Original Article

A Core Outcome Set for Interventions to Prevent and/or Treat Delirium in Palliative Care

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Abstract

Context. Delirium is a serious neurocognitive syndrome which is highly prevalent in people approaching the end of life. Existing trials of interventions to prevent or treat delirium in adults receiving palliative care report heterogeneous outcomes.

Objectives. To undertake an international consensus process to develop a core outcome set for trials of interventions, designed to prevent and/or treat delirium, for adults receiving palliative care.

Methods. The core outcome set development process included a systematic review, qualitative interviews, modified Delphi method and virtual consensus meetings using nominal group technique (Registration http://www.comet-initiative.org/studies/details/796). Participants included family members, clinicians, and researchers with experience of delirium in palliative care.

Results. Forty outcomes were generated from the systematic review and interviews informing the Delphi Round one survey. The international Delphi panel comprised 92 participants including clinicians (n = 71, 77%), researchers (n = 13, 14%), and family members (n = 8, 9%). Delphi Round two was completed by 77 (84%) participants from Round one. Following the consensus meetings, four outcomes were selected for the core outcome set: 1) delirium occurrence (incidence and prevalence); 2) duration of delirium until resolution defined as either no further delirium in this episode of care or death; 3) overall delirium symptom profile (agitation, delusions or hallucinations, delirium symptoms and delirium severity); 4) distress due to delirium (person with delirium, and/or family and/or carers [including healthcare professionals]).

Conclusion. Using a rigorous consensus process, we developed a core outcome set comprising four delirium-specific outcomes for inclusion in future trials of interventions to prevent and/or treat delirium in palliative care. J Pain Symptom Manage 2023;66:293–300.

Key Words

Delirium, palliative care, core outcome set, clinical trials

Key Message

This international key stakeholder-informed consensus study describes the development of a core outcome set for studies evaluating interventions to prevent and/or treat delirium in palliative care. Following a rigorous consensus process, the final core outcome set comprises four delirium-specific outcomes and will help to reduce heterogeneity in future outcome selection.

This work was conducted at King's College London and the University of York

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Accepted for publication: 30 May 2023.

0885-3924/$ - see front matter
https://doi.org/10.1016/j.jpainsymman.2023.05.013

Introduction

Delirium is a serious neurocognitive syndrome with a prevalence that increases exponentially as a person approaches end of life.[1] In people with advanced cancer, delirium affects approximately one in ten presenting to the emergency department.[2] Reported prevalence ranges from 13% to 42% on admission to an inpatient palliative care unit[3] and occurs in 25%–88% of people in the final days of life.[4] In advanced illness, delirium is an independent predictor of mortality and can signify the transition to end of life.[5] The phrase "terminal delirium" is often used to refer to the occurrence of likely irreversible delirium when a person is dying and when seeking a potentially treatable cause of the delirium does not align with the goals of care.[6] Furthermore, delirium symptoms cause distress for the individual themselves, their family members, and the health professionals who provide care for them.[7] The presence of delirium can impair a person's ability to communicate with their family and friends and profoundly impacts the dying and bereavement experience.

Delirium in a palliative care population is both preventable and potentially reversible.[8] This may be achievable in up to 50% of cases with advanced cancer.[4] The most effective approach to delirium management is to treat the underlying medical precipitants when such treatment is possible depending on illness trajectory, and if it is aligned with preferences and goals of care.[9] Yet there are only a limited number of studies of comparative effectiveness and harms of interventions to prevent and/or treat delirium for people receiving palliative care.[10] Despite the studies being few in number, there still is substantial heterogeneity in the selection of outcomes and measures.[10] The aim of a core outcome set (COS) is to reduce such heterogeneity and have the most optimal selection of outcomes among studies evaluating similar interventions in a similar patient population.[11]

A COS is an agreed-upon minimum set of outcomes considered most important by key stakeholders for measurement and reporting in *all* studies relating to a specific health condition.[12] Another feature of COS development is the inclusion of patients, family members and clinicians who may have different perspectives from researchers as to those outcomes most important to measure in all trials. Over the last three decades, the value of a COS in reducing heterogeneity of outcome selection has been demonstrated in many specialties.[13] However in the field of palliative care, core outcome sets have only started emerging.[14,15]

Given the prevalence of delirium in people receiving palliative care and at end of life and the absence of an existing COS, our objective was to undertake a rigorous international consensus process to develop a COS for trials of interventions, designed to prevent and/or treat delirium, for adults receiving palliative care.

Methods

We followed the Core Outcome Measures in Effectiveness Trials (COMET) guidelines[16] for this COS development study. We report its development following the Core Outcome Set–Standards for Reporting.[17] (Supplementary Table 1).

To commence the item generation process required for a COS, we conducted a systematic review of outcomes reported in published trials and registered trial protocols (1980 to November 2020). A detailed description of the systematic review methods and findings has been published.[10] Briefly the systematic review followed standard methodology including two authors independently searching electronic, systematic review, and trial registration databases, extracting data, assigning outcomes according to COMET taxonomy,[18] and performing risk of bias and quality of outcome reporting assessment.

The item generation process subsequently included semi-structured qualitative interviews with family members of people that had experienced delirium in a palliative care context as well as clinicians involved in the management of these patients. We did not recruit patients with experience of delirium whilst receiving palliative care due to the presence of advanced and progressive illness. Subsequent item reduction and consensus methods comprised a two-round, web-based modified Delphi consensus process. To gain final consensus, this Delphi process was followed by a series of virtual consensus meetings via Zoom using Google Jamboard and a modified nominal group technique.[19]

Recruitment of Participants for Qualitative Interviews, Delphi Panel, and Consensus Meeting

We sought a purposive and international sample from three stakeholder groups: 1) clinical researchers; 2) clinicians; and 3) family members of people who experienced delirium in a palliative care context. We recruited family member participants using a multimodal strategy, including a designated study Twitter account, snowballing (i.e., research participants passing on recruitment materials to other potential participants), existing patient and public involvement groups, and personal contacts. Additional strategies to recruit expert clinicians and delirium researchers included personalized recruitment emails sent to corresponding authors of studies included in our systematic review, flyers posted in UK National Health Service organizations, and via specialist interest groups of palliative care and geriatric organizations (Supplementary Table 2).

