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TITLE

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

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KEYWORDS

Delirium; core outcome set; systematic review; research methods

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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.

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

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.[1 2] 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,[3] those receiving palliative care services,[4] and a significant number of hospitalized patients, including the acute and critically ill. Prevalence rates in hospitalized patients range from 25% to 80%.[5-8]

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;[9-12] and escalating public healthcare costs. [13-15] Delirium also carries long term consequences including impaired physical functioning[16 17] and loss of independence resulting in long-term care placement;[5] caregiver burden;[18 19] decreased quality of life;[20] cognitive decline, and increased risk of dementia and Alzheimer's disease.[11]

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).[21 22] Although the importance and value of COS for standardizing outcomes

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

Scope of Core Outcome Set Development

The scope of our COS will include our four patient populations of interest, considered at high risk of developing delirium.[3 5 23 24] These include (1) critically ill adults and children receiving care in high acuity settings, including intensive care and high dependency units; (2) non-critically ill adults and children hospitalized in acute care settings including postoperative surgical and medical patients, and patients presenting to an emergency department (ED); (3) adults and children receiving palliative care, either in a hospital, hospice, or community setting; and (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. We recognize that certain subpopulations such as children and older adults with dementia spanning these patient populations may need a distinct COS or outcomes for substitution within a COS. This decision will be made following identification and mapping of outcomes during our systematic review and from interviews with patients/family.

METHODS

We will use methods outlined in the OMERACT handbook[25] and those endorsed by the COMET initiative.[26] Our study steering group will comprise two experts with clinical and/or research expertise in delirium and a patient/family representative for each of our four patient populations. We will use the COMET Checklist for Public Research Partners and the COS Study Developers Involved in Designing a COS study checklist[27] to guide and optimize our engagement with patients/family around the COS design and conduct.

Information Sources

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

Systematic Review

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

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

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.[30] Two investigators will assess independently quality of describing and reporting outcomes using the six-point MOMENT scoring system with a score of ≥4 representing high quality outcome reporting.[31] 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 though 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.[25] We will use the outcome matrix as recommended by the ORBIT project to organize outcomes.[32] 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.[33]

Study sample: We will use purposive[34] and maximum variation sampling[35] to identify patient and family participants with the characteristics shown in Table 1 (minimum of 1 representative of each characteristic) for each patient group. For pragmatic reasons related to resource availability, we will only be able to recruit participants fluent in English. We will recruit a sample of 15 to 20 participants for each patient group which should to be sufficient to achieve saturation.[36] We will adjust our sample size using a stopping criterion of three consecutive interviews with no additional material to terminate data collection.

Table 1: Stakeholder Sampling Characteristics

Stakeholder group	Characteristic
Patients/family members[a]	
	Age (≤65; >65)
	Sex (male; female)
	Partner status (has partner; no partner)
	Country of residence (North America; Europe/UK; Australasia; other)
Expert clinicians[b]	
	Profession (physician, nurse, allied health)
	Years of relevant clinical experience (<5; 5 to 10; >10),
	Country of residence (North America; Europe/UK; Australasia; other).
Trialists/researchers[c]	
	Stage of research career (early: <5 years; mid: 5 to 15 years; senior >15 years)
	Country of residence (North America; Europe/UK; Australasia; other).

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

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

c Authors of published (over last 10 years) or ongoing clinical trials evaluating interventions aimed at preventing or treating delirium.

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.[37] 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.[38]

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 at 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 α=5% to detect a difference of 1.0 to 1.5 points between rounds on the Grading of Recommendations Assessment, Development and Evaluations Scale[39] (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

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

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

We will provide participants with outcomes identified through systematic review and interviews common to all four patient groups. Additionally, we will provide those outcomes specific to one of our four patient groups *only* to participant representatives of that group. We will ask participants to score each outcome using the GRADE Scale[39] which ranges from 1 to 9 (1 to 3 = not important for inclusion; 4 to 6 = important but not critical; 7 to 9 = critical for inclusion). We selected this scoring system to facilitate maximum discrimination between questionnaire items as noted by COMET,[40 41] and to enable testing of our methodological hypotheses. To avoid presentation bias, we will randomize outcome presentation for each participant. We will provide the opportunity to add additional outcomes. We will send three email completion reminders at two-week intervals. We will collect demographic information to describe our study sample; and to provide each respondent with a unique identifier, enabling personalized reminders for completion of subsequent rounds.

