeat the Delphi process and consensus meeting to select measures for each core outcome. We will recruit 240 Delphi participants giving us 80% power to detect a 1.0 to 1.5 point (9-point scale) difference by feedback method between rounds. We will analyze differences for subsequent scores, magnitude of opinion change, items retained, and level of agreement.

### Ethics and dissemination

We are obtaining research ethics approvals according to local governance. Participation will be voluntary and data deidentified. Support from three international delirium organizations will be instrumental in dissemination and core outcome set uptake. We will disseminate through peer-reviewed open access publications, and present at conferences selected to reach a wide range of knowledge users.

1  
2  
3 Word Count: 300  
4  
5  
6

7 This Core Outcome Set is registered on the COMET website [http://www.comet-](http://www.comet-initiative.org/studies/details/796)  
8 [initiative.org/studies/details/796](http://www.comet-initiative.org/studies/details/796).  
9

10  
11 The systematic review is registered on PROSPERO-ID: CRD42016052704  
12 [https://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42016052704](https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016052704)  
13  
14

15  
16  
17 The study is funded by the Canadian Institutes of Health Research  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## STRENGTHS and LIMITATIONS

### Strengths

- Rigorous systematic review and core outcome set development methods that adhere to Cochrane and COMET guidelines
- Engagement with survivors of delirium during development of the protocol
- Support of three international Delirium Societies (American, Australasian, European) will facilitate participant recruitment, dissemination, and uptake of our core outcome sets

### Potential Limitations

- Ability to recruit and retain participants, particularly delirium survivors and their family members. We are using multi-modal recruitment strategies and seeking advice from organizations experienced in recruitment and retention of patient/family participants.
- Ability to recruit participants with broad geographical representation.
- Inability to come to consensus on the core outcomes or the measures for these outcomes.
- Important outcomes are identified that are difficult to measure due to the absence of valid and reliable measures.

## INTRODUCTION

Delirium is a complex syndrome characterized by an acute confusional state with rapid onset, a fluctuating course, circadian disturbances, reduced or increased motor activity, as well as changes in cognition, notably in the domains of attention and higher-level thought processing.<sup>1 2</sup> Delirium is a common, serious, and potentially preventable source of morbidity, with devastating impacts on quality of life, and mortality. Delirium impacts all age groups, from infants to the very elderly. This includes patients, including those accessing primary care, resident in nursing homes,<sup>3</sup> those receiving palliative care services,<sup>4</sup> and a significant number of hospitalized patients, including the acute and critically ill. Prevalence rates in hospitalized patients range from 25% to 80%.<sup>5-8</sup>

Delirium is not a benign, self-limiting condition. As well as increased mortality, delirium is associated with prolonged length of stay (LOS); higher rates of unintentional device removal; falls and incontinence in the elderly; significant emotional distress for patients, families, caregivers, and healthcare professionals;<sup>9-12</sup> and escalating public healthcare costs.<sup>13-15</sup> Delirium also carries long term consequences including impaired physical functioning<sup>16 17</sup> and loss of independence resulting in long-term care placement;<sup>5</sup> caregiver burden;<sup>18 19</sup> decreased quality of life;<sup>20</sup> cognitive decline, and increased risk of dementia and Alzheimer's disease.<sup>11</sup>

With increased recognition of delirium as a common, costly, and potentially preventable condition associated with adverse outcomes, encouragingly studies examining interventions to prevent and/or treat delirium continue to proliferate. Currently, there is no systematic approach to the selection and reporting of outcomes and their measures in these studies resulting in reporting of numerous and varied study outcomes and measures for these outcomes. This hinders progress towards improvements in care, as to best inform the evidence base, outcomes must be selected, defined, and measured consistently across studies of similar interventions in similar populations. Core outcome sets (COS), developed using rigorous consensus processes involving key stakeholders including patients and carers, comprise outcomes perceived as fundamental to measure in all trials related to a specific and defined area of interest (such as a disease, condition, or intervention).<sup>21 22</sup> Although the importance and value of COS for standardizing outcomes

1  
2  
3 and measurement across trials is increasingly recognized, in general, they are still in their  
4 infancy and as yet have not been developed for trials of interventions to prevent or treat  
5 delirium. Therefore we aim to develop international consensus on two COS appropriate  
6 for trials of interventions designed to (1) prevent or (2) treat delirium, irrespective of  
7 study population. We also aim to identify additional core outcomes specific to four  
8 patient groups: the critically ill; patients requiring hospitalization in an acute care setting;  
9 palliative care; and older adults living in residential care or the community.  
10  
11  
12  
13  
14  
15  
16

### 17 Scope of Core Outcome Set Development

18  
19 The scope of our COS will include our four patient populations of interest, considered at  
20 high risk of developing delirium.<sup>3 5 23 24</sup> These include (1) critically ill adults and children  
21 (medical, surgical, and trauma) receiving care in high acuity settings, including intensive  
22 care and high dependency units; (2) non-critically ill adults and children hospitalized in  
23 acute care settings including surgical (all surgeries) and medical patients, and patients  
24 presenting to an emergency department (ED); (3) adults and children receiving palliative  
25 care, either in a hospital, hospice, or community setting; and (4) older adults (65 and  
26 over) living in nursing or residential care homes or living in their own homes and defined  
27 as at risk of delirium by study authors. We recognize that certain subpopulations such as  
28 children and older adults with dementia spanning these patient populations may need a  
29 distinct COS or outcomes for substitution within a COS. This decision will be made  
30 following identification and mapping of outcomes during our systematic review and from  
31 interviews with patients/family.  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43

## 44 **METHODS**

45 We will use methods outlined in the OMERACT handbook<sup>25</sup> and those endorsed by the  
46 COMET initiative.<sup>26</sup> Our study steering group will comprise two experts with clinical  
47 and/or research expertise in delirium and a patient/family representative for each of our  
48 four patient populations. We will use the COMET Checklist for Public Research Partners  
49 and the COS Study Developers Involved in Designing a COS study checklist<sup>27</sup> to guide  
50 and optimize our engagement with patients/family around the COS design and conduct.  
51  
52  
53  
54  
55  
56  
57

