Development of a core outcome set for ventilation trials in neurocritical care patients with acute brain injury: protocol for a Delphi consensus study of international stakeholders

Jean Digitale,1 Gregory Burns,2 Nicholas Fong,3,4 Julian Boesel,5 Chiara Robba,6 Robert D Stevens,7 Raphaël Cinotti,8 Romain Pirracchio1,3

ABSTRACT

Introduction There is little consensus and high heterogeneity on the optimal set of relevant clinical outcomes in research studies regarding extubation in neurocritical care patients with brain injury undergoing mechanical ventilation. The aims of this study are to: (1) develop a core outcome set (COS) and (2) reach consensus on a hierarchical composite endpoint for such studies.

Methods and analysis The study will include a broadly representative, international panel of stakeholders with research and clinical expertise in this field and will involve four stages: (1) a scoping review to generate an initial list of outcomes represented in the literature, (2) an investigator meeting to review the outcomes for inclusion in the Delphi surveys, (3) four rounds of online Delphi consensus-building surveys and (4) online consensus meetings to finalise the COS and hierarchical composite endpoint.

Ethics and dissemination This study received ethical approval from the French Society of Anesthesia and Critical Care Medicine Institutional Review Board (SFAR CERAR-IRB 00010254-2023-029). The study results will be disseminated through communication to stakeholders, publication in a peer-reviewed journal, and presentations at conferences.

Trial registration number This study is registered with the Core Outcome Measures in Effectiveness Trials (COMET) Initiative.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ International panel of experts from different fields (eg, physicians, respiratory therapists, nurses, caregivers and patients) to ensure that selected outcomes are valid and patient-centric.
⇒ Multistage implementation of the iterative Delphi process to systematically gather stakeholder opinion and build consensus.
⇒ The survey and consensus meetings will be conducted in English, which is a barrier to participation for some stakeholders who do not speak English.
⇒ Effort will be required to prevent attrition over multiple rounds of surveys.

The importance of prespecifying and standardising outcomes is increasingly being recognised.3 4 Consolidated Standards of Reporting Trials guidelines note that primary and secondary trial outcomes should be defined and prespecified in advance, including how and when they will be assessed.5 Consistent outcomes across studies allow for comparison and meta-analysis, enabling creation of more robust evidence-based guidelines and recommendations. The Standard Protocol Items: Recommendations for Interventional Trials guidelines6 now explicitly recommend the use of core outcome sets (COSs) for clinical trials to ensure that they collect the same outcomes in consistent ways. A COS is defined as an ‘agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or healthcare’.7 The Core Outcome Measures in Effectiveness Trials (COMET) Initiative7 serves as a clearinghouse for information on the current state of COS, including best practices for
Recently Blackwood et al. have made an effort to develop a COS for trials on MV in the general critical care population. Stakeholders identified six outcomes (time to extubation, reintubation, duration of MV, critical care and/or hospital length of stay, health-related quality of life at 6 months and mortality at 60 days) and defined appropriate measures for each outcome based on expert consensus. This represents an important advance in the field, but these outcomes may not be appropriate for all subgroups of critically ill patients. For example, although the outcomes included in the COS proposed by Blackwood et al. are also relevant for neurocritical care patients, the appropriate metrics used to evaluate them may differ. Neurocritical care patients, in particular, experience longer duration of MV, higher extubation failure risk and higher rates of tracheotomy compared with critically ill patients in general. In neurocritical care patients, the natural history of neurologic recovery, which varies considerably depending on aetiology, lesion size, neuroanatomical location and associated features such as cerebral oedema, greatly interferes with extubation. This is reflective of additional challenges encountered in the process of liberation from MV in this subgroup of critically care patients. Indeed, in addition to the standard assessment used to predict extubation success, additional or alternative factors may be considered when evaluating patients with neurological injury. For instance, the timing to define a successful extubation or to consider reintubation, or the metrics to evaluate the quality of health may differ in the neurocritical care population. Additionally, since ventilation-related pathophysiology is likely to affect cerebral oxygenation and haemodynamics, as well as the brain-related clinical course (dynamics of consciousness, delirium, sedation need) and neurocognitive long-term outcome, surrogate outcomes associated with these aspects may be of interest.

A recent consensus conference concluded that there is a dearth of evidence for best clinical practices of MV, weaning and extubation in this population. As more research in neurocritical care patients is needed, a COS specific to this population could guide primary and secondary outcomes of interest to ensure that evidence can be synthesised effectively.

Beyond a COS, a single composite hierarchical endpoint could also be useful to future investigators to enable comparability among studies. A COS is a set of outcomes. If a single primary outcome is desired (eg, to increase power), it can be challenging to choose among multiple relevant options. A composite