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

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

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

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

Nested Methodological Studies

We will conduct nested methodological studies to:

1. Determine if Delphi feedback provided as the proportion of participants scoring the outcome between 7 and 9 (indicating critical for inclusion) as opposed to mean

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

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

Delphi Feedback

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

Statistical Analysis: We will analyze differences between feedback groups in terms of: (a) subsequent scores and magnitude of opinion change; (b) items retained at Delphi end; and (c) level of agreement between patient population groups. We will calculate the percentage of items for which a participant changed their score between rounds; and the mean absolute change in score (ignoring direction of change). We will compare results according to randomization group using an independent t test overall and by patient population group. For each outcome, we will use linear regression to compare R2 scores between feedback groups and among patient population groups, adjusting for R1 scores and testing for the interaction between feedback groups and patient populations.

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

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

To explore the impact of feedback on consensus between patient population groups, we will transform the unit of analysis to be the questionnaire item (outcome), with each observation an aggregate statistic. We will use linear regression to determine, for each outcome, and for each feedback group, the absolute difference (ignoring direction) in mean R2 scores, adjusting for the participant's R1 score. We will compare absolute mean differences between patient population groups across outcomes between the two feedback groups using a paired t test. Finally, we will compare responses irrespective of patient population groups within each randomization arm, calculate the standard deviation for each outcome separately for R1 and R2, and calculate the reduction in each outcome's variability between rounds. We will compare mean reductions in standard deviation across all outcomes between feedback groups using a paired t test.

Given the anticipated number of statistical tests, we expect 5 % to result in a P value ≤ 0.05 by chance; therefore we will examine the percentage of tests with P ≤ 0.05 in relation to this expected percentage.

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[42] 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.

Analysis: We will analyze interview transcripts using content analysis[43-46] employing an inductive, four-step content analysis process[47]. 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.[48]

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.

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.

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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.

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COMPETING INTERESTS STATEMENT

The authors have no competing interests to declare.