Semi-Structured Interviews

Semi-structured interviews with family members and clinicians were conducted by telephone or Zoom by the same interviewer (LR) with experience in the

conduct of interviews for COS development between July and October 2020. The interview guide incorporated COMET plain language[20] to help orient participants to the terms "study outcomes" and "core outcome set." Interviews were audio recorded, professionally transcribed, and content analysed[21] by two authors (AB and LR) to identify outcomes.

Delphi Methods

We conducted a modified Delphi consensus process consisting of two rounds between April and August 2021. To compile the Round one questionnaire, outcomes generated from the systematic review and interviews were reduced to consider duplication (i.e., removing redundant outcomes), those related to aggregate population data rather than individual patient outcomes (e.g., number of patients receiving analgesia), and grouping of similar outcomes with the removal of measurement characteristics.[22] The final list of outcomes was then reviewed by four researchers external to the core research team and two family members for wording clarity (with lay descriptions of medical terms to aid understanding) and for grouping into outcome domains.

We used the bespoke DelphiManager software, Version 4 (COMET Initiative, Liverpool, UK). Participants were directed to self-select their key stakeholder group (i.e., family member, clinician, and researcher) on enrolment. Participants were instructed to score the importance of each outcome for COS inclusion, without consideration of measurability or feasibility. Importance was scored using the Grading of Recommendations Assessment, Development and Evaluations (GRADE) Scale[23] which is recommended by COMET to facilitate maximum discrimination between questionnaire items.[24,25] Scoring of this 9-point Likert scale is as follows: one to three considered not important; four to six important but not critical; and seven to nine as critical for inclusion. Participants were provided with an "Unable to Score" response option and the opportunity to suggest additional outcomes. To avoid presentation bias, the DelphiManager software randomized outcome domain presentation order.

For Delphi Round one scores, we determined the proportion of participants rating each outcome with scores of seven to nine (critically important), four to six (important but not critical), and one to three (not important) for the entire expert panel, and separately for each stakeholder group. Additional suggested outcomes were duplicated and worded appropriately for inclusion in Round two. For Round two, participants received their own Round one scores and summarized scores, with visual representation using histograms. Participants were asked to re-score the importance of each outcome. If a participant changed their score sufficiently to move it into a new category (e.g., from "important but not critical" to "critical for inclusion"), participants were offered the opportunity to provide a free-text reason for this change. We sent three email completion reminders using the DelphiManager software for both Delphi rounds.

Consensus Meetings

Between October and November 2021, we hosted a series of online consensus meetings using Zoom given the pandemic restrictions to travel. On meeting commencement, we reminded participants of the meeting aim (i.e., gaining consensus on the inclusion of outcomes for the COS) and provided data on the scores for each outcome (overall and by stakeholder group) from the Delphi. As recommended by COMET,[12] items brought forward for discussion were those scored as "critical for inclusion" by ≥70% of respondents and "not important" by <15%.[12] Using Google Jamboard and nominal group technique methods,[19] we held iterative rounds of small group and then whole group discussions. Discussion was followed by a ranking of outcomes from most critical to least critical for COS inclusion at the end of each discussion. Following consensus meetings, participants were emailed an anonymized online voting Google form for voting on the inclusion or exclusion of outcomes for which consensus was not reached during the meetings as well as suggested amendments to the wording of outcomes voted for inclusion. The final COS was compiled and sent to consensus meeting participants for final endorsement.

The study was funded by the Canadian Institutes of Health Research. It received approval from the Research Ethics Boards of the University of Toronto (July 2, 2020, 34296), King's College London (July 10, 2018, LRS-17/18-6646), and the UK Health Research Authority (HRA) and Health and Care Research Wales (November 29, 2018, 18/LO/1321). Written informed consent was obtained from all study participants. The Del-COrS project is registered with the COMET initiative (October 2015, 796, http://www.comet-initiative.org/studies/details/796). We previously published the study protocol.[26]

Results

Our systematic review identified 13 studies (2,863 participants) from which we identified nine delirium-specific outcomes and 13 non-delirium-specific outcomes within eight COMET taxonomy categories.[10]

We recruited 16 participants with experience of delirium in palliative care including clinicians, clinician researchers and family members from the UK and Australia to participate in semi-structured interviews. Interview data generated an additional 49 potential outcomes for consideration in the COS not identified in the systematic review. Only six outcomes were

Table 1
Outcomes Identified by Interview Participants

Outcome (N = 16 Participants)	n (%)
Level of distress to patient	10 (63)
Level of distress to family	10 (63)
Delirium severity	9 (56)
Delirium duration	8 (50)
Degree of agitation[a]	7 (44)
Patient comfort/pain	6 (38)
Cognitive function[a]	6 (38)
Delirium resolution[a]	5 (31)
Use of medications to manage delirium including number, dose, type (rescue)	5 (31)
Ability to remain at home	4 (25)
Safety including risk of harm and falls	4 (25)
Sleep	3 (19)
Quality of life − patient[a]	3 (19)
Physical functioning	3 (19)
Discharge destination	3 (19)
Family/caregiver burden	3 (19)
Drowsiness/withdrawal/decreased level of consciousness due to medication used to treat delirium	3 (19)
Delirium risk e.g., infection, nutrition, hydration, constipation, continence, physical status,and transfers	3 (19)
Hydration status[a]	2 (13)
Staff care burden	2 (13)
Return to baseline physical status	2 (13)
Ability to perform activities of daily living	2 (13)
Use of psychoactive/antipsychotic medication	2 (13)
Level of staff distress	2 (13)
Number of patient transfers	2 (13)
Post-traumatic stress disorder/trauma	2 (13)
Family/carer wellbeing	2 (13)
Eating/nutrition	2 (13)
Length of stay	2 (13)
Quality of life − family	1 (6)
Need for assistance to mobilize	1 (6)
Ability to interact/communicate	1 (6)
Patient wellbeing − physical, mental, and cognitive	1 (6)
Dementia progression	1 (6)
Level of confusion	1 (6)
Orientation	1 (6)
Ability to live independently	1 (6)
Ability to return to work	1 (6)
Time to delirium recognition	1 (6)
Occurrence of complicated grief	1 (6)
Use of restraint	1 (6)
Delirium type	1 (6)
Change in goals of care	1 (6)
Use of additional non-pharmacological interventions e.g., one to one supervision	1 (6)
Overall symptoms	1 (6)
Caregiver satisfaction	1 (6)
Delirium occurrence	1 (6)
Behaviors including shouting out	1 (6)
Hallucinations	1 (6)
Mortality[a]	1 (6)
Fear or anxiety about delirium recurrence	1 (6)
Place of death	1 (6)
Need for specialist input e.g., psychiatry	1 (6)
Time to delirium recurrence	1 (6)
Number of delirium episodes/recurrence	1 (6)

