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DOI:

[10.1186/s12916-021-02015-3](https://doi.org/10.1186/s12916-021-02015-3)

*Document Version*

Peer reviewed version

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*Citation for published version (APA):*

Rose, L., Burry, L., Agar, M., Blackwood, B., Campbell, N. L., Clarke, M., Devlin, J. W., Lee, J., Marshall, J. C., Needham, D. M., Siddiqi, N., & Page, V. (2021). A core outcome set for studies evaluating interventions to prevent and/or treat delirium for adults requiring an acute care hospital admission: an international key stakeholder informed consensus study. *BMC Medicine*, 19(1), Article 143. <https://doi.org/10.1186/s12916-021-02015-3>

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# A Core Outcome Set for Research Evaluating Interventions to Prevent and/or Treat Delirium in Critically Ill Adults: An International Consensus Study (Del-COrS)

**OBJECTIVES:** Delirium in critically ill adults is highly prevalent and has multiple negative consequences. To-date, trials of interventions to prevent or treat delirium report heterogeneous outcomes. To develop international consensus among key stakeholders for a core outcome set for future trials of interventions to prevent and/or treat delirium in critically ill adults.

**DESIGN:** Core outcome set development, as recommended by the Core Outcome Measures in Effectiveness Trials Handbook. Methods of generating items for the core outcome set included a systematic review and qualitative interviews with ICU survivors and family members. Consensus methods include a two-round web-based Delphi process and a face-to-face meeting using nominal group technique methods.

**SUBJECTS:** International representatives from three stakeholder groups: 1) clinical researchers, 2) ICU interprofessional clinicians, and 3) ICU survivors and family members.

**SETTING:** Telephone interviews, web-based surveys, and a face-to-face consensus meeting held at the 2019 European Delirium Association's annual meeting in Edinburgh, Scotland.

**INTERVENTION:** None.

**MEASUREMENTS AND MAIN RESULTS:** Qualitative interviews with 24 ICU survivors and family members identified 36 potential outcomes; six were additional to the 97 identified from the systematic review. After item reduction, 32 outcomes were presented in Delphi Round 1; 179 experts participated, 38 ICU survivors/family members (21%), 100 clinicians (56%), 41 researchers (23%). Three additional outcomes were added to Round 2; 134 Round 1 participants (75%) completed it. Upon conclusion of the consensus building processes, the final core outcome set comprised seven outcomes: delirium occurrence (including prevalence or incidence); delirium severity; time to delirium resolution; health-related quality of life; emotional distress (i.e., anxiety, depression, acute and posttraumatic stress); cognition (including memory); and mortality.

**CONCLUSIONS:** This core outcome set, endorsed by the American and Australian Delirium Societies and European Delirium Association, is recommended for future clinical trials evaluating delirium prevention or treatment interventions in critically ill adults.

**KEY WORDS:** clinical trials; delirium; intensive care; core outcome set

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DOI: 10.1097/CCM.0000000000005028

**D**elirium is a highly prevalent (1) and possibly preventable syndrome occurring in the critically ill (2). With a pathogenesis that remains unclear, delirium is associated with many short- and long-term adverse physiologic, emotional, and cognitive outcomes (3, 4). Despite the frequent occurrence of delirium and a rapid increase in the number of clinical trials evaluating interventions focused on its reduction, few interventions have been found to effectively prevent it (5, 6), and no pharmacologic interventions are effective for treating it (7). Multicomponent strategies (e.g., the A" for Assessment, Prevention, and Manage Pain; "B" for Both Spontaneous Awakening Trials and Spontaneous Breathing Trials; "C" for Choice of Analgesia and Sedation; "D" for Delirium Assess, Prevent, and Manage; "E" for Early Mobility and Exercise; "F" for Family Engagement and Empowerment [ABCDEF] bundle) that address delirium risk factors are, however, recommended (8). The discovery of new interventions to reduce delirium in the ICU and clinical trials to rigorously evaluate their efficacy and safety is paramount. To inform evidence-based clinical decisions, results from individual delirium trials need to be compared and synthesized. However, in the absence of a core outcome set (COS), including the harmonization of measurement tools, important barriers to evidence synthesis remain.