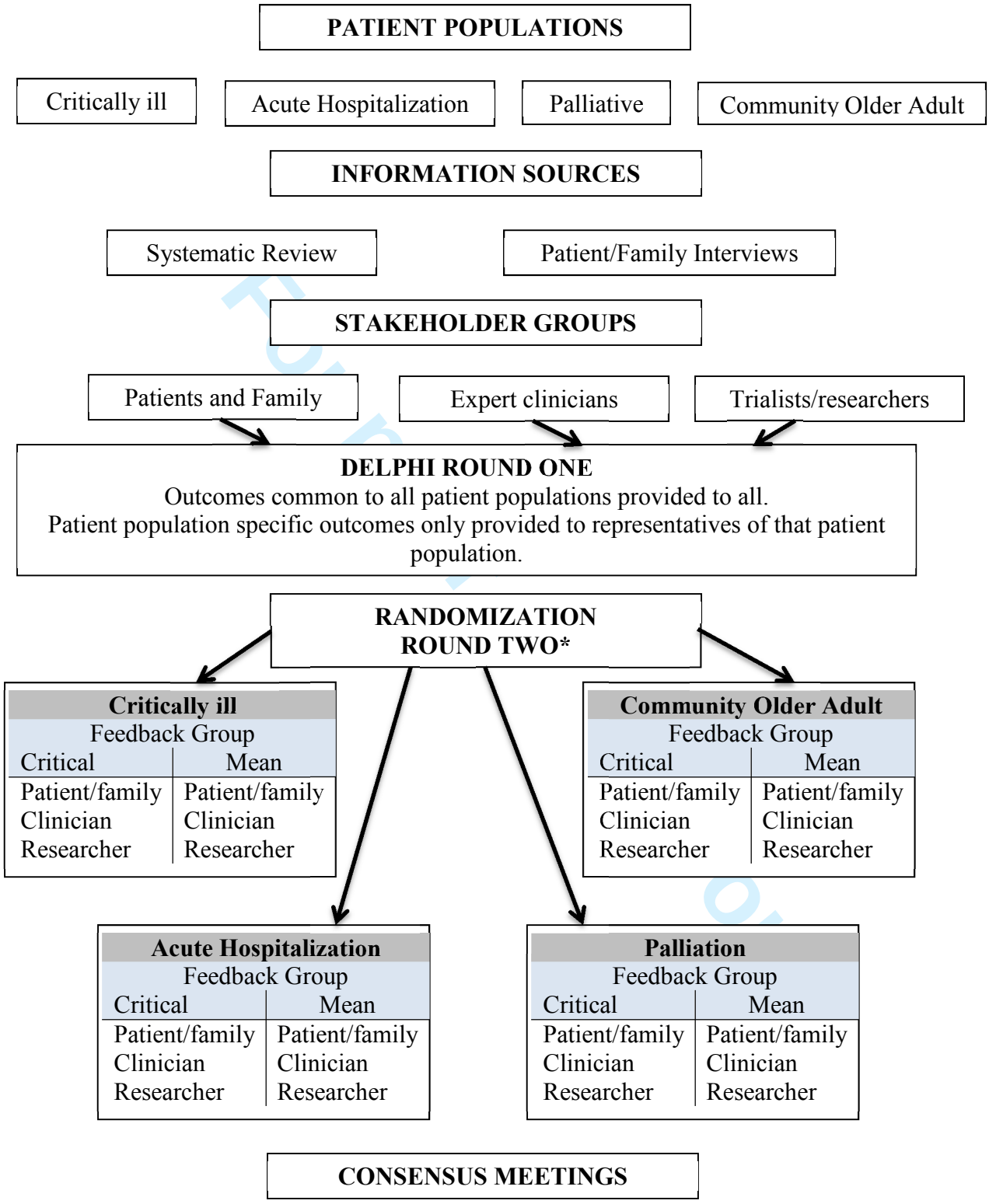

Figure 1: Flow of core outcome set development
* We will conduct an third Delphi round if additional outcomes are identified in round one

BMJ Open

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

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TITLE

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

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KEYWORDS

Delirium; core outcome set; systematic review; research methods

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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.

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

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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.[1 2] 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,[3] those receiving palliative care services,[4] and a significant number of hospitalized patients, including the acute and critically ill. Prevalence rates in hospitalized patients range from 25% to 80%.[5-8]

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;[9-12] and escalating public healthcare costs. [13-15] Delirium also carries long term consequences including impaired physical functioning[16 17] and loss of independence resulting in long-term care placement;[5] caregiver burden;[18 19] decreased quality of life;[20] cognitive decline, and increased risk of dementia and Alzheimer's disease.[11]

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).[21 22] Although the importance and value of COS for standardizing outcomes

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

Scope of Core Outcome Set Development

The scope of our COS will include our four patient populations of interest, considered at high risk of developing delirium.[3 5 23 24] These include (1) critically ill adults and children receiving care in high acuity settings, including intensive care and high dependency units; (2) non-critically ill adults and children hospitalized in acute care settings including postoperative surgical and medical patients, and patients presenting to an emergency department (ED); (3) adults and children receiving palliative care, either in a hospital, hospice, or community setting; and (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. We recognize that certain subpopulations such as children and older adults with dementia spanning these patient populations may need a distinct COS or outcomes for substitution within a COS. This decision will be made following identification and mapping of outcomes during our systematic review and from interviews with patients/family.

METHODS

We will use methods outlined in the OMERACT handbook[25] and those endorsed by the COMET initiative.[26] Our study steering group will comprise two experts with clinical and/or research expertise in delirium and a patient/family representative for each of our four patient populations. We will use the COMET Checklist for Public Research Partners and the COS Study Developers Involved in Designing a COS study checklist[27] to guide and optimize our engagement with patients/family around the COS design and conduct.