## 58 **Information Sources**

1  
2  
3 We will conduct: (1) a systematic review of outcomes and measures reported in  
4 published and ongoing trials of interventions to prevent or treat delirium (1980 onwards);  
5 and (2) qualitative study comprising one-on-one interviews with patient survivors, family  
6 members, and patient advocacy groups to identify outcomes important to patients and  
7 families that have experienced delirium.  
8  
9  
10  
11  
12

### 13 14 **Systematic Review**

15  
16 *Search Strategy and Data Sources:* We will develop an electronic search strategy through  
17 an iterative process informed by an experienced medical information specialist. We will  
18 search the following electronic databases, adjusting vocabulary and syntax for each, from  
19 1980 to present: Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed  
20 Citations, CINAHL, Embase Classic+Embase, PsychINFO, and Web of Science. To  
21 avoid limiting the scope of outcomes identified, we will not apply a study design filter.  
22 We will limit inclusion to studies published in English. A second librarian will review the  
23 search strategy prior to execution using the Peer Review for Electronic Search Strategies  
24 (PRESS) template.<sup>28 29</sup> We will search for relevant systematic reviews in the Cochrane  
25 Library, PROSPERO, and Joanna Briggs and unpublished studies and ongoing trials on  
26 the International Clinical Trials Registry Platform (<http://apps.who.int/trialsearch>).  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36

37  
38 *Study Selection:* Two investigators will independently screen titles and abstracts for  
39 eligible studies. Inclusion criteria include: (1) one of the four patient groups of interest;  
40 (2) pharmacological and non-pharmacological intervention for delirium prevention,  
41 treatment, or both; (3) compared to usual care, other pharmacological agents, or other  
42 non-pharmacological interventions; and (4) randomized (individual, cluster, and cross  
43 over randomization), quasi-randomized, and non-randomized intervention studies. If we  
44 identify <5 intervention studies in any of the four patient groups, we will expand our  
45 inclusion criteria to include observational studies with a control group. We will examine  
46 full-text publications of potentially relevant articles for eligibility. We will screen the  
47 reference lists of eligible studies and systematic reviews for additional eligible studies for  
48 inclusion. We will resolve disagreements through discussion; if unable to achieve  
49 consensus, we will refer to an independent arbiter from among the study team.  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

*Data extraction:* Two investigators will independently extract data from eligible studies on publication date, design, participant characteristics, study objectives, intervention, comparator, outcomes, their definition, and measures used to document outcomes.

*Quality assessment:* Two investigators will assess independently risk of bias using the Cochrane Risk of Bias tool for randomized and quasi-randomized studies and the Scottish Intercollegiate Guidelines Network (SIGN) checklists for non-randomized studies.<sup>30</sup> Two investigators will assess independently quality of describing and reporting outcomes using the six-point MOMENT scoring system with a score of  $\geq 4$  representing high quality outcome reporting.<sup>31</sup> The six elements (each scored as 1 point) include: (1) Was the primary outcome stated? (2) Was the primary outcome clearly defined so that another researcher would be able to reproduce its measurement? (3) Were the secondary outcomes clearly stated? (4) Were the secondary outcomes clearly defined? (5) Do the authors explain the choice of outcomes they have selected? (6) Were methods used to enhance quality of outcome measurement, if appropriate? We will resolve disagreements through discussion; if unable to achieve consensus, will refer to an independent arbiter.

*Data synthesis:* We will generate tables of outcomes, their descriptions, and measures. We will tabulate the proportion of included studies that report on each outcome and rank order the outcomes accordingly. We will calculate the frequency of the following scenarios: (1) outcomes reported with the same title and definition; (2) outcomes reported with the same title but different definition; and (3) outcomes reported with different titles but the same definition. We will then map outcomes to the OMERACT domains.<sup>25</sup> We will use the outcome matrix as recommended by the ORBIT project to organize outcomes.<sup>32</sup> Steering group members will review the outcome list to identify those with similar wording or meaning to be reduced to a single outcome for the purposes of the Delphi round one questionnaire.

### **Qualitative Study**

We will conduct patient and family member interviews as evidence indicates that they may hold different views about which outcomes are of relevance compared to healthcare professionals.<sup>33</sup>



1  
2  
3 *Study sample:* We will use purposive<sup>34</sup> and maximum variation sampling<sup>35</sup> to identify  
4 patient and family participants with the characteristics shown in Table 1 (minimum of 1  
5 representative of each characteristic) for each patient group. For the patient groups  
6 representing high acuity settings, acute care settings, and palliative care, we will also  
7 target parents and where possible children that have experienced delirium. For pragmatic  
8 reasons related to resource availability, we will only be able to recruit participants fluent  
9 in English. We will recruit a sample of 15 to 20 participants for each patient group which  
10 should to be sufficient to achieve saturation.<sup>36</sup> We will adjust our sample size using a  
11 stopping criterion of three consecutive interviews with no additional material to terminate  
12 data collection.  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22

23 **Table 1: Stakeholder Sampling Characteristics**

24 Stakeholder group	25 Characteristic
26 Patients/family members <sup>a</sup>	27 28 Age ( $\leq 65$ ; $>65$ ) 29 Sex (male; female) 30 Partner status (has partner; no partner) 31 Country of residence (North America; Europe/UK; 32 Australasia; other)
35 Expert clinicians <sup>b</sup>	36 37 Profession (physician, nurse, allied health) 38 Years of relevant clinical experience ( $<5$ ; 5 to 10; $>10$ ), 39 Country of residence (North America; Europe/UK; 40 Australasia; other).
42 Trialists/researchers <sup>c</sup>	43 44 Stage of research career (early: $<5$ years; mid: 5 to 15 45 years; senior $>15$ years) 46 Country of residence (North America; Europe/UK; 47 Australasia; other).