A COS is an agreed-upon minimum set of outcomes to be measured and reported in "all" studies relating to a specific health condition or intervention (9). The importance of a COS to inform the design of trials evaluating interventions to prevent and/or treat delirium for critically ill adults has been highlighted in recent years. The 2017 Intensive Care Delirium Research Agenda emphasized the need for a consistent approach to selecting, defining, and measuring outcomes (10). Use of uniform, standardized measurement tools for delirium case identification and severity rating, as well as development and uptake of a COS for clinical studies in delirium, comprised two of five research priorities in the 2019 Scientific Think Tank report from National Institutes of Health-funded Network for Investigation of Delirium: Unifying Scientists group (<https://deliriumnetwork.org/>). A Comparative Effectiveness Review from the Agency for Healthcare Research and Quality made the same recommendation (11).

The proven benefits of a COS in the context of a high delirium prevalence in critically ill adults, the

deleterious outcomes associated with its occurrence, and the paucity of effective delirium prevention and treatment strategies in the ICU provide a strong rationale for the development of a COS. Thus, our objectives were to develop international consensus on a COS appropriate for clinical trials of interventions designed to prevent and/or treat delirium for critically ill adults.

## METHODS

We followed the Core Outcome Measures in Effectiveness Trials (COMET) guidelines (12) and report development of this COS in accordance with COS-STAndards for Reporting guidelines (13). These reporting guidelines are hosted on the Equator Network and were developed by an international expert group in recognition of the lack of clarity and transparency of COS reporting. Item generation methods to propose outcomes of interest comprised: 1) a systematic review (14) of outcomes reported in published trials and registered trial protocols, and 2) qualitative research using semistructured interviews to identify outcomes of importance to ICU survivors and family members. Item reduction and consensus building to refine, select, and finalize outcomes comprised a 1) two-round, international, web-based Delphi followed by 2) an in-person meeting, using modified nominal group technique (15), hosted by the European Delirium Association.

The study is funded by the Canadian Institutes of Health Research and approved by the Research Ethics Boards of the University of Toronto, King's College London, Sunnybrook Health Sciences Center (Toronto, ON, Canada), and the U.K. Health Research Authority and Health and Care Research Wales. This project is registered with the COMET initiative (<http://www.comet-initiative.org/studies/details/796>). The study protocol and systematic review results have been published previously (14, 16).

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

Using purposive sampling, we sought an international sample from three ICU relevant stakeholder groups: 1) clinical researchers, 2) clinicians, and 3) ICU survivors and family members. We recruited ICU survivor and family participants using a multimodal strategy including a designated study Twitter account, patient/

family support/advocacy groups (e.g., ICU Steps in the United Kingdom [<http://www.icusteps.org/>]), snowballing techniques, flyers in family ICU waiting areas, and personal contacts. Recruitment materials sought participants who self-identified (or having a family member) as having previously experienced delirium. For qualitative interviews, we continued to recruit for interviews until we considered data saturation to have been achieved, that is, not identifying new outcomes. Similarly, we used a multimodal strategy to recruit expert clinicians and delirium researchers, including recruitment flyers sent through membership lists of the American Delirium Society and Australasian Delirium Association, and to attendees of the European Delirium Association 2019 meeting as we made the assumption these members/attendees would have clinical and/or research experience in delirium. We also made in-person announcements at the American Delirium Society 2019 meeting, sent personalized recruitment e-mails by one of the lead investigators (L.R.) to all corresponding authors of studies identified via our systematic review, posted flyers in U.K. National Health Service organizations, used snowballing techniques, and personal contacts.

Our inclusion criteria were 1) to have clinical and/or research experience of delirium in the ICU and 2) to be able to read English as we did not have sufficient resources to translate the Delphi materials into other languages. Delphi participants were asked to confirm whether they had clinical and/or research experience of delirium in the ICU before being sent the link to the Delphi survey.

### Semistructured Interviews

Semistructured telephone item generation interviews with ICU survivors and family members were conducted in English by a single experienced interviewer (L.R.). The interview guide incorporated language from the COMET plain language summary (17) to orient participants to terms such as study outcomes and COS. On interview commencement, participants were asked to describe their experience of delirium either as a patient or family member and to identify how they knew this was delirium. All interviews were audio recorded, transcribed verbatim, and content analyzed (18) to identify outcomes for potential inclusion in the COS.