Information Sources

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

Systematic Review

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

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

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.[30] Two investigators will assess independently quality of describing and reporting outcomes using the six-point MOMENT scoring system with a score of ≥4 representing high quality outcome reporting.[31] 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 though 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.[25] We will use the outcome matrix as recommended by the ORBIT project to organize outcomes.[32] 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.[33]

Study sample: We will use purposive[34] and maximum variation sampling[35] to identify patient and family participants with the characteristics shown in Table 1 (minimum of 1 representative of each characteristic) for each patient group. For the patient groups representing high acuity settings, acute care settings, and palliative care, we will also target parents and where possible children that have experienced delirium. For pragmatic reasons related to resource availability, we will only be able to recruit participants fluent in English. We will recruit a sample of 15 to 20 participants for each patient group which should to be sufficient to achieve saturation.[36] We will adjust our sample size using a stopping criterion of three consecutive interviews with no additional material to terminate data collection.

Table 1: Stakeholder Sampling Characteristics

Stakeholder group	Characteristic
Patients/family members[a]	
	Age (≤65; >65)
	Sex (male; female)
	Partner status (has partner; no partner)
	Country of residence (North America; Europe/UK; Australasia; other)
Expert clinicians[b]	
	Profession (physician, nurse, allied health)
	Years of relevant clinical experience (<5; 5 to 10; >10),
	Country of residence (North America; Europe/UK; Australasia; other).
Trialists/researchers[c]	
	Stage of research career (early: <5 years; mid: 5 to 15 years; senior >15 years)
	Country of residence (North America; Europe/UK; Australasia; other).

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

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

c Authors of published (over last 10 years) or ongoing clinical trials evaluating interventions aimed at preventing or treating delirium.

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.[37] 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.[38]

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. For the patient groups representing high acuity settings, acute care settings, and palliative care, we will also aim to have a minimum of 5 participants representing paediatrics in each group if deemed appropriate to combine in the same COS development process following our systematic review work. 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 at 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 α=5% to detect a difference of 1.0 to 1.5 points between rounds on the Grading of Recommendations Assessment, Development and Evaluations Scale[39] (range 1 to 9) by

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

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

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

We will provide participants with outcomes identified through systematic review and interviews common to all four patient groups. Additionally, we will provide those outcomes specific to one of our four patient groups *only* to participant representatives of that group. We will ask participants to score each outcome using the GRADE Scale[39] which ranges from 1 to 9 (1 to 3 = not important for inclusion; 4 to 6 = important but not

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

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

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

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

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

Nested Methodological Studies

We will conduct nested methodological studies to:

1. Determine if Delphi feedback provided as the proportion of participants scoring the outcome between 7 and 9 (indicating critical for inclusion) as opposed to mean scores influences subsequent scores, magnitude of change, items retained, and level of agreement (overall and by patient population group).
2. Qualitatively explore the process of patient/family engagement and participation throughout COS development to determine barriers and facilitators as well as modification of our processes if needed; and
3. Determine if Delphi versus nominal group technique influences which measures are retained for outcomes included in the COS.

Delphi Feedback

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

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

between feedback groups and among patient population groups, adjusting for R1 scores and testing for the interaction between feedback groups and patient populations.

To ascertain feedback group differences for items retained, we will create contingency tables, for each feedback group, to categorize the number of items retained by (i) both feedback groups; (ii) critical response feedback group only; (iii) mean feedback group only; and (iv) neither. We will determine percentage of items for which there was agreement to retain and percentage of discordant items retained by only one feedback group. To ascertain differences between feedback groups in terms of the level of agreement of items retained across patient population groups, we will generate contingency tables categorizing number of items retained by (i) all; (ii) 1 group only; (iii) 2 groups only; (iv) 3 groups only; and (iv) none. We will calculate the percentage agreement and percentage of discordant items.

To explore the impact of feedback on consensus between patient population groups, we will transform the unit of analysis to be the questionnaire item (outcome), with each observation an aggregate statistic. We will use linear regression to determine, for each outcome, and for each feedback group, the absolute difference (ignoring direction) in mean R2 scores, adjusting for the participant's R1 score. We will compare absolute mean differences between patient population groups across outcomes between the two feedback groups using a paired t test. Finally, we will compare responses irrespective of patient population groups within each randomization arm, calculate the standard deviation for each outcome separately for R1 and R2, and calculate the reduction in each outcome's variability between rounds. We will compare mean reductions in standard deviation across all outcomes between feedback groups using a paired t test.