49  
50 a Patients that survived delirium within the last 18 months and family members that  
51 had direct contact with patients while experiencing delirium within the last 18  
52 months irrespective of survival i.e., we will interview family members of patients  
53 that did and did not survive the ICU.  
54

55 b Physicians, nurses, and allied health professionals that do not meet the criteria of  
56 a trialist.  
57  
58  
59  
60

- 1  
2  
3 c Authors of published (over last 10 years) or ongoing clinical trials evaluating  
4 interventions aimed at preventing or treating delirium.  
5  
6

7  
8 *Data Collection:* An experienced qualitative researcher will conduct semi-structured  
9 telephone interviews enabling representation across a wide geographic area. Following  
10 clarification of what a study outcome is and the importance of COS, patient/family  
11 members will be asked to suggest outcomes of relevance to them when considering their  
12 experience of delirium; why these outcomes are important; and to identify which  
13 outcomes they would consider core and why. All interviews will be audio-recorded and  
14 transcribed for analysis.  
15  
16  
17  
18  
19

20  
21  
22 *Data Analysis:* The experienced qualitative researcher and study investigator will  
23 independently examine interview transcripts using content analysis methods.<sup>37</sup> Outcomes  
24 that do not duplicate those identified from the systematic review will be categorized into  
25 domains and noted as only being identified by patients/family. Discussion with another  
26 investigator and the patient/family representative on the steering committee will confirm  
27 outcomes are: of relevance, not duplicative; and are allocated to the appropriate domain.<sup>38</sup>  
28  
29  
30  
31  
32  
33

### 34 **Delphi Consensus Building Exercise**

35  
36 *Participants, Recruitment and Sample Size:* We will use the eligibility criteria and  
37 sampling strategy shown in Table 1 ensuring a minimum of two participants from each  
38 stakeholder group (patients/family members; expert clinicians; trialists/researchers)  
39 representing each of the demographic variables and categories within those variables. If  
40 required we will modify our recruitment advertising to target individuals meeting our  
41 demographic targets. For the patient groups representing high acuity settings, acute care  
42 settings, and palliative care, we will also aim to have a minimum of 5 participants  
43 representing paediatrics in each group if deemed appropriate to combine in the same COS  
44 development process following our systematic review work. We will aim to maintain a  
45 minimum of 20 participants representing each stakeholder group (total 60 participants)  
46 for each patient population (total 240 participants) throughout Delphi rounds (R). Based  
47 on an estimated attrition of 30% across rounds, we will target recruitment of 310  
48 participants. A sample size of 240 participants will give us 80% power with two sided  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 test at  $\alpha=5\%$  to detect a difference of 1.0 to 1.5 points between rounds on the Grading of  
4 Recommendations Assessment, Development and Evaluations Scale<sup>39</sup> (range 1 to 9) by  
5 feedback groups when standard deviations for change vary between 1.4 and 4.1. A priori  
6 we anticipate there may be differences in responses provided by patients and family  
7 members compared to those provided by clinicians and researchers. We will test for  
8 interaction and if significant examine each group separately.  
9  
10  
11  
12  
13

14  
15 We will recruit expert clinicians using recruitment flyers sent through membership lists  
16 of the European, American, and Australasian Delirium Associations/Societies as well as  
17 professional societies of clinicians treating to our patient groups. We will continue to  
18 enrol participants until our sample size and maximum variation targets are met. We will  
19 send personalized recruitment emails to all trialists/researchers identified via our  
20 systematic review. As patient/family recruitment may poses challenges, we will use a  
21 multi-modal strategy including contact with relevant patient/family support/advocacy  
22 groups/charities as well as generic organizations such as the James Lind Alliance and  
23 COMET, use of social media including twitter and patient-focused Facebook pages,  
24 advertisements placed on public and patient involvement websites, hospital patient  
25 engagement and patient and public involvement groups, snowballing techniques, and  
26 personal contacts.  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37

38  
39 *Round One:* We will include all outcomes identified through our systematic review and  
40 patient/family interviews. We will describe outcomes in lay terms, with medical terms in  
41 brackets, to improve comprehensibility by all. We will seek advice from our  
42 patient/family steering group members for lay descriptions. To introduce the Delphi, we  
43 will provide plain language summaries developed by COMET. We will program the  
44 Delphi using the online e-management system such as the one developed by COMET.  
45 Prior to execution, we will pilot the questionnaire with 8 individuals (patients, family  
46 members, healthcare professionals and trialists) to assess face validity, understanding,  
47 and acceptability.  
48  
49  
50  
51  
52  
53  
54

55  
56 We will provide participants with outcomes identified through systematic review and  
57 interviews common to all four patient groups. Additionally, we will provide those  
58  
59  
60

1  
2  
3 outcomes specific to one of our four patient groups *only* to participant representatives of  
4 that group. We will ask participants to score each outcome using the GRADE Scale<sup>39</sup>  
5 which ranges from 1 to 9 (1 to 3 = not important for inclusion; 4 to 6 = important but not  
6 critical; 7 to 9 = critical for inclusion). We selected this scoring system to facilitate  
7 maximum discrimination between questionnaire items as noted by COMET,<sup>40 41</sup> and to  
8 enable testing of our methodological hypotheses. To avoid presentation bias, we will  
9 randomize outcome presentation for each participant. We will provide the opportunity to  
10 add additional outcomes. We will send three email completion reminders at two-week  
11 intervals. We will collect demographic information to describe our study sample; and to  
12 provide each respondent with a unique identifier, enabling personalized reminders for  
13 completion of subsequent rounds.  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23

24 We will examine data distribution of importance scores attributed to each outcome and  
25 calculate the mean and standard deviation. We will determine the proportion of  
26 participants rating each outcome as 7 to 9, 4 to 6, and 1 to 3. To reduce participant  
27 burden, we will retain for R2 those items scored between 7 and 9 (critical importance) by  
28  $\geq 50\%$  and between 1 and 3 (not important) by  $< 15\%$  of respondents. We will apply  
29 these criteria separately for patient group.  
30  
31  
32  
33  
34  
35  
36

37 *Round Two:* The steering group will review any additional outcomes provided in R1 to  
38 determine if they represent new outcomes for inclusion and to ensure wording is  
39 understandable by all participants. We will provide participants with their own R1  
40 response, summarized responses according to their patient population group, and the  
41 summarized responses of patient/family member participants (also according to patient  
42 group), and ask them to re-score the importance of each outcome. We will provide any  
43 new outcomes from R1 for scoring on the 1 to 9 importance scale. As with R1, we will  
44 send 3 email completion reminders at two-week intervals.  
45  
46  
47  
48  
49  
50  
51  
52

53 If new outcomes are identified in R1, we will conduct a third round comprising *only* these  
54 items to enable two rounds of importance scoring. Items to be brought forward to the  
55 consensus meeting will be those scored between 7 and 9 by  $\geq 70\%$  of participants and  
56  
57  
58  
59  
60

1  
2  
3 between 1 and 3 by <15 % of participants. We will identify items separately for (a)  
4 patients/family and (b) healthcare professionals and researchers combined.  
5  
6  
7