[a]Also identified in systematic review.

identified by both interview participants and from the systematic review (Table 1). The most frequently suggested outcomes were "level of distress to patient" and "level of distress to family" (identified by 10/16 (63%) participants). During the item reduction stage, we removed 31 outcomes considered duplicative, referring to the aggregate population as opposed to individual data, or that could be grouped once measurement characteristics were removed (Supplementary Table 3). We retained 40 outcomes for inclusion in the Delphi Round one (Table 2).

Table 2
Round 1 Delphi Participants

N = 92	n (%)
Country of residence	
United Kingdom	40 (44)
Europe	21 (23)
Australia and New Zealand	9 (10)
Canada	9 (10)
Asia	7 (8)
United States of America	2 (2)
Other	4 (4)
Experience with delirium in the palliative care context	
Clinician	71 (77)
Researcher	13 (14)
Family member	8 (9)
Profession of healthcare profession participants (N = 71)	
Physician	56 (79)
Nurse or nurse practitioner	12 (17)
Physical, occupational or respiratory therapist	2 (3)
Other healthcare profession	1 (1)
Years of clinical experience (N = 71)	
>10 yrs	58 (82)
6-10 yrs	9 (13)
3-5 yrs	3 (4)
<3 yrs	1 (1)

The international Delphi Round one panel comprised 92 participants with experience of delirium in palliative care as either clinicians (n = 71, 77%), researchers (n = 13, 14%) or family members (n = 8, 9%) (Table 2). Of the 40 outcomes presented in Delphi Round one, 21 were considered "critical for inclusion" by ≥70% of participants (Supplementary Table 4). Twenty-six additional outcomes were proposed with five of these additional outcomes included in the Delphi Round two after review by the study team. These were 1) caregiver burden, 2) economic burden, 3) patient satisfaction with the intervention, 4) staff awareness of delirium, and 5) adverse effects of antipsychotic medication. Therefore 45 outcomes were presented for importance scoring in Round two.

Round two was completed by 77 participants (84% of the Round one participants). Of the 45 outcomes scored, 27 met the consensus criteria for inclusion (Table 3). Twelve outcomes were scored as "critical for inclusion" by all three stakeholder groups. Of the five outcomes added to Round two, only "caregiver burden" and "staff awareness of delirium" met the inclusion criteria.

We hosted two virtual consensus meetings to accommodate international participation. Meeting one comprised fourteen participants including three family members. During Meeting one following the nominal group technique discussion, eight of the 27 outcomes

Table 3
Round 2 Delphi Scores

	Overall		Family (N = 6)	Clinician (N = 58)	Researcher (N = 13)
Outcomes	Mean (SD)		% Critical		
Patient distress	8.2 (1.0)	97	83	100	92
Agitation	8.0 (1.0)	97	83	98	100
Risk factors and potentially reversible causes appropriately addressed	8.0 (1.1)	95	83	97	92
Quality of life (patient)	7.9 (1.0)	94	83	97	85
Harm including falls or injury	7.8 (1.1)	92	50	98	85
Need for interventions to prevent harm e.g., physical restraints, one-to-one supervision	7.7 (1.1)	90	83	93	77
Delirium occurrence (incidence and prevalence)	7.7 (1.2)	88	83	86	100
Duration of delirium	7.7 (1.0)	88	100	88	85
Delirium severity	7.8 (1.2)	88	67	88	100
Delusions or hallucinations	7.7 (1.2)	88	100	88	85
Need for further intervention e.g., rescue medication	7.5 (1.3)	87	100	88	77
Delirium symptoms	7.5 (1.1)	84	83	85	85
Family/carer distress	7.5 (1.2)	83	67	88	69
Adverse events/side effects of the intervention to prevent or treat delirium	7.5 (1.1)	83	50	86	85
Overall symptom profile	7.3 (1.5)	82	100	81	77
Capacity to communicate	7.3 (1.3)	81	67	81	85
Delirium resolution	7.5 (1.2)	81	67	83	77
Level of sedation	7.5 (1.2)	81	83	83	69
Goals of care changed to an end of life focus as a consequence of delirium	7.5 (1.4)	78	83	79	69
Time to delirium recognition	7.4 (1.4)	76	100	72	83
Staff awareness of delirium	7.4 (1.6)	75	83	76	69
Cognitive function	7.5 (1.4)	75	67	74	85
Caregiver burden	7.3 (1.2)	73	50	79	54
Quality of life (family/carer)	7.2 (1.3)	73	50	76	69
Delirium type- hyperactive, hypoactive, mixed presentation	7.2 (1.4)	71	67	72	69
Duration of terminal delirium	7.1 (1.4)	71	100	67	77
Ability to perform activities of daily living	6.8 (1.3)	70	33	67	100
Mortality/survival	6.9 (1.6)	69	50	69	77
Number of times that delirium re-occurs	7.1 (1.3)	68	83	66	69
Psychological well-being (post-delirium)	7.2 (1.4)	68	50	71	62
Patient satisfaction with the intervention	7.0 (1.4)	67	83	68	54
Pain	7.1 (1.6)	66	100	64	62
Dehydration	6.8 (1.7)	65	83	64	62
Complicated grief (family/carer)	6.9 (1.4)	63	80	67	39
Adverse effects of antipsychotic medication	6.7 (1.4)	62	33	66	62
Time to delirium recurrence	6.6 (1.3)	58	83	57	54
Delirium free survival	6.7 (1.4)	57	33	58	62
Caregiver satisfaction	6.8 (1.6)	55	67	57	39
Discharge disposition	6.5 (1.3)	53	33	60	31
Economic burden	6.4 (1.6)	51	60	48	62
Place of death	6.5 (1.8)	49	67	48	46
Physical functioning	6.4 (1.4)	48	17	45	77
Length of stay	6.2 (1.6)	40	33	37	54
Dementia progression	6.2 (1.6)	38	20	38	46
Staff distress	6.4 (1.4)	36	0	41	31