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

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[42] 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.

Analysis: We will analyze interview transcripts using content analysis[43-46] employing an inductive, four-step content analysis process[47]. 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.[48]

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

Key Project Milestones	Start Date	End date
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.

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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.

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COMPETING INTERESTS STATEMENT

The authors have no competing interests to declare.

Figure 1: Flow of Core Outcome Set Development

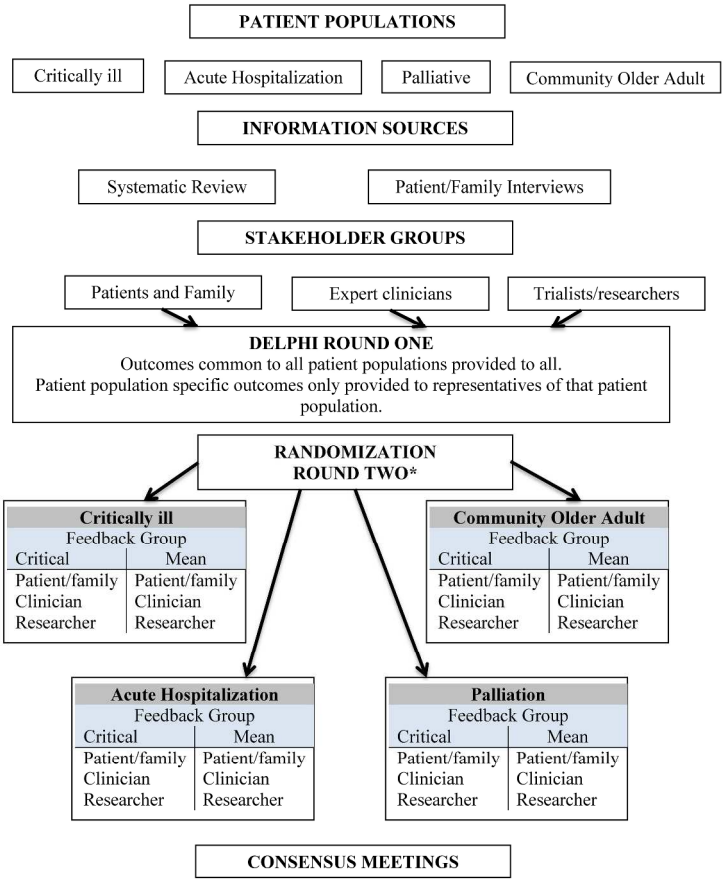

Figure 1: Flow of core outcome set development
* We will conduct an third Delphi round if additional outcomes are identified in round one

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

3. Adults and children receiving palliative care, either in a hospital, hospice, or community setting
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

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

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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Geriatric medicine, Intensive care, Palliative care
Keywords:	Delirium & cognitive disorders < PSYCHIATRY, core outcome set, systematic review, research methods

TITLE

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

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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.

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

The study is funded by the Canadian Institutes of Health Research

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.[1 2] 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,[3] those receiving palliative care services,[4] and a significant number of hospitalized patients, including the acute and critically ill. Prevalence rates in hospitalized patients range from 25% to 80%.[5-8]

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;[9-12] and escalating public healthcare costs. [13-15] Delirium also carries long term consequences including impaired physical functioning[16 17] and loss of independence resulting in long-term care placement;[5] caregiver burden;[18 19] decreased quality of life;[20] cognitive decline, and increased risk of dementia and Alzheimer's disease.[11]

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).[21 22] Although the importance and value of COS for standardizing outcomes

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

Scope of Core Outcome Set Development

The scope of our COS will include our four patient populations of interest, considered at high risk of developing delirium.[3 5 23 24] These include (1) critically ill adults and children (medical, surgical, and trauma) receiving care in high acuity settings, including intensive care and high dependency units; (2) non-critically ill adults and children hospitalized in acute care settings including surgical (all surgeries) and medical patients, and patients presenting to an emergency department (ED); (3) adults and children receiving palliative care, either in a hospital, hospice, or community setting; and (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. We recognize that certain subpopulations such as children and older adults with dementia spanning these patient populations may need a distinct COS or outcomes for substitution within a COS. This decision will be made following identification and mapping of outcomes during our systematic review and from interviews with patients/family.