8  
9 In the event of significant attrition (defined as loss of more than 30% of participants  
10 within a stakeholder group) between rounds 1 and 2 we will engage in additional  
11 recruitment for Round 2. A priori we anticipate this may be particularly problematic for  
12 patients in the palliative group.  
13  
14

### 15 16 17 **Nested Methodological Studies**

18 We will conduct nested methodological studies to:

- 19 1. Determine if Delphi feedback provided as the proportion of participants scoring the  
20 outcome between 7 and 9 (indicating critical for inclusion) as opposed to mean  
21 scores influences subsequent scores, magnitude of change, items retained, and level  
22 of agreement (overall and by patient population group).  
23
- 24 2. Qualitatively explore the process of patient/family engagement and participation  
25 throughout COS development to determine barriers and facilitators as well as  
26 modification of our processes if needed; and  
27
- 28 3. Determine if Delphi versus nominal group technique influences which measures are  
29 retained for outcomes included in the COS.  
30  
31  
32  
33  
34  
35  
36  
37  
38

### 39 **Delphi Feedback**

40 *Randomization and Allocation:* We will randomize (1:1 stratified by patient population  
41 group) using a computer-generated schedule developed by the study statistician. We will  
42 generate a questionnaire for each Delphi participant using this allocation schedule.  
43  
44 Participants will be randomized to receive feedback as either the proportion of  
45 participants scoring the outcome as critical (for their patient population group) or patient  
46 population group mean response (Figure 1).  
47  
48  
49  
50

51  
52  
53 *Statistical Analysis:* We will analyze differences between feedback groups in terms of:  
54 (a) subsequent scores and magnitude of opinion change; (b) items retained at Delphi end;  
55 and (c) level of agreement between patient population groups. We will calculate the  
56 percentage of items for which a participant changed their score between rounds; and the  
57  
58  
59  
60

1  
2  
3 mean absolute change in score (ignoring direction of change). We will compare results  
4 according to randomization group using an independent t test overall and by patient  
5 population group. For each outcome, we will use linear regression to compare R2 scores  
6 between feedback groups and among patient population groups, adjusting for R1 scores  
7 and testing for the interaction between feedback groups and patient populations.  
8  
9

10  
11  
12  
13 To ascertain feedback group differences for items retained, we will create contingency  
14 tables, for each feedback group, to categorize the number of items retained by (i) both  
15 feedback groups; (ii) critical response feedback group only; (iii) mean feedback group  
16 only; and (iv) neither. We will determine percentage of items for which there was  
17 agreement to retain and percentage of discordant items retained by only one feedback  
18 group. To ascertain differences between feedback groups in terms of the level of  
19 agreement of items retained across patient population groups, we will generate  
20 contingency tables categorizing number of items retained by (i) all; (ii) 1 group only; (iii)  
21 2 groups only; (iv) 3 groups only; and (iv) none. We will calculate the percentage  
22 agreement and percentage of discordant items.  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32

33 To explore the impact of feedback on consensus between patient population groups, we  
34 will transform the unit of analysis to be the questionnaire item (outcome), with each  
35 observation an aggregate statistic. We will use linear regression to determine, for each  
36 outcome, and for each feedback group, the absolute difference (ignoring direction) in  
37 mean R2 scores, adjusting for the participant's R1 score. We will compare absolute mean  
38 differences between patient population groups across outcomes between the two feedback  
39 groups using a paired t test. Finally, we will compare responses irrespective of patient  
40 population groups within each randomization arm, calculate the standard deviation for  
41 each outcome separately for R1 and R2, and calculate the reduction in each outcome's  
42 variability between rounds. We will compare mean reductions in standard deviation  
43 across all outcomes between feedback groups using a paired t test.  
44  
45  
46  
47  
48  
49  
50  
51  
52

53  
54 Given the anticipated number of statistical tests, we expect 5 % to result in a P value  $\leq$   
55 0.05 by chance; therefore we will examine the percentage of tests with  $P \leq 0.05$  in  
56 relation to this expected percentage.  
57  
58  
59  
60

### **Outcome Consensus Meeting**

We will hold consensus meetings to determine the outcomes for inclusion in the two COS's; prevention and/or treatment of delirium irrespective of patient population. We will identify additional outcomes for inclusion in COS specific to our four patient populations. We will aim to be as representative of all stakeholders as possible<sup>42</sup> as we anticipate there may be differences between stakeholder groups in the priority given to outcomes. To ensure we have meaningful input across participant groups, we will invite Delphi participants to attend the meeting. Due to the large size of our Delphi panel, we will randomly select eight participants to represent each of the stakeholder groups; two representing each patient population group.

We will provide the consensus panel with outcomes established as critical using either method of feedback for inclusion via the Delphi across all four patient groups. We will use a modified nominal group technique to work towards consensus that includes small and whole group discussion and ranking. Ranking will be discussed with the aim of agreeing upon the top four or five outcomes across all patients and the top one to two specific to each patient population. To ensure there is no duplication in the final proposed set, each outcome will be discussed to ensure it relates to a distinct construct. If required we may hold an additional or standalone consensus meeting for patients and family members to enable facilitation of their understanding and thus informed voting on outcomes for the COS.

### **Process Evaluation of Patient/Family Participant Engagement**

We will conduct a process evaluation of patient/family participant engagement and participation throughout COS development.

*Participants:* We will recruit participants to take part in semi-structured interviews to determine barriers and facilitators to participation as well as recommendations for improvement strategies to inform future COS development. We will recruit 15 to 20 participants. Interviews will be audio recorded and transcribed verbatim.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

*Analysis:* We will analyze interview transcripts using content analysis<sup>43-46</sup> employing an inductive, four-step content analysis process<sup>47</sup>. An experienced qualitative researcher and an investigator will independently identify, code, and categorize important meanings and predominant themes from the text. Following an immersive reading of the transcripts, initial patterns and recurring categories will be identified by relevant highlighting sections. The second step will seek similarities and differences between participant accounts. Third and fourth steps involve creation of codes and their application over the volume of interviews respectively. The larger team will be involved in in-depth reading of the coding to ensure credibility. NVivo 10 software will be used for all facets of the analysis.