were excluded. The outcomes "delirium occurrence," "duration of delirium," and "patient distress" were voted for inclusion (Supplementary Table 5). Meeting two comprised seven participants (no family members). These participants excluded 16 outcomes; "delirium occurrence" was voted for inclusion. Meeting two participants proposed that nine outcomes should be combined into three amended outcomes i.e., "duration of delirium until resolution," "overall delirium symptom profile," and "distress due to delirium" (Supplementary Table 6).

Subsequent confirmatory voting with Meeting one participants resulted in consensus on the following decisions 1) to combine "duration of delirium" and "duration of terminal delirium" into a single outcome; 2) to broaden the definition of "overall symptom profile" to encompass delirium-specific symptoms; and 3) to consider "patient distress," "family/carer distress," and "staff distress" as a single outcome of "distress due to delirium." The rationale for this was that the person in whom distress was occurring was considered a measurement parameter. Outcomes excluded after confirmatory voting were "quality of life (patient)," "risk factors and potentially reversible causes appropriately addressed," "need for rescue medication," "need for physical restraint or supervision," "harm including falls or injury," "capacity to communicate" and "cognitive function" (Supplementary Table 7).

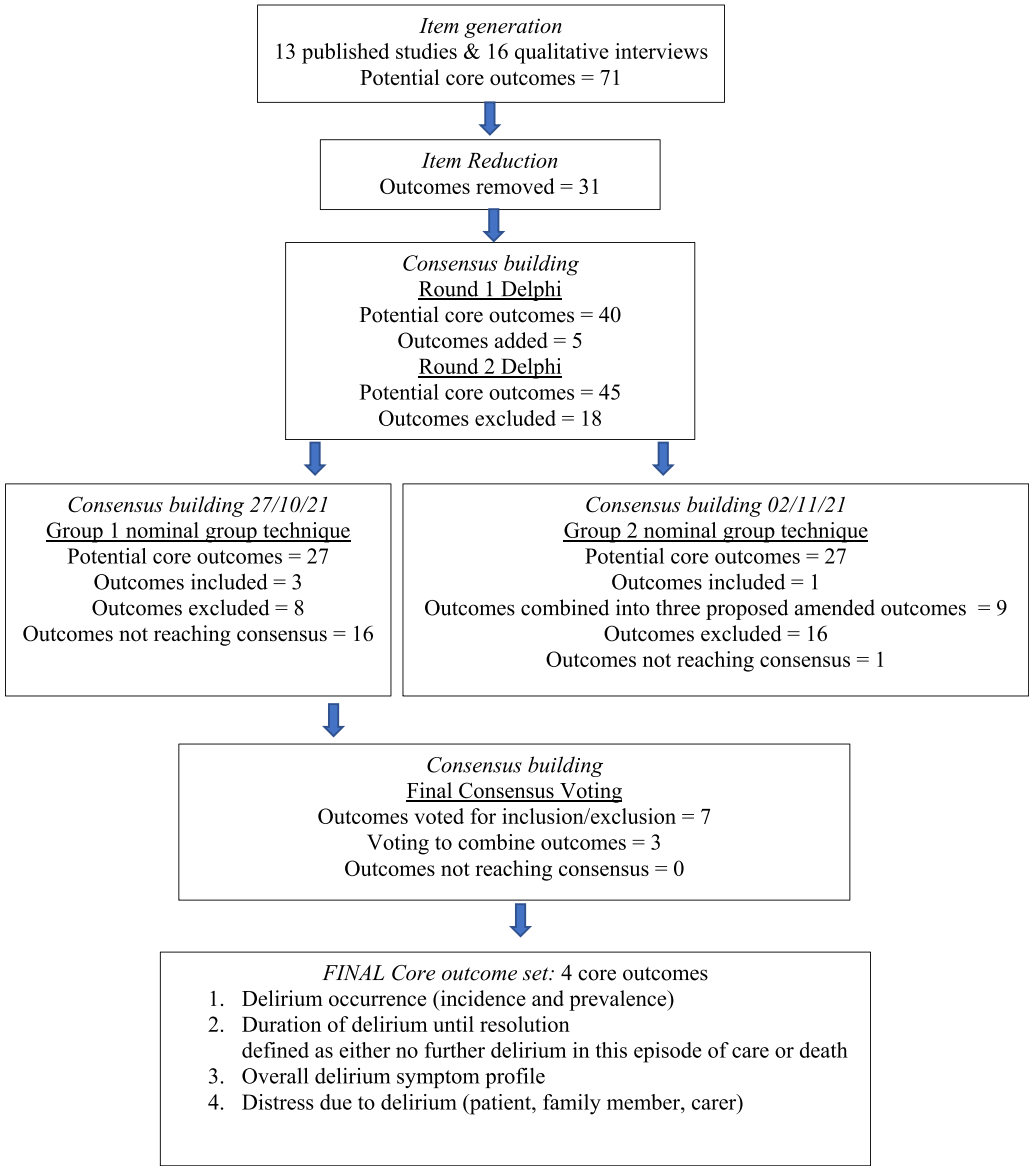

Fig. 1. Development of a core outcome set for trials of interventions to prevent and/or treat delirium for adults requiring palliative care.

The final four outcomes voted for inclusion in the COS for future trials of interventions to prevent and/or treat delirium in palliative care are 1) delirium occurrence (both incidence and prevalence), 2) duration of delirium until resolution defined as either no further delirium in this episode of care or death, 3) overall delirium symptom profile (including agitation, delusions or hallucinations, delirium symptoms, and delirium severity) and 4) distress due to delirium (measured in the person with delirium, and/or the family and/or the carers (including healthcare professional) as appropriate) (Fig. 1).