### Modified Delphi Methods

Delphi response rates are improved when fewer items are considered (19). Thus, the study team reduced items by removing redundant, aggregate population, and feasibility or process outcomes. Outcomes describing adverse events, side effects, and complications not specific to delirium were grouped as a single outcome. We further reduced outcomes by removing those identified in less than or equal to 5% of studies unless mentioned in ICU survivor/family member interview transcripts. Outcomes were then reviewed for clarity of wording including development of lay descriptions of medical terms to aid understanding and grouped into relevant domains.

We used the bespoke DelphiManager software, Version 4 (COMET Initiative, Liverpool, United Kingdom) to administer Delphi rounds. Participants were asked to self-select their preferred key stakeholder group (i.e., patient/family, clinician, researcher) and to rate the importance of outcomes for COS inclusion, without consideration of measurability or feasibility, using the nine-point Grading of Recommendations Assessment, Development and Evaluations (GRADE) Scale (20). Scores 1–3 were considered not important, 4–6 important but not critical, and 7–9 as critical for inclusion. This scoring system, recommended by COMET, facilitates maximum discrimination between questionnaire items (21, 22). Participants were provided an “Unable to Score” response option and the opportunity to suggest additional outcomes perceived as missing from the outcomes provided. To avoid presentation bias, outcome domain presentation order was randomized using the DelphiManager software (COMET Initiative).

Upon completion of Delphi Round 1, we calculated mean and SD of the GRADE importance scores and determined the proportion of participants rating each outcome with scores of 7–9, 4–6, and 1–3 for the entire Delphi panel and separately for each of our three stakeholder groups. The study team reviewed suggested outcomes for inclusion in Round 2 and worded appropriately. Participants who completed Round 1 were invited to participate in Round 2. Participants received their own Round 1 scores and the summarized scores, with visual representation using histograms, for each outcome. Participants were asked to rescore outcome importance based on this feedback. If a participant



changed an importance score so that it moved into a new category (e.g., from “important but not critical” to “critical for inclusion”), participants were prompted to provide a free-text reason for this change. For both Rounds, we sent three completion reminders by e-mail via the DelphiManager software (COMET Initiative).

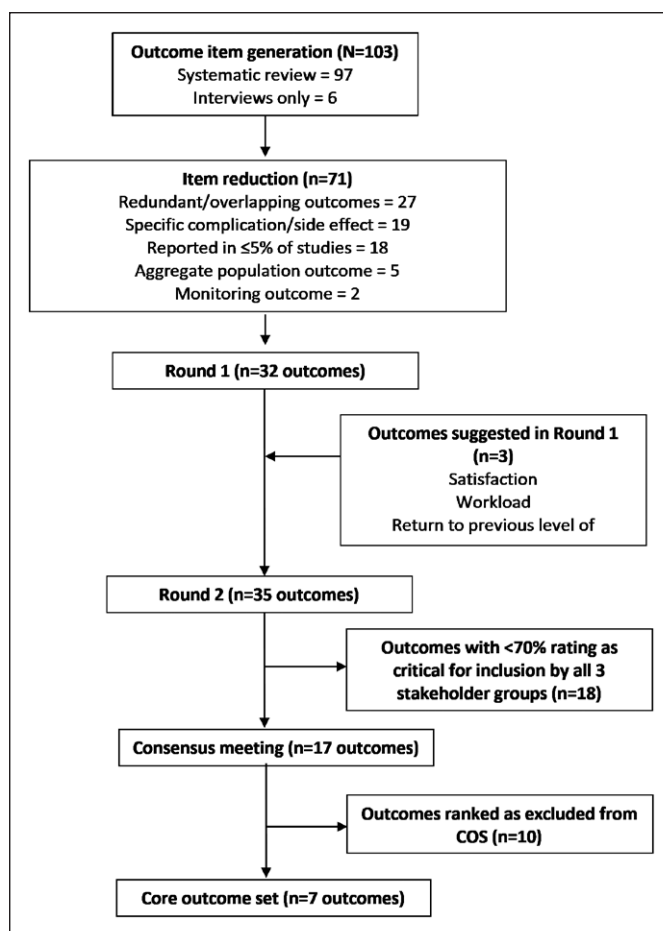
## Face-to-Face Consensus and Nominal Group Technique Methods

To better inform our in-person consensus meeting, we calculated mean and SD Round 2 importance scores and determined the proportion of participants rating each outcome as critical for inclusion overall and by stakeholder group. Outcomes brought to the consensus meeting met the following criteria established a priori, as recommended by COMET (9), scored as “critical for inclusion” by greater than or equal to 70% of respondents and “not important” by less than 15% considering all participants and each of the three key stakeholder groups.