### **Instruments to Measure Outcomes**

During our systematic review we will also extract measures for outcomes reported in studies meeting our inclusion criteria. We will assess the measurement and psychometric properties of measures of the outcomes selected for our two COS (prevention and treatment) using the COSMIN check list.<sup>48</sup>

*Participants:* We will invite all Delphi participants involved in establishment of the COSs to participate in a second Delphi to establish measures for these outcomes. We will recruit additional participants if required due to attrition. We will recruit an additional 24 participants to take part in a separate consensus building exercise using only a modified nominal group technique to address the following hypothesis: measures selected for the COS are influenced by the method used for consensus building (Delphi versus nominal group technique).

*Procedures:* We will use the same Delphi methods as described above to establish one set of measures each for the two COS (prevention and treatment) including the same nested study design of randomization to two feedback methods (Delphi group). We will provide 'measure cards' provided standardized descriptions of the measures, psychometric properties, and feasibility of use (i.e., time to complete, number of items) in language understandable to all participants. We will use the same nominal group technique methods as described for the COS consensus meetings to establish a second set of



measures (nominal group technique group). We will provide to the same description of the measures and their psychometric properties as provided to the Delphi method group. Additionally, we will invite a psychometrician, clinicians and/or researchers with familiarity with the measures to the nominal group technique group thus enabling informed discussion.

*Statistical Analysis:* We will perform the same statistical analyses as described for the COS Delphi to determine differences related to consensus group method. To ascertain differences in terms of measures retained between consensus group methods, we will create contingency tables to categorize number of items retained on completion by (i) both Delphi and nominal group technique groups; (ii) Delphi group only; (iii) nominal group technique only; and (iv) neither. We will determine the percentage of items for which there was agreement along with the percentage of discordant items, retained by one consensus group method but not the other.

### **Final Consensus**

We will hold a final steering group meeting to review the findings of the consensus building exercises. Depending on the number of measures rated as critical to include we will hold a second consensus meeting using the methods described above to guide final decisions.

**Table 2: Study Timeline**

<b>Key Project Milestones</b>	<b>Start Date</b>	<b>End date</b>
Systematic review	May 2017	Feb 2018
Patient and family member interviews	Oct 2017	Feb 2018
Delphi consensus and nested methodological study	April 2018	Mar 2019
Consensus meeting	Jun 2019	Jun 2019
Process evaluation patient/family interviews	Feb 2018	Mar 2020
Consensus on measures	Sept 2019	Mar 2020
Knowledge translation/dissemination	Jun 2019 onwards	

## ETHICS AND DISSEMINATION

We are seeking research ethics board approvals as required by local governance. We will obtain written consent from participants in interviews and consensus meetings.

Participation in Delphi rounds will be considered indicative of consent. Consent will emphasize the voluntary nature of participation and anonymity.

Knowledge users within our investigator team as well as the support of three international Delirium Societies (American, Australasian, European) will be instrumental in dissemination of the COS's and subsequent uptake. We will provide a one page summary (clinicians/researchers and in lay language for patients and families) to these Societies for distribution among their networks and engage with them to seek additional opportunities to present our findings (educational seminars/workshops). We will disseminate our findings through peer-reviewed and open access publications, and presentations at international conferences purposefully selected to reach a wide range of knowledge users taking into account geographic locations. We will engage with journal editors and funding agencies to promote awareness of our COS's.

## REFERENCES

1. American Psychiatric Association, . *Diagnostic and Statistical Manual (5th edition)*. Washington, DC: American Psychiatric Association, 2013.
2. Trzepacz P, Meagher D. *Oxford Textbook of Psychiatry (2nd edition)*. London, UK: Oxford University Press, 2009.
3. Siddiqi N, Young J, House A, et al. Stop Delirium! A complex intervention to prevent delirium in care homes: a mixed-methods feasibility study. *Age Ageing* 2011;**40**:90-98.
4. Hosie A, Davidson P, Agar M, et al. Delirium prevalence, incidence, and implications for screening in specialist palliative care inpatient settings: a systematic review. *Palliat Med* 2012;**27**:486-98.
5. Inouye S, Westendorp R, Saczynski J. Delirium in elderly people. *Lancet* 2014;**383**:911–22.
6. Mistraletti G, Carloni E, Cigada M, et al. Sleep and delirium in the intensive care unit. *Minerva Anestesiol* 2008;**74**(6):329-33.
7. Daoud A, Duff JP, Joffe AR, et al. Diagnostic accuracy of delirium diagnosis in pediatric intensive care: a systematic review. *Crit Care* 2014;**18**(5):489.
8. Bellapart J, Boots R. Potential use of melatonin in sleep and delirium in the critically ill. *Br J Anaesth* 2012;**108**(4):572-80.
9. Zaal IJ, Slooter AJ. Delirium in critically ill patients: epidemiology, pathophysiology, diagnosis and management. *Drugs* 2012;**72**(11):1457-71.
10. Bickel H, Gradinger R, Kochs E, et al. High risk of cognitive and functional decline after postoperative delirium. A three-year prospective study. *Dement Geriatr Cogn Disord* 2008;**26**:26-31.
11. O'Malley G, Leonard M, Meagher D. The delirium experience: A review. *J Psychosomatics* 2008;**65**:223-28.
12. Corsinovi L, Bo M, Ricauda Aimonino N, et al. Predictors of falls and hospitalization outcomes in elderly patients admitted to an acute geriatric unit. *Arch Gerontol Geriatr* 2009;**49**:142-45.
13. Leslie D, Marcantonio E, Zhang Y, et al. One-year health care costs associated with delirium in the elderly population. *Arch Intern Med* 2008;**14**:27-32.