Discussion

This study employed rigorous methodology to develop a COS that comprises four delirium-specific outcomes for use in future trials of interventions to prevent and/or treat delirium for adults receiving palliative care and at end of life. This COS will inform future trial design and promote consistency in outcome selection. Lack of consistency has been identified as a barrier to interpreting the effect of existing interventional studies designed to prevent or treat delirium in this patient population.[27] Core outcome sets are increasingly recognized as beneficial for studies conducted in a palliative care patient population.[15] This COS is the third of a set of core outcome sets that is designed for application in studies of interventions for delirium prevention or treatment. Other core outcome sets developed by our team are for adults in intensive care[28] and in acute care settings.[29] These core outcome sets are all

endorsed by the American and Australian Delirium Societies and the European Delirium Association.

Our participants considered the outcome "delirium occurrence (including incidence and prevalence)" as a critical outcome for inclusion which is consistent with the core outcomes sets in intensive care and acute care settings.[28,29] Occurrence is an umbrella term that enables measurement of the effectiveness of interventions in both prevention and treatment trials. As opposed to the inclusion of a standalone outcome relating to the "duration of terminal delirium," our participants considered this a measurement parameter within the outcome of "duration of delirium." In contrast to the other patient populations for whom we have developed core outcome sets in which the emphasis is on resolution, terminal delirium is unique to the palliative care population. This form of delirium is generally irreversible and ends with death.[30] These considerations led to a consensus that the outcome "duration of delirium" should be further described as "until resolution defined as either no further delirium in this episode of care or death." Notably, "mortality" was not considered a critically important outcome in this patient population unlike the critical care delirium core outcome set due to known life-limiting illnesses receiving palliative care.

Our Delphi participants voted the following outcomes through to the final stage of the consensus-building process: "overall symptom profile," "delirium severity," "delirium symptoms," "agitation," and "delusions or hallucinations." The concept of "overall symptom profile" identified by interview participants and discussed in consensus meetings was viewed to represent the holistic nature of palliative care. In general, symptoms are not considered individually. Outcomes such as "agitation," "delusions or hallucinations," and "delirium severity" were viewed as components of the overall delirium symptom profile. This differs from the acute and intensive care settings whereby "delirium severity" was considered most important for inclusion in isolation.[28,29] Hence consensus was reached that these outcomes could be included as a single outcome of "overall delirium symptom profile."

Our COS includes the outcome of "distress due to delirium." During both qualitative interviews and consensus meeting discussions, participants placed strong emphasis on the emotional distress as a result of delirium experienced by people during receipt of palliative care and particularly at end of life. Participants also emphasized that this distress was experienced not only by the person with delirium, but also by their family members witnessing delirium, as well as healthcare professionals providing their care. Indeed, participants identified that family member distress may be greater than that experienced by the patient themselves. Participants also reinforced the holistic nature of palliative care which focuses on improving the experience and outcomes of family members and carers as well as the person with delirium. Furthermore, patient and family distress may be transferred to healthcare professionals.[31] For this reason, we have emphasized in the description of this outcome within this COS that its measurement pertains to this wider group. This description was preferred to any other outcome specifically measured only in family members. Patients' emotional distress is included in both the COS for adults in intensive care and acute care. However, in both these core outcome sets the focus was limited to patient distress with family or healthcare provider distress perceived as not critical for consideration.[28,29]

Strengths and Weaknesses/Limitations of the Study

The strengths of our study are the adherence to the recommended COMET guidelines using a multi-stage consensus-building approach with international representation and the inclusion of family members of adults who experienced delirium while receiving palliative care. Interviews with these family members and palliative care clinicians identified multiple outcomes not identified in our systematic review. Limitations include the lack of participation from individuals unable to read or speak English and no representation from adults who experienced delirium in a palliative care context due to poor survival rates in this population. Furthermore, there were few allied and "other" healthcare professionals compared to physicians and nurses represented in the study. These professional groups may have differing views regarding core outcome selection for adults with delirium in palliative care settings.

Conclusion

This COS represents a key step in standardizing the approach to outcome selection for researchers designing trials of interventions to prevent and/or treat delirium in adults requiring palliative care and at end of life. The COS comprises outcomes that are relevant and meaningful for clinicians, researchers and family members. Through widespread dissemination across academic and social media avenues and support from international delirium organizations, we anticipate uptake and integration into future trial protocols. Further work is needed to achieve consensus regarding the optimal measurement instruments, the time horizon for measurement, analysis metrics, and the method of aggregation for each of the core outcomes.

Disclosures and Acknowledgments

Ingrid Amgarth-Duff, Bronagh Blackwood, Jason Boland, Shirley Bush, John Devlin, Domenica Disalvo, Imogen Featherstone, Maja Garcia, Annmarie Hosie, Miriam Johnson, Peter Lawlor, Jacques Lee, Dale Needham, Valerie Page as members of the Del-COrS team.

This study was funded by a grant from the Canadian Institutes of Health Research (CIHR, funding number 503043). The CIHR had no involvement in the study design, data collection, analysis, interpretation of data, writing of the report or in the decision to submit the article for publication. The authors declare that there is no conflict of interest.