METHODS

We will use methods outlined in the OMERACT handbook[25] and those endorsed by the COMET initiative.[26] Our study steering group will comprise two experts with clinical and/or research expertise in delirium and a patient/family representative for each of our four patient populations. We will use the COMET Checklist for Public Research Partners and the COS Study Developers Involved in Designing a COS study checklist[27] to guide and optimize our engagement with patients/family around the COS design and conduct.

Information Sources

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

Systematic Review

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

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

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.[30] Two investigators will assess independently quality of describing and reporting outcomes using the six-point MOMENT scoring system with a score of ≥4 representing high quality outcome reporting.[31] 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 though 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.[25] We will use the outcome matrix as recommended by the ORBIT project to organize outcomes.[32] 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.[33]

Study sample: We will use purposive[34] and maximum variation sampling[35] to identify patient and family participants with the characteristics shown in Table 1 (minimum of 1 representative of each characteristic) for each patient group. For the patient groups representing high acuity settings, acute care settings, and palliative care, we will also target parents and where possible children that have experienced delirium. For pragmatic reasons related to resource availability, we will only be able to recruit participants fluent in English. We will recruit a sample of 15 to 20 participants for each patient group which should to be sufficient to achieve saturation.[36] We will adjust our sample size using a stopping criterion of three consecutive interviews with no additional material to terminate data collection.

Table 1: Stakeholder Sampling Characteristics

Stakeholder group	Characteristic
Patients/family members[a]	
	Age (≤65; >65)
	Sex (male; female)
	Partner status (has partner; no partner)
	Country of residence (North America; Europe/UK; Australasia; other)
Expert clinicians[b]	
	Profession (physician, nurse, allied health)
	Years of relevant clinical experience (<5; 5 to 10; >10),
	Country of residence (North America; Europe/UK; Australasia; other).
Trialists/researchers[c]	
	Stage of research career (early: <5 years; mid: 5 to 15 years; senior >15 years)
	Country of residence (North America; Europe/UK; Australasia; other).

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

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

c Authors of published (over last 10 years) or ongoing clinical trials evaluating interventions aimed at preventing or treating delirium.

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.[37] 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.[38]

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 (patients/family members; expert clinicians; trialists/researchers) representing each of the demographic variables and categories within those variables. If required we will modify our recruitment advertising to target individuals meeting our demographic targets. For the patient groups representing high acuity settings, acute care settings, and palliative care, we will also aim to have a minimum of 5 participants representing paediatrics in each group if deemed appropriate to combine in the same COS development process following our systematic review work. 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 at 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 α=5% to detect a difference of 1.0 to 1.5 points between rounds on the Grading of Recommendations Assessment, Development and Evaluations Scale[39] (range 1 to 9) by feedback groups when standard deviations for change vary between 1.4 and 4.1. A priori we anticipate there may be differences in responses provided by patients and family members compared to those provided by clinicians and researchers. We will test for interaction and if significant examine each group separately.

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

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

We will provide participants with outcomes identified through systematic review and interviews common to all four patient groups. Additionally, we will provide those

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

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

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

If new outcomes are identified in R1, we will conduct a third round comprising *only* these items to enable two rounds of importance scoring. Items to be brought forward to the consensus meeting will be those scored between 7 and 9 by ≥70 % of participants and

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

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

Nested Methodological Studies

We will conduct nested methodological studies to:

1. Determine if Delphi feedback provided as the proportion of participants scoring the outcome between 7 and 9 (indicating critical for inclusion) as opposed to mean scores influences subsequent scores, magnitude of change, items retained, and level of agreement (overall and by patient population group).
2. Qualitatively explore the process of patient/family engagement and participation throughout COS development to determine barriers and facilitators as well as modification of our processes if needed; and
3. Determine if Delphi versus nominal group technique influences which measures are retained for outcomes included in the COS.