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
14. Barr J, Fraser G, Puntillo K, et al. American College of Critical Care Medicine: Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013;**41**:278–80.
15. Traube C, Mauer E, Gerber L, et al. Cost associated with pediatric delirium in the ICU. *Crit Care Med* 2016.
16. Buurman B, Hoogerduijn J, de Haan R, et al. Geriatric conditions in acutely hospitalized older patients: prevalence and one-year survival and functional decline. *PLoS One* 2011;**6**:e26951.
17. Rudolph J, Inouye S, Jones R, et al. Delirium: an independent predictor of functional decline after cardiac surgery. *J Am Geriatr Soc* 2010;**58**:643-49.
18. Carbone M, Gugliucci M. Delirium and the family caregiver: the need for evidence-based education interventions. *Gerontologist* 2015;**55**:345-52.
19. Finucane A, Lugton J, Kennedy C, et al. The experiences of caregivers of patients with delirium, and their role in its management in palliative care settings: an integrative literature review. *Psychooncology* 2016.
20. Crocker E, Beggs T, Hassan A, et al. Long-term effects of postoperative delirium in patients undergoing cardiac operation: a systematic review. *Ann Thorac Surg* 2016;pii: S0003-4975(16)30402-7.
21. Clarke M. Standardising outcomes for clinical trials and systematic reviews. *Trials* 2007;**8**:39.
22. Sanderson T, Morris M, Calnan M, et al. What outcomes from pharmacologic treatments are important to people with rheumatoid arthritis? Creating the basis of a patient core set. *Arthrit Care Res* 2010;**62**:640–46.
23. Gagnon P. Treatment of delirium in supportive and palliative care. *Curr Opin Support Palliat Care* 2008;**2**:60-66.
24. LaHue, SC, Liu V. Loud and clear: sensory impairment, delirium, and functional recovery in critical illness. *Am J Respir Crit Care Med* 2016 **194**:252-3.
25. Tugwell P, Boers M, Brooks P, et al. OMERACT: an international initiative to improve outcome measurement in rheumatology. *Trials* 2007;**8**:38.
26. Williamson P, Altman D, Blazeby J, et al. Developing core outcome sets for clinical trials: issues to consider. *Trials* 2012;**13**:132.

- 1  
2  
3  
4 27. COMET PoPPIE group. Checklist for public research partners and core outcome set  
5 (COS) study developers involved in designing a COS study. Secondary Checklist  
6 for public research partners and core outcome set (COS) study developers  
7 involved in designing a COS study. 2015. [http://www.comet-](http://www.comet-initiative.org/assets/downloads/COS%20study%20development%20-%20PPI%20checklist%2016-03-16.pdf)  
8 [initiative.org/assets/downloads/COS%20study%20development%20-](http://www.comet-initiative.org/assets/downloads/COS%20study%20development%20-%20PPI%20checklist%2016-03-16.pdf)  
9 [%20PPI%20checklist%2016-03-16.pdf](http://www.comet-initiative.org/assets/downloads/COS%20study%20development%20-%20PPI%20checklist%2016-03-16.pdf).  
10  
11  
12  
13  
14 28. McGowan J, Sampson M, Salzwedel DM, et al. PRESS Peer Review of Electronic  
15 Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol* 2016;**75**:40-46.  
16  
17 29. Sampson M, McGowan J, Cogo E, et al. An evidence-based practice guideline for the  
18 peer review of electronic search strategies. *J Clin Epidemiol* 2009;**62**(9):944-52.  
19  
20 30. Scottish Intercollegiate Guidelines Network. Methodology Checklists. 2015.  
21 [www.sign.ac.uk/methodology/checklists.html](http://www.sign.ac.uk/methodology/checklists.html)  
22  
23  
24  
25  
26  
27 31. Harman N, IA B, P C, et al. MOMENT--Management of Otitis Media with Effusion  
28 in Cleft Palate: protocol for a systematic review of the literature and identification  
29 of a core outcome set using a Delphi survey. *Trials* 2013;**14**:70.  
30  
31 32. Kirkham J, Dwan K, Altman D, et al. The impact of outcome reporting bias in  
32 randomised controlled trials on a cohort of systematic reviews. *BMJ*  
33 **2010**;**340**:c365.  
34  
35  
36 33. Boers M, Kirwan J, Tugwell P, et al. The OMERACT handbook. Ottawa:  
37 OMERACT, 2014.  
38  
39  
40 34. Pope C, Mays N. Qualitative Research: Reaching the parts other methods cannot  
41 reach: an introduction to qualitative methods in health and health services  
42 research. *BMJ* 1995;**311**(6996):42-45.  
43  
44  
45 35. Patton M. Purposeful sampling. *Qualitative evaluation and research methods*. Beverly  
46 Hills, CA: Sage, 1990:169-86.  
47  
48  
49 36. Francis J, Johnston M, Robertson C, et al. What is an adequate sample size?  
50 Operationalising data saturation for theory-based interview studies. *Psychol*  
51 *Health* 2010;**25**:1229-45.  
52  
53  
54 37. Elo S, Kyngäs H. The qualitative content analysis process. *J Adv Nurs* 2008;**62**:107-  
55 15.  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
38. Macefield R, Jacobs M, Korfage I, et al. Developing core outcomes sets: methods for identifying and including patient-reported outcomes (PROs). *Trials* 2014; **15**:49.
  39. The GRADE working group. GRADE. Secondary GRADE 2016.  
<http://www.gradeworkinggroup.org/>.
  40. Sinha I, Smyth R, Williamson P. Using the Delphi technique to determine which outcomes to measure in clinical trials: recommendations for the future based on a systematic review of existing studies. *PLoS Med* 2011; **8**: e1000393.
  41. The COMET Initiative. The COMET Initiative. Secondary The COMET Initiative 2011. <http://www.comet-initiative.org>.
  42. Simon L, Strand V, Bingham C, et al. OMERACT 11: international consensus conference on outcome measures. *J Rheumatol* 2014; **41**:145-49.
  43. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse Educ Today* 2004; **24**(2):105-12.
  44. Onwuegbuzie A, Dickinson W, Leech N, et al. A qualitative framework for collecting and analyzing data in focus group research. *Int J Qual Meth* 2009; **8**:1-21.
  45. Carlsen B, Glenton C. What about N? A methodological study of sample-size reporting in focus group studies. *BMC Med Res Methodol* 2011; **11**:26.
  46. Vaismoradi M, Turunen H, Bondas T. Content analysis and thematic analysis: Implications for conducting a qualitative descriptive study. *Nursing & health sciences* 2013; **15**(3):398-405.
  47. Burnard F. Teaching the analysis of textual data: an experiential approach. *Nurse Educ Today* 1996; **16**:278–81.
  48. Terwee CB, Mokkink LB, Knol DL, et al. Rating the methodological quality in systematic reviews of studies on measurement properties: a scoring system for the COSMIN checklist. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2012; **21**(4):651-7.

### **AUTHOR CONTRIBUTIONS**

LR and VP conceived of the study. LR, MA, LB, NC, JL, NS, and VP developed the study protocol and funding applications to support conduct of the study. Additionally, MC advised on the design of the nested methodological studies as well as contributed to design of the protocol. All authors contributed to drafting and editing of the manuscript, as well as read and approved the final version.