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Supplementary Table 1

Core Outcome Set-Standards for Reporting: The COS-STAR Statement

Section/topic	Item number	Checklist item	Page number
Title/abstract			
Title	1a	Identify in the title that the paper reports the development of a COS	1
Abstract	1b	Provide a structured summary	1
Introduction			
Background and objectives	2a	Describe the background and explain the rationale for developing the COS	1, 2
	2b	Describe the specific objectives with reference to developing a COS	2
Scope	3a	Describe the health condition(s) and population(s) covered by the COS	1, 2
	3b	Describe the intervention(s) covered by the COS	2
	3c	Describe the setting(s) in which the COS is to be applied	2
Methods			
Protocol/Registry entry	4	Indicate where the COS development protocol can be accessed, if available and/or the study registration details	3
Participants	5	Describe the rationale for stakeholder groups involved in the COS development process, eligibility criteria for participants from each group and a description of how the individuals involved were identified	2
Information sources	6a	Describe the information sources used to identify an initial list of outcomes	3
	6b	Describe how outcomes were dropped/combined, with reasons (if applicable)	3, 4, 5, Fig. 1
Consensus process	7	Describe how the consensus process was undertaken	2, 3
Outcome scoring	8	Describe how outcomes were scored and scores summarised	3
Consensus definition	9a	Describe the consensus definition	3
	9b	Describe the procedure for determining how outcomes were included or excluded from consideration during the consensus process	2, 3
Ethics and consent	10	Provide a statement regarding the ethics and consent issues for the study	3
Results			
Protocol deviations	11	Describe any changes from the protocol (if applicable), with reasons, and a describe what impact these changes have on the results	N/A
Participants	12	Present data on the number and relevant characteristics of the people involved at all stages of COS development	Table 2, 4, 5
Outcomes	13a	List all outcomes considered at the start of the consensus process	Table 1, Table 3
	13b	Describe any new outcomes introduced and any outcomes dropped, with reasons, during the consensus process	4, 5
Core outcome set	14	List the outcomes in the final core outcome set	5, 6, Fig. 1
Discussion			
Limitations	15	Discuss any limitations in the COS development process	7
Conclusions	16	Provide an interpretation of the final COS in the context of other evidence, and implications for future research	7
Other information			
Funding	17	Describe sources of funding, role of funders	8
Conflicts of interest	18	Describe any conflicts of interest within the study team and how these were managed	8

Supplementary Table 2

List of Palliative Care Organizations and Special Interest Groups Contacted During the Recruitment Phase

Europe	Association for Palliative Medicine
	British Geriatrics Society
	Cicely Saunders Institute
	European Association for Palliative Care
	European Geriatric Medicine Society
	Irish Association for Palliative Care
	Marie Curie Research Voices Group
	Norwegian Association for Palliative Medicine
	Polish Association for Palliative Care
	Swiss Society for Palliative Medicine, Care and Support
	UK Palliative Trainee Research Collaborative
Australasia	Australasian Delirium Association
	Australian & New Zealand Society for Geriatric Medicine
	Maridulu Budyari Gumal
	Palliative Care Nurses Australia
	Palliverse
	The Royal Australian & New Zealand College of Psychiatrists
Asia	Asia Pacific Hospice Palliative Care Network
	Hospis Malaysia
	Institute of Palliative Medicine
	Japanese Society for Palliative Medicine
	Japan Geriatrics Society
	Pallium India
	Thai Palliative Care Society
	The Palliative Care Association of Sri Lanka
Africa	African Center for Research on End of Life Care
	African Palliative Care Association
	Kenya Hospices and Palliative Care Association
	Palliative Care Association of Malawi
	Palliative Care Association of Uganda
North America	American Academy of Hospice and Palliative Medicine
	American Delirium Society
	Canadian Hospice Palliative Care Association
	Canadian Geriatrics Society
	Center to Advance Palliative Care
	Palliative Care Research Cooperative Group
South America	Latin American Delirium Group
Global	Global Partners in Care
	Network for Investigation of Delirium: Unifying Scientist (NIDUS)

Supplementary Table 3
Item Reduction for the Delphi Round 1 Questionnaire

Outcome	Source	Item reduction	Reason for redundancy/ modification	Final R1 Wording
Mortality/survival	SR and Interview	INC	-	Mortality/survival
Delirium incidence	SR	INC-MOD	Variable use of terms including "incidence," "prevalence," and "occurrence rate." Combined as delirium occurrence	Delirium occurrence (incidence and prevalence)
Delirium occurrence	Interview	INC-MOD	Includes incidence and prevalence	Delirium occurrence (incidence and prevalence)
Delirium free survival	SR	INC	-	Delirium free survival
Duration of delirium	Interview	INC	-	Duration of delirium
Duration of first delirium episode	SR	INC-MOD	Modified to encompass any episode of delirium given that time horizon is a measurement characteristic	Duration of delirium
Duration of terminal delirium from occurrence to death	SR	INC-MOD	Modified to duration of terminal delirium given that time horizon is a measurement characteristic	Duration of terminal delirium
Proportion of patient-days with delirium symptoms	SR	REDUN	Considered redundant as overlapping with duration of delirium	-
Delirium resolution	SR and Interview	INC	-	Delirium resolution
Delirium severity	SR and interview	INC	-	Delirium severity
Need for specialty input e.g., psychiatry	Interview	REDUN	Considered as reflection of delirium severity	-
Hyperactive delirium severity	SR	REDUN	Considered to be incorporated within delirium severity	-
Delirium symptoms	SR	INC	-	Delirium symptoms
Delirium type	Interview	INC-MOD	Included with types of delirium listed	Delirium type – i.e., hyperactive, hypoactive, mixed presentation
Number of delirium episodes/ recurrence	Interview	INC-MOD	Modified to clarify distinct episodes of delirium re-occurring	Number of times that delirium re-occurs
Time to delirium recurrence	Interview	INC	-	Time to delirium recurrence
Time to delirium recognition	Interview	INC	-	Time to delirium recognition
Hallucinations	Interview	INC-MOD	Modified to include symptoms of psychosis	Delusions or hallucinations
Degree of agitation	SR and Interview	INC-MOD	Shortened to exclude reference to measurement	Agitation
Behaviors including shouting out	Interview	REDUN	Redundant with "agitation"	-
Pain	SR	INC	-	Pain
Patient comfort/pain	Interview	REDUN	Redundant with "Pain"	-
Overall symptoms	Interview	INC-MOD	Modified for clarity	Overall symptom profile
Other symptoms	SR	REDUN	Addressed by "overall symptom profile"	-
Sleep	Interview	REDUN	Redundant with "overall symptom profile"	-
Dehydration symptoms	SR	INC-MOD	Shortened to dehydration	Dehydration
Hydration status	SR and Interview	REDUN	Considered redundant as overlapping with dehydration	-
Considering risk factors for delirium e.g., infection, nutrition, hydration, constipation, continence, physical status, and transfers	Interview	INC-MOD	Wording modified, inclusion of "potentially" and "appropriately"	Risk factors and potentially reversible causes appropriately addressed
Number of patient transfers	Interview	REDUN	Included in context of risk factors and addressed by "Risk factors and potentially reversible causes appropriately addressed"	-
Eating/nutrition	Interview	REDUN	Addressed as a risk factor in "Risk factors and potentially reversible causes appropriately addressed" and functionally in "Ability to perform activities of daily living"	-