Delphi Feedback

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

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

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

To ascertain feedback group differences for items retained, we will create contingency tables, for each feedback group, to categorize the number of items retained by (i) both feedback groups; (ii) critical response feedback group only; (iii) mean feedback group only; and (iv) neither. We will determine percentage of items for which there was agreement to retain and percentage of discordant items retained by only one feedback group. To ascertain differences between feedback groups in terms of the level of agreement of items retained across patient population groups, we will generate contingency tables categorizing number of items retained by (i) all; (ii) 1 group only; (iii) 2 groups only; (iv) 3 groups only; and (iv) none. We will calculate the percentage agreement and percentage of discordant items.

To explore the impact of feedback on consensus between patient population groups, we will transform the unit of analysis to be the questionnaire item (outcome), with each observation an aggregate statistic. We will use linear regression to determine, for each outcome, and for each feedback group, the absolute difference (ignoring direction) in mean R2 scores, adjusting for the participant's R1 score. We will compare absolute mean differences between patient population groups across outcomes between the two feedback groups using a paired t test. Finally, we will compare responses irrespective of patient population groups within each randomization arm, calculate the standard deviation for each outcome separately for R1 and R2, and calculate the reduction in each outcome's variability between rounds. We will compare mean reductions in standard deviation across all outcomes between feedback groups using a paired t test.

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

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[42] 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.

Analysis: We will analyze interview transcripts using content analysis[43-46] employing an inductive, four-step content analysis process[47]. 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.[48]

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

Key Project Milestones	Start Date	End date
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.

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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.

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COMPETING INTERESTS STATEMENT

The authors have no competing interests to declare.

Figure 1: Flow of Core Outcome Set Development

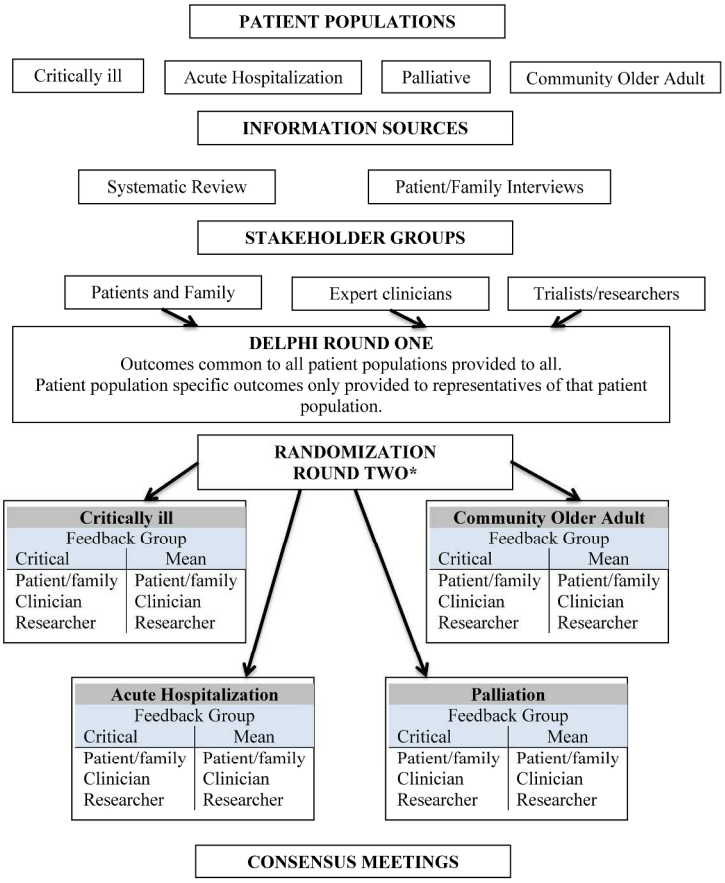

Figure 1: Flow of core outcome set development
* We will conduct an third Delphi round if additional outcomes are identified in round one

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

3. Adults and children receiving palliative care, either in a hospital, hospice, or community setting
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

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