### **FUNDING STATEMENT**

This study is not funded. Dr. Louise Rose holds a Canadian Institutes of Health Research New Investigator Award. Jennifer Ansell has received funding towards her PhD Studentship through the University of Toronto.

### **COMPETING INTERESTS STATEMENT**

The authors have no competing interests to declare.

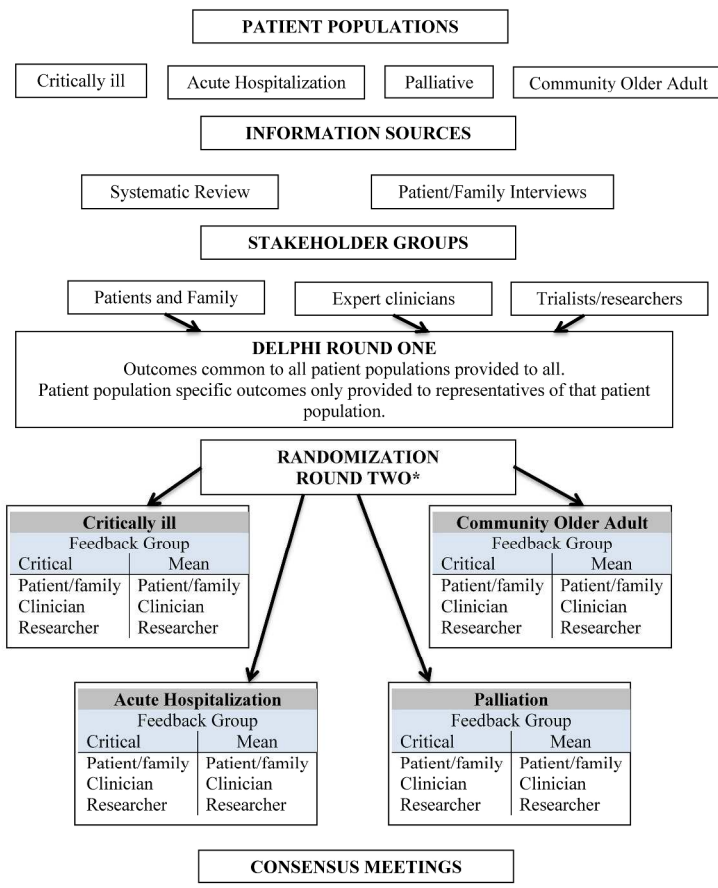
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Figure 1: Flow of Core Outcome Set Development

For peer review only



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



**Figure 1: Flow of core outcome set development**  
\* We will conduct an third Delphi round if additional outcomes are identified in round one

279x361mm (300 x 300 DPI)

## Appendix: Search Strategy: Medline

Patient Group 1: critically ill adults and children receiving care in high acuity settings, including intensive care and high dependency units

1 ((postoperati\* or post-operati\* or postsurg\* or post-surg\*) adj1 ("cognitive dysfunction" or "brain dysfunction")).tw,kw,kf.

2 Delirium/

3 deliri\*.tw,kw,kf.

4 Psychoses, Substance-Induced/

5 (psychos\* adj3 (toxic\* or exogenous\* or chemical\* or drug or drugs or medication\* or substance\*)).tw,kw,kf.

6 (acute brain adj (dysfunction\* or failure\* or syndrome\*)).tw,kw,kf.

7 (cloud\* adj3 consciousness\*).tw,kw,kf.

8 clouded state\*.tw,kw,kf.

9 ((psycho-organic syndrome\* or psychoorganic syndrome\* or organic psychosyndrome\* or organic psycho-syndrome\*) adj3 acute).tw,kw,kf.

10 exp Confusion/ci

11 Hallucinations/

12 hallucinat\*.tw,kw,kf.

13 or/1-12 [DELIRIUM]

14 exp Animals/ not (exp Animals/ and Humans/)

15 13 not 14 [ANIMAL-ONLY REMOVED]

16 Intensive Care Units/

17 Burn Units/

18 Coronary Care Units/

19 Respiratory Care Units/

20 exp Intensive Care Units, Pediatric/

21 exp Critical Care/

22 ((intensive or critical or acute) adj3 care).tw,kw,kf.

23 (ICU or ICUs or SICU or SICUs or CCU or CCUs).tw,kw,kf.

24 (PICU or PICUs or NICU or NICUs).tw,kw,kf.

25 (burn? adj3 (unit? or centre? or center?)).tw,kw,kf.

26 ((cardiac or coronary or heart) adj3 (unit? or centre? or center?)).tw,kw,kf.

27 (respiratory adj3 (unit? or centre? or center?)).tw,kw,kf.

28 ((surgical or surger\*) adj3 (unit? or centre? or center?)).tw,kw,kf.

29 (high dependency adj3 (unit? or centre? or center?)).tw,kw,kf.

30 ((stepdown or step-down) adj3 (unit? or centre? or center?)).tw,kw,kf.

31 (HDU or HDUs or SDU or SDUs or EDSDU or EDSDUs).tw,kw,kf.

32 ((special\* or dedicated or intens\*) adj weaning adj3 (unit? or centre? or center? or program\* or ward?)).tw,kw,kf.

33 Critical Illness/

34 (critical\* adj (ill or illness\*)).tw,kw,kf.

35 or/16-34

36 15 and 35 [DELIRIUM IN THE ICU]

37 limit 36 to yr="1980-current"

38 limit 37 to english language

2. Non-critically ill adults and children hospitalized in acute care settings including postoperative surgical and medical patients, those presenting to ED

1 ((postoperati\* or post-operati\* or postsurg\* or post-surg\*) adj1 ("cognitive dysfunction" or "brain dysfunction")).tw,kw,kf.

2 Delirium/

3 deliri\*.tw,kw,kf.

4 Psychoses, Substance-Induced/

5 (psychos\* adj3 (toxic\* or exogenous\* or chemical\* or drug or drugs or medication\* or substance\*)).tw,kw,kf.

6 (acute brain adj (dysfunction\* or failure\* or syndrome\*)).tw,kw,kf.

7 (cloud\* adj3 consciousness\*).tw,kw,kf.

8 clouded state\*.tw,kw,kf.