(*Continued*)

Supplementary Table 3
Continued

Outcome	Source	Item reduction	Reason for redundancy/ modification	Final R1 Wording
Physical functioning	SR	INC	-	Physical functioning
Return to baseline physical status	Interview	REDUN	Measurement, encompassed in "physical functioning"	-
Ability to return to work	Interview	REDUN	Overlaps with "physical functioning," noted to be less relevant to palliative care population	-
Need for assistance to mobilize	Interview	REDUN	Encompassed by "physical functioning"	-
Ability to perform activities of daily living	Interview	INC	-	Ability to perform activities of daily living
Ability to live independently	Interview	REDUN	Considered overlapping with "ability to perform activities of daily living"	-
Communication capacity	SR	INC-MOD	Wording adjusted for clarity	Capacity to communicate
Ability to interact/ communicate	Interview	REDUN	Overlapping with "capacity to communicate"	-
Cognitive function	SR and Interview	INC	-	Cognitive function
Level of confusion	Interview	REDUN	Redundant with "cognitive function"	-
Orientation	Interview	REDUN	Redundant with "cognitive function"	-
Level of distress to patient	Interview	INC-MOD	Shortened to patient distress	Patient distress
Level of distress to family	Interview	INC-MOD	Shortened and reference to carer included	Family/carer distress
Level of distress to staff	Interview	INC-MOD	Shortened to staff distress	Staff distress
Post-traumatic stress disorder/ trauma	Interview	INC-MOD	Combined as psychological well-being (postdelirium)	Psychological well-being (post-delirium)
Fear or anxiety about delirium recurrence	Interview	REDUN	Encompassed in psychological well-being (postdelirium)	-
Occurrence of complicated grief	Interview	INC-MOD	Modified to clarify complicated grief of family/carer	Complicated grief (family/ carer)
Quality of life	SR and Interview	INC-MOD	Modified to specify quality of life for the patient	Quality of life (patient)
Patient wellbeing – physical, mental, cognitive	Interview	REDUN	Considered partly overlapping with "quality of life (patient)" and addressed in separate outcomes for "physical functioning," "psychological well-being (postdelirium)" and "cognitive function"	-
Quality of life -family	Interview	INC-MOD	Modified to specify family or carer	Quality of life (family/carer)
Caregiver satisfaction	Interview	INC	-	Caregiver satisfaction
Family/caregiver burden	Interview	REDUN	Considered partly overlapping and addressed in 'quality of life (family/carer) and "caregiver satisfaction"	-
Family/carer wellbeing	Interview	REDUN	Considered partly overlapping and addressed in 'quality of life (family/carer) and "caregiver satisfaction"	-
Change in goals of care	Interview	INC-MOD	Modified to include change in goals of care towards an end of life focus and provide an example	Goals of care changed to an end of life focus as a consequence of delirium i.e., cessation of life-prolonging interventions
Place of death	Interview	INC	-	Place of death
Length of stay	Interview	INC	-	Length of stay
Discharge destination	Interview	INC-MOD	Broadened to "disposition"	Discharge disposition
Ability to be at home	Interview	REDUN	Redundant with "discharge disposition"	-
Need for further intervention	SR	INC-MOD	Modified to include rescue medication	Need for further intervention e.g., rescue medication
	Interview	REDUN		-

(*Continued*)

Supplementary Table 3
Continued

Outcome	Source	Item reduction	Reason for redundancy/ modification	Final R1 Wording
Use of medications to manage delirium including number, dose, type (rescue)			Addressed by "need for further intervention" e.g., rescue medication	
Use of psychoactive/ antipsychotic medication	Interview	REDUN	Addressed by "need for further intervention" e.g., rescue medication	-
Use of restraint	Interview	INC-MOD	Combined into interventions to prevent harm	Need for interventions to prevent harm e.g., physical restraints, one-to-one supervision
Use of additional non-pharmacological interventions e.g., one to one supervision	Interview	INC-MOD	Combined into interventions to prevent harm	Need for interventions to prevent harm e.g., physical restraints, one-to-one supervision
Staff care burden	Interview	REDUN	In context of requiring one to one nursing supervision. Addressed by "Need for interventions to prevent harm e.g., physical restraints, one-to-one supervision"	-
Adverse events/ effects	SR	INC	Modified to clarify that adverse events/side effects are referring to the intervention	Adverse events/side effects of the intervention to prevent or treat delirium
Side effects of neuroleptics	SR	REDUN	Considered redundant as combined into adverse events/side effects	-
Other adverse events	SR	REDUN	Considered redundant as combined into adverse events/side effects	-
Drowsiness/withdrawal/ decreased level of consciousness due to medication used to treat delirium	Interview	INC-MOD	Summarized as "level of sedation"	Level of sedation
Safety including risk of harm and falls	Interview	INC-MOD	Wording adjusted to focus on harm due to delirium	Harm including falls or injury
Dementia progression	Interview	INC	-	Dementia progression
Delivery of care	SR	REDUN	Process outcomes related to level of adherence to study	-

SR = systematic review; INC = included unchanged; INC-MOD = included but wording modified; REDUN = redundant/overlapping outcome

Supplementary Table 4
Round 1 Delphi Scores

Outcomes	Overall		Family (N = 8)	Clinician (N = 71)	Researcher (N = 13)
	Mean (SD)		% Critical		
Agitation	8.0 (0.9)	98	100	99	92
Patient distress	8.2 (1.1)	96	100	100	69
Risk factors and potentially reversible causes appropriately addressed	8.0 (1.2)	88	75	92	77
Delusions or hallucinations	7.7 (1.2)	87	100	87	77
Delirium severity	7.6 (1.4)	83	88	82	85
Harm including falls or injury	7.7 (1.3)	83	75	86	69
Need for further intervention e.g., rescue medication	7.5 (1.4)	81	100	80	77
Quality of life (patient)	7.7 (1.5)	81	100	82	67
Need for intervention to prevent harm	7.4 (1.6)	79	88	81	62
Duration of delirium	7.5 (1.4)	78	75	78	85
Adverse events due to the intervention to prevent or treat delirium	7.5 (1.3)	77	50	80	77
Delirium occurrence (incidence and prevalence)	7.6 (1.5)	76	75	73	92
Cognitive function	7.5 (1.5)	76	75	76	77
Delirium resolution	7.4 (1.5)	75	75	77	62
Delirium symptoms	7.4 (1.3)	75	75	78	62
Family/carer distress	7.5 (1.4)	75	88	80	39
Capacity to communicate	7.2 (1.5)	72	75	72	69
Psychological well-being (post-delirium)	7.3 (1.3)	72	50	78	54
Level of sedation	7.3 (1.5)	72	100	70	62
Overall symptom profile	7.2 (1.8)	70	100	68	69
Goals of care changed to an end of life focus as a consequence of delirium	7.3 (1.6)	70	100	67	69
Delirium type	7.3 (1.4)	69	88	68	62
Number of times that delirium re-occurs	7.2 (1.4)	69	88	66	69
Quality of life (family/carer)	7.2 (1.6)	68	75	70	50
Pain	7.2 (1.8)	66	88	65	62
Time to delirium recurrence	6.9 (1.5)	64	88	62	58
Mortality/survival	6.9 (1.7)	64	63	61	85
Time to delirium recognition	7.2 (1.6)	63	88	59	73
Duration of terminal delirium	7.0 (1.7)	62	88	59	62
Ability to perform activities of daily living	6.7 (1.8)	62	63	59	77
Dehydration	6.8 (1.9)	60	75	61	46
Complicated grief (family/carer)	6.9 (1.6)	59	86	63	23
Caregiver satisfaction	6.8 (1.8)	57	75	58	39
Delirium free survival	6.6 (1.8)	54	63	52	62
Discharge disposition	6.5 (1.5)	51	63	55	23
Length of stay	6.3 (1.8)	51	63	49	54
Physical functioning	6.6 (1.6)	50	50	47	69
Place of death	6.3 (2.1)	48	71	48	39
Dementia progression	6.2 (1.8)	47	43	43	69
Staff distress	6.5 (1.6)	45	25	51	23

NB: participants self-selected the stakeholder group they most identified with during Round 1

Supplementary Table 5
Consensus Meeting Decisions: Meeting 1 (Fourteen Participants)

Outcomes Included	Outcomes Excluded	Outcomes Not Reaching Consensus	Comments
Patient distress	Staff awareness of delirium	Cognitive function	
Delirium occurrence (incidence and prevalence)	Time to delirium recognition	Capacity to communicate	
Duration of delirium	Level of sedation	Delirium resolution	
	Adverse events/side effects of the intervention to prevent or treat delirium	Risk factors and potentially reversible causes appropriately addressed	
	Goals of care changed to an end of life focus as a consequence of delirium	Quality of life (patient)	
	Duration of terminal delirium	Harm including falls or injury	
		Need for physical restraint or supervision to prevent harm	
	Delirium type − hyperactive, hypoactive, mixed presentation	Need for rescue medication	
	Ability to perform activities of daily living	Delirium severity	Initial discussion about combining these outcomes into one "overall symptom profile." Not entered into voting.
		Agitation	
		Delirium symptoms	
		Delusions or hallucinations	
		Overall symptom profile	
		Family/carer distress	Initial discussion about combining caregiver outcomes into one outcome. Not entered into voting. "Quality of life (family/carer)" and "caregiver burden" not voted for inclusion individually.
		Quality of life (family/carer)	
		Caregiver burden	

Supplementary Table 6

Consensus Meeting Decisions: Meeting 2 (Seven Participants)

Outcomes Included	Outcomes Included in Amended Format		Outcomes Excluded	Outcomes Not Reaching Consensus
Delirium occurrence (incidence and prevalence)	Duration of delirium until resolution defined as either no further delirium in this episode of care or death	Combined two outcomes ("duration of delirium" and "delirium resolution") into one outcome	Quality of life (patient) Risk factors and potentially reversible causes appropriately addressed	Cognitive function
	Overall delirium symptom profile	Combined four outcomes ("agitation," "delusions or hallucinations," "delirium symptoms" and "delirium severity") into one outcome	Need for rescue medication Need for physical restraint or supervision Capacity to communicate	
	Distress due to delirium (patient, family member, carer)	Option to measure patient distress and/or family and/or carer (including healthcare professionals) distress.	Harm including falls or injury Staff awareness of delirium Time to delirium recognition Level of sedation Adverse events/side effects of the intervention to prevent or treat delirium Goals of care changed to an end of life focus as a consequence of delirium Duration of terminal delirium Delirium type − hyperactive, hypoactive, mixed presentation Ability to perform activities of daily living Quality of life (family/carer) Caregiver burden	

Supplementary Table 7

Confirmatory Voting. Meeting one via electronic voting form: 14 attendees, 13 completed voting. Meeting two during consensus meeting: seven attendees, six completed voting

Outcome or Proposal	Number Voting to Include/Exclude Outcome or Accept Proposal (%)	Action
Exclude "Quality of life (patient)"	12 (63)	Excluded
Exclude "Risk factors and potentially reversible causes appropriately addressed"	11 (58)	Excluded
Exclude "Need for rescue medication"	16 (84)	Excluded
Exclude "Need for physical restraint or supervision"	18 (95)	Excluded
Exclude "Harm including falls or injury"	15 (74)	Excluded
Exclude "Capacity to communicate"	15 (79)	Excluded
Include "Cognitive function"	6 (32)	Excluded
Proposal: "Overall delirium symptom profile"	18 (95)	Accepted: to encompass agitation, delusions or hallucinations, delirium symptoms and delirium severity
Proposal: "Duration of delirium until resolution"	16 (84)	Accepted: defined as either no further delirium in this episode of care or death
Proposal: "Distress due to delirium"	16 (84)	Accepted: option to measure patient distress and/or family and or/carer (including healthcare professionals) distress