For pragmatic reasons, we timed our consensus meeting with the 2019 European Delirium Association meeting and advertised the opportunity to participate in the COS meeting to registrants as well as using previously described recruitment methods to ensure representation of all stakeholders. At the consensus meeting, we provided an overview of results to date and the aim of the meeting, that is, consensus on the outcomes for COS inclusion. Using nominal group technique methods, we held iterative rounds of small and whole group discussion, with ranking from most critical to least critical for COS inclusion at the end of each discussion.

## RESULTS

**Figure 1** presents an overview of outcome selection during the entire consensus process. During item generation, our systematic review identified 194 studies, with 74,582 participants, published between 1980 and March 2019. For these 194 studies, we extracted data on study outcomes and their definitions and identified 97 outcomes within 19 COMET taxonomy categories (23). We recruited four ICU survivors and 20 family members (total  $n = 24$ ) to participate in qualitative research interviews from Canada (11; 46%), the United States (6; 25%), and the United Kingdom (7; 29%). From these interviews, 36 potential outcomes were identified (**Table 1**). The most commonly identified



**Figure 1.** Outcome selection process. COS = core outcome set.

outcomes in the interview dataset were 1) “ability to live alone independently/manage activities of daily living” (13 participants, 54%); 2) “ability to get back to previous cognitive abilities/long-term cognitive outcomes” (13; 54%); and “delirium severity” (12; 50%). Six were considered outcomes not identified in the systematic review and brought forward for consideration in the Delphi Round 1 item reduction phase.

Item reduction methods resulted in selection of 32 outcomes for the Delphi Round 1. Decisions relating to item reduction are displayed in **Table E1** (<http://links.lww.com/CCM/G349>). We recruited 179 participants for the Delphi international expert panel, 46 (26%) were ICU survivors or family members, with 10 of the 46 also being healthcare professionals (**Table 2**). Of the 32 outcomes provided in Round 1, 16 (50%) met a priori consensus criteria for inclusion in the COS considering all participant responses and nine (28%) by all three stakeholder groups (**Table 3**). Despite being identified in ICU survivor and family member interviews as an outcome of importance, “use of chemical

**TABLE 1.**  
**Outcomes Identified by ICU Survivor and Family Interview Participants**

Outcome (N = 24 participants)	n (%)
Ability to live alone independently/manage activities of daily living <sup>a</sup>	13 (54)
Ability to return to previous cognitive abilities	13 (54)
Delirium severity	12 (50)
Delirium duration	10 (42)
Fear and anxiety	10 (42)
Agitation <sup>b</sup>	9 (38)
Safety—falls/injury, treatment interference (pulling out catheters)	8 (33)
Being able to mobilize/physical functioning after discharge	6 (25)
Delirium reoccurrence <sup>a</sup>	6 (25)
Sleep quantity and quality	6 (25)
Quality of life/recovery	5 (21)
Acute stress and posttraumatic stress disorder	5 (21)
Time to delirium diagnosis (better recognition of delirium) <sup>a</sup>	5 (21)
Repeated infection as a risk factor for delirium <sup>a</sup>	5 (21)
Use of physical restraint	4 (17)
Use of drugs to control agitated behaviors (chemical restraint) <sup>a</sup>	4 (17)
Impact of delirium on family (stress—emotional wellbeing) <sup>a</sup>	4 (17)
Length of stay	3 (13)
Mortality/survival	3 (13)
Symptoms such as pain and fatigue	3 (13)
Delirium type (symptoms)	2 (8)
Delirium resolution	2 (8)
Physiologic changes (blood pressure, heart rate)	2 (8)
Ability to return to previous lifestyle	2 (8)
Depression	2 (8)

(Continued)

**TABLE 1. (Continued).**  
**Outcomes Identified by ICU Survivor and Family Interview Participants**

Outcome (N = 24 participants)	n (%)
Time to mobilization	2 (8)
Sedative doses	2 (8)
Medication to treat delirium other than antipsychotics	1 (4)
Return of previous memory	1 (4)
Enjoyment of life	1 (4)
Physical functioning (in hospital)	1 (4)
Hospital readmission <sup>b</sup>	1 (4)
Return of personality	1 (4)
Discharge disposition	1 (4)
Psychologic recovery	1 (4)
Delirium incidence	1 (4)

<sup>a</sup>Not identified in systematic review.

<sup>b</sup>Identified in systematic review but reported in < 5% of studies.

restraint” did not meet consensus criteria considering patient and family Round 1 responses alone with 55% scoring 7 or greater. Alternatively, “analgesic drug use” was scored as critical for inclusion by 78% of patient and family participants, but only 56% of clinician and 39% of researcher respondents.

For Round 2 of the Delphi consensus process, three additional outcomes were included based on those suggested by Round 1 participants and after review by the investigator team: workload, satisfaction, and return of physical functioning. Of the 179 Round 1 participants, 134 (75%) participated in Round 2. Of the 35 outcomes provided in Round 2, 21 (60%) met consensus criteria for inclusion in the COS considering all participant responses, 17 (49%) by all three stakeholder groups (Table 4). Of the three added outcomes, only “return of physical functioning” met inclusion criteria (83% rating as critical for inclusion overall). In Round 2, the proportion of participants rating the top ranking outcomes (i.e., “delirium occurrence,” “delirium duration,” “adverse events,” “mortality,” “cognition including memory,” “delirium severity,” “emotional distress”) as critical for inclusion increased. More ICU survivors/family member participants rated “delirium

**TABLE 2.**  
**Delphi Round 1 Participant Characteristics**

Participant Characteristics, <i>N</i> = 179	<i>n</i> (%)
Country of residence	
United Kingdom	97 (54)
Europe	26 (15)
United States	17 (9)
Canada	17 (9)
Australia and New Zealand	12 (7)
Asia	5 (3)
South America	5 (3)
Involvement with ICU delirium	
Research and clinical work	90 (51)
ICU survivors and family members	36 (20)
Clinical work only	35 (20)
ICU survivors/ family members also healthcare professionals	10 (6)
Research work only	8 (4)
Profession of healthcare profession participants ( <i>N</i> = 143)	
Physician	71 (50)
Nurse or nurse practitioner	50 (35)
Physio, respiratory, or occupational therapist	6 (4)
Other healthcare profession	16 (11)
Years of ICU experience ( <i>N</i> = 143)	
< 3	27 (19)
3–5	21 (15)
6–10	17 (12)
> 10	72 (50)
Not reported	6 (4)

reoccurrence,” an outcome included from interviews representing this stakeholder group, as critical for inclusion compared with clinicians or researchers (96% vs 71% vs 79%). “Delirium severity” was also considered critical for inclusion by more survivors/family member participants (96% vs 88% vs 82%).

Twelve experts (including 4 ICU survivors/family members) participated in the in-person consensus meeting. After the first round of small and large group discussions and use of nominal group technique ranking exercises, six outcomes were excluded from the COS (**Table E2**, <http://links.lww.com/CCM/G349>). At the end of the consensus meeting, seven outcomes were selected for the COS for trials of interventions to prevent and/or treat ICU delirium in critically ill adults. These include 1) “delirium occurrence”; 2) “cognition including memory”; 3) “mortality”; 4) “emotional distress including anxiety, depression, acute stress and posttraumatic stress disorder”; 5) “delirium severity”; 6) “health-related quality of life”; and 7) “time to delirium resolution.”

## DISCUSSION

The Del-CORs team has developed a COS to be used in future trials of interventions to prevent and/or treat delirium for critically ill adults. This COS has been developed by international membership and key stakeholder consideration and is endorsed by the American and Australian Delirium Societies and European Delirium Association. The multimodal recruitment strategy and rigorous consensus process employed, including qualitative interviews with ICU survivors and family members as an item generation step, ensured input of key stakeholders has been considered. We recommend that future trials of interventions to prevent and/or treat delirium in critically ill adults use this Del-CORs COS. As with any COS, existence of the delirium COS for critically ill adults does not preclude selection of other outcomes to be measured in a trial but rather represents the minimum that is recommended to be measured in all future relevant trials.

The delirium COS for critically ill adults includes three outcomes specific to the characterization of delirium: “delirium occurrence,” “delirium severity,” and “time to delirium resolution.” During the item reduction phase to generate the Delphi questionnaire, the outcomes “delirium prevalence” and “delirium incidence” were collapsed into one outcome “delirium occurrence.” This was considered appropriate due to the challenges of ascertaining the true delirium onset, and thus incidence of delirium in the critically ill given the presence of coma and the occurrence of delirium prior to ICU admission (24). Delirium occurrence may be more relevant in trials of interventions to prevent

**TABLE 3.**  
**Round 1 Delphi Scores**

Outcomes	Overall		Survivors and Family (n = 38)	Clinicians (n = 100)	Researchers (n = 41)
	Mean (SD)	% Critical	% Critical	% Critical	% Critical
Delirium duration	8.0 (1.2)	87	77	90	90
Adverse events/side effects	7.8 (1.2)	87	83	90	85
Delirium occurrence	8.0 (1.2)	86	77	86	90
Mortality	7.9 (1.4)	86	88	87	83
Cognition including memory	7.8 (1.2)	85	84	86	88
Delirium severity	7.8 (1.3)	83	94	81	78
Emotional distress (anxiety, depression, acute stress, and posttraumatic stress disorder)	7.7 (1.4)	83	89	80	80
Health-related quality of life	7.5 (1.3)	79	83	82	68
Sleep	7.5 (1.5)	75	83	78	63
Sedative drug use	7.3 (1.5)	74	73	73	73
Quality of sedation	7.2 (1.5)	73	72	73	71
Delirium resolution	7.3 (1.6)	72	77	71	68
Recurrence of delirium	7.2 (1.5)	72	82	70	68
Use of chemical restraint	7.2 (1.7)	72	55	76	73
Agitation occurrence	7.3 (1.4)	70	77	70	63
Use of antipsychotic medications	7.2 (1.6)	70	72	68	71
Length of stay	7.1 (1.5)	69	53	73	68
Physical functioning	7.1 (1.5)	68	64	73	63
Ventilation duration	7.1 (1.7)	68	64	73	60
Use of physical restraint	7.2 (1.8)	67	55	70	71
Reintubation	6.9 (1.7)	65	68	70	48
Pain scores (quality of analgesia)	6.9 (1.6)	64	68	64	56
Readmission	6.9 (1.6)	63	62	66	56
Treatment interference	6.9 (1.7)	62	67	60	56
Delirium type	6.8 (1.7)	61	66	58	65
Study process outcomes	6.6 (1.7)	60	68	49	62
Analgesic drug use	6.9 (1.5)	58	78	56	39
Time without delirium	6.7 (1.7)	56	63	51	65
Discharge disposition	6.8 (1.6)	56	58	54	56
Emotional wellbeing (family)	6.6 (1.7)	53	64	51	45
Time to delirium onset	6.5 (1.7)	49	50	50	50
Costs	5.9 (1.8)	39	21	49	27



**TABLE 4.**  
**Round 2 Delphi Scores**

Outcomes	Overall		Survivors and Family (n = 27)	Clinicians (n = 68)	Researchers (n = 39)
	Mean (sd)	% Critical	% Critical	% Critical	% Critical
Delirium occurrence	8.3 (0.9)	95	93	97	92
Cognition including memory	8.1 (1.0)	95	93	96	95
Delirium duration	8.2 (1.0)	94	85	98	92
Adverse events/side effects	8.0 (1.0)	94	89	96	95
Mortality	8.1 (1.1)	92	92	93	90
Emotional distress including anxiety, depression, acute stress, and posttraumatic stress disorder	7.9 (1.3)	89	89	94	82
Delirium severity	7.9 (1.2)	88	96	88	82
Health-related quality of life	7.7 (1.2)	86	93	91	74
Delirium resolution	7.7 (1.3)	86	96	86	85
Sleep	7.6 (1.3)	83	89	86	72
Return of physical functioning	7.6 (1.1)	83	85	88	74
Physical functioning	7.4 (1.2)	81	81	84	77
Quality of sedation	7.4 (1.4)	80	73	81	82
Sedative drug use	7.5 (1.3)	79	78	82	74
Recurrence of delirium	7.3 (1.4)	79	96	71	79
Agitation occurrence	7.4 (1.2)	76	78	81	67
Use of chemical restraint	7.4 (1.3)	76	48	85	77
Length of stay	7.2 (1.4)	75	63	83	69
Use of physical restraint	7.4 (1.4)	74	56	78	74
Ventilation duration	7.3 (1.5)	72	67	75	69
Use of antipsychotic medications	7.2 (1.4)	71	71	71	72
Discharge disposition	7.0 (1.4)	68	67	74	59
Pain scores (quality of analgesia)	7.0 (1.4)	67	65	71	62
Delirium type	7.0 (1.5)	66	74	62	67
Reintubation	7.0 (1.5)	64	77	66	51
Readmission	6.8 (1.4)	64	62	67	59
Treatment interference	7.0 (1.5)	63	76	56	58
Time without delirium	6.9 (1.4)	61	70	59	62
Analgesic drug use	6.9 (1.4)	59	81	54	51
Study intervention process outcomes	6.6 (1.6)	53	75	30	68
Family member emotional wellbeing	6.6 (1.6)	52	74	48	44
Workload	6.3 (1.6)	46	48	48	44
Time to delirium onset	6.3 (1.5)	42	52	38	44
Satisfaction	6.0 (1.8)	42	67	40	23
Costs	5.8 (1.5)	28	16	36	21

delirium. However, many delirium treatment trials identified in the systematic review (14) informing this COS included delirium occurrence as an outcome as the intervention was commenced before a patient able to be assessed for delirium. “Delirium severity” was an outcome identified as important by 50% of ICU survivor/family member participants during qualitative interviews. It also had a higher proportion of this key stakeholder group scoring it as critical for inclusion. Delirium severity was considered the degree of distress associated with delirium symptoms such as delusions, disorientation, and psychomotor agitation (25). Patient recall of distress or family member recall of distress watching a loved one experience agitated delirium may have contributed to this critical importance scoring. Despite being advised to ignore issues around measurement during voting on outcome importance, difficulty measuring delirium severity, particularly in patients receiving mechanical ventilation (26), or unfamiliarity with using severity measures in clinical practice, may have contributed to fewer researcher and clinician participants rating it as critical for importance. Difficulties in measuring delirium severity in the critically ill will make this outcome challenging.

During the in-person meeting, much discussion was devoted to selection of the outcome “time to delirium resolution.” This somewhat composite outcome was considered inclusive of the three outcomes “delirium duration,” “delirium reoccurrence,” and “delirium resolution” as it would require measurement of the time delirium commenced and the time delirium finally resolved. This was considered preferable by our experts to “delirium duration” as it was considered more indicative of the end of delirium. Other composite outcomes such as “delirium and coma-free days” that account for competing outcomes of death or coma were eliminated during the item reduction phase as redundant because of “delirium duration” and “mortality” being already present in the list. However, “time to delirium resolution” may cause substantial measurement challenges as delirium may continue or reoccur after ICU and hospital discharge.

Inclusion of “cognition including memory” as an outcome in the delirium COS for critically ill adults is understandable considering that delirium is an independent risk factor for long-term cognitive impairment (27, 28). This impairment is frequently of great concern patients (and their families) given it influences their ability to return to home or resume activities that are of great importance (e.g., driving). Measurement

of cognition may present challenges; however, previous work has failed to establish consensus on an appropriate measure in the critically ill (29). Similarly, the relationship between delirium and outcomes measuring patient emotional distress is well documented (30). The relationship between delirium and physical functioning, however, is less clear (31) and may have contributed to the decision to incorporate outcomes related to physical functioning into the outcome “health-related quality of life.”

Other published COS relevant to critically ill adults include COS for clinical research in acute respiratory failure survivors (29, 32) and trials of interventions intended to modify the duration of ventilation for ICU patients receiving invasively mechanically ventilation (33) and for extracorporeal membrane oxygenation (34). The delirium COS for critically ill adults overlaps with four outcomes of the COS for clinical research in acute respiratory failure survivors “cognitive function and symptoms,” “mental health conditions and symptoms,” “health-related quality of life,” and “mortality.” “Health-related quality of life” and “mortality” also included in the extracorporeal membrane oxygenation COS and duration of ventilation COS. Mortality at hospital discharge or at 60 days is also one of three elements of a minimal common outcome measure set for coronavirus disease 2019 (COVID-19) clinical research proposed by the World Health Organization Working Group on the Clinical Characterization and Management of COVID-19 infection (35). As the number of COS with relevance to studies of interventions for critically ill patients increase, it is likely a COS for all future studies in the critically ill regardless of the intervention being studied may emerge.

COS development offers the opportunity for health service users, policy-makers, health technology assessors, research and health system funders, and those delivering health services to participate in outcome selection efforts. This involvement enhances research relevance, value, and patient-centeredness and may facilitate more rapid understanding of effective treatments and their adoption into clinical practice (36). Now that the delirium COS for critically ill adults has been established via rigorous consensus-based methods, our next steps are to establish consensus on the measures and measurement timeframes, that is, what tools to measure and when to measure each of the seven outcomes. Consensus regarding measurement timeframes will further define outcomes such as cognition

and emotional distress included in this COS as acute or long-term outcomes. Given overlap with four outcomes included in other COS for critically ill patients, we consider measures recommended for use in these COS are likely pertinent when designing studies of interventions designed to prevent or treat delirium

Strengths of this study include a rigorous systematic review and inclusion of ICU survivors and family members in the item generation phase, the large international stakeholder panel with approximately 25% representation from ICU survivors and family members, and strict adherence to COMET COS development methods. Limitations include exclusion of studies reporting outcomes published in languages other than English and ability to conduct interviews with only English-speaking ICU survivors and family in our item generation phase. Selection bias may have occurred, in that patients with poor cognitive function as a result of delirium would be unlikely to participate or that those recalling a particularly bad delirium experience were more likely to participate. Although we originally intended to develop a delirium COS relevant to pediatric patients, the lack of trials in this patient population and the volume of trials in the adult population meant we focused this COS on adults only. The systematic review search was completed in March 2019 and as such does not include outcomes from more recent trials. Due to the timing of the Delphi and the face-to-face consensus meeting, we were unable to conduct a third Delphi Round confirming importance scores of the three additional outcomes suggested in Round 1.

## CONCLUSIONS

With development of the delirium COS for critically ill adults and subsequent widespread dissemination with the support of organizations invested in identifying effective interventions to prevent or treat delirium through improving delirium research, we recommend that delirium researchers adopt the COS as part of future research protocols. Such adoption will improve patient- and family-centeredness of outcome selection. Adoption will also improve homogeneity of reported outcomes, thereby increasing statistical power, precision of meta-analyses, and the ability to make evidence-based decisions to improve the clinical care of critically ill adults for whom delirium is highly prevalent.

## ACKNOWLEDGMENTS

We thank Becky Skidmore for assistance with search strategy development; Viviane Grassmann for coordinating the systematic review; Angela Sung, Jennifer Ansell for help with data extraction Shelley Gershman for assisting with participant recruitment including managing the Twitter account and the European Delirium Association for hosting the consensus meeting. The Del-CORs Group are as follows: Philip Devendra, Rich Jones, Imogen Featherstone, Leslie Fornear, Annmarie Hosie, Miriam Johnson, Jordan Rivera, Nadine Schofield, Angela Sung.

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This Core Outcome Set is registered on the Core Outcome Measures in Effectiveness Trials website (<http://www.comet-initiative.org/studies/details/796>).

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

Prof. Rose and Dr. Page conceived the ICU delirium core outcome set. Prof. Rose, and Drs. Burry, Agar, Campbell, Clarke, Lee, Marshall, Devlin, Needham, Siddiqi, and Page contributed to protocol development and the systematic review. Prof. Rose conducted the interviews. Prof. Rose, Dr. Needham, and Dr. Page recruited participants. Prof. Rose led the Delphi exercise. Prof. Rose and Dr. Page led the consensus meeting. Prof. Rose wrote the first article draft, and all authors including Drs. Blackwood, Devlin, and Needham from the Del-CORs group critically revised the article for important contents and approved the final version.

Supported, in part, by the Canadian Institutes of Health Research.

Dr. Rose's institution received funding from Canadian Institutes of Health Research (CIHR). Dr. Agar disclosed that this study was supported by research funding by the CIHR, with funds held by the University of Toronto. Dr. Campbell received funding from Astellas Pharma, and he disclosed that he is a member of, and is on the Board of Directors for, the American Delirium Society. Dr. Clarke disclosed that he is a member of the Core Outcome Measures in Effectiveness Trials Management Group. Dr. Marshall received funding from AM Pharma (Data Safety Monitoring Board Chair). Dr. Needham's institution received funding from the National Institutes of Health (NIH); he holds NIH/National Institute on Aging funding: grant number R24AG054259; he received funding from Haisco-USA Pharmaceuticals; and he received support for article research from the NIH. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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