9 ((psycho-organic syndrome\* or psychoorganic syndrome\* or organic psychosyndrome\* or organic psycho-syndrome\*) adj3 acute).tw,kw,kf.

10 exp Confusion/ci

11 Hallucinations/

12 hallucinat\*.tw,kw,kf.

13 or/1-12 [DELIRIUM]

14 exp Animals/ not (exp Animals/ and Humans/)

15 13 not 14 [ANIMAL-ONLY REMOVED]

16 Inpatients/

17 inpatient\*.tw,kw,kf.

18 Adolescent, Hospitalized/

19 Child, Hospitalized/

20 exp Hospitalization/

21 Emergency Service, Hospital/

22 (emergency adj2 (care or center? or centre? or department? or dept? or room? or service? or unit or units or ward?)).tw,kw,kf.

23 (("A and E" or "A & E") adj2 (care or center? or centre? or department? or dept? or room? or service? or unit or units or ward?)).tw,kw,kf.

24 hospital\*.tw,kw,kf.

25 ((emergency or medical\* or surg\*) adj3 patient?).tw,kw,kf.

26 Postoperative Care/

27 ((postoperati\* or post-operati\* or postsurg\* or post-surg\*) adj3 (care or patient?)).tw,kw,kf.

28 or/16-27

29 15 and 28 [DELIRIUM IN INPATIENTS/HOSPITALIZED CARE]

30 limit 29 to yr="1980-CURRENT"

31 limit 30 to english language

1  
2  
3 3. Adults and children receiving palliative care, either in a hospital, hospice, or community setting  
4 1 ((postoperati\* or post-operati\* or postsurg\* or post-surg\*) adj1 ("cognitive dysfunction" or "brain  
5 dysfunction")).tw,kw,kf.  
6  
7 2 Delirium/  
8 3 deliri\*.tw,kw,kf.  
9 4 Psychoses, Substance-Induced/  
10 5 (psychos\* adj3 (toxic\* or exogenous\* or chemical\* or drug or drugs or medication\* or  
11 substance\*)).tw,kw,kf.  
12 6 (acute brain adj (dysfunction\* or failure\* or syndrome\*)).tw,kw,kf.  
13 7 (cloud\* adj3 consciousness\*).tw,kw,kf.  
14 8 clouded state\*.tw,kw,kf.  
15 9 ((psycho-organic syndrome\* or psychoorganic syndrome\* or organic psychosyndrome\* or organic  
16 psycho-syndrome\*) adj3 acute).tw,kw,kf.  
17 10 exp Confusion/ci  
18 11 Hallucinations/  
19 12 hallucinat\*.tw,kw,kf.  
20 13 or/1-12 [DELIRIUM]  
21 14 exp Animals/ not (exp Animals/ and Humans/  
22 15 13 not 14 [ANIMAL-ONLY REMOVED]  
23 16 Inpatients/  
24 17 inpatient\*.tw,kw,kf.  
25 18 Adolescent, Hospitalized/  
26 19 Child, Hospitalized/  
27 20 exp Hospitalization/  
28 21 Emergency Service, Hospital/  
29 22 (emergency adj2 (care or center? or centre? or department? or dept? or room? or service? or unit  
30 or units or ward?)).tw,kw,kf.  
31 23 (("A and E" or "A & E") adj2 (care or center? or centre? or department? or dept? or room? or  
32 service? or unit or units or ward?)).tw,kw,kf.  
33 24 hospital\*.tw,kw,kf.  
34 25 ((emergency or medical\* or surg\*) adj3 patient?).tw,kw,kf.  
35 26 Postoperative Care/  
36 27 ((postoperati\* or post-operati\* or postsurg\* or post-surg\*) adj3 (care or patient?)).tw,kw,kf.  
37 28 or/16-27  
38 29 15 and 28 [DELIRIUM IN INPATIENTS/HOSPITALIZED CARE]  
39 30 limit 29 to yr="1980-CURRENT"  
40 31 limit 30 to english language  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

4. Older adults (65 and over) living in nursing or residential care homes or living in their own homes and defined as at risk of delirium by study authors.

1 ((postoperati\* or post-operati\* or postsurg\* or post-surg\*) adj1 ("cognitive dysfunction" or "brain dysfunction")).tw,kw,kf.

2 Delirium/

3 deliri\*.tw,kw,kf.

4 Psychoses, Substance-Induced/

5 (psychos\* adj3 (toxic\* or exogenous\* or chemical\* or drug or drugs or medication\* or substance\*)).tw,kw,kf.

6 (acute brain adj (dysfunction\* or failure\* or syndrome\*)).tw,kw,kf.

7 (cloud\* adj3 consciousness\*).tw,kw,kf.

8 clouded state\*.tw,kw,kf.

9 ((psycho-organic syndrome\* or psychoorganic syndrome\* or organic psychosyndrome\* or organic psycho-syndrome\*) adj3 acute).tw,kw,kf.

10 exp Confusion/ci

11 Hallucinations/

12 hallucinat\*.tw,kw,kf.

13 or/1-12 [DELIRIUM]

14 exp Animals/ not (exp Animals/ and Humans/)

15 13 not 14 [ANIMAL-ONLY REMOVED]

16 exp Aged/

17 Health Services for the Aged/

18 (geriatric\* or psychogeriatric\* or psycho-geriatric\* or gerontolog\* or elder\$2 or old-age? or senior\*).tw,kw,kf.

19 (older adj2 (adult? or age? or female? or male? or man or men or patient? or person? or people? or population? or resident? or woman\* or women\*)).tw,kw,kf.

20 Homes for the Aged/

21 ((facility or facilities or home or homes) adj "for the aged").tw,kw,kf.

22 exp Nursing homes/

23 nursing home?.tw,kw,kf.

24 (nursing facility or nursing facilities).tw,kw,kf.

25 care home?.tw,kw,kf.

26 (care facility or care facilities).tw,kw,kf.

27 (residen\* adj1 (care or health care or healthcare)).tw,kw,kf.

28 ((care or healthcare or service?) adj "for the aged").tw,kw,kf.

29 (aged care or aged healthcare or aged health care or aged service?).tw,kw,kf.

30 or/16-29

31 15 and 30 [DELIRIUM IN THE ELDERLY]

32 limit 31 to yr="1980-CURRENT"

33 limit 32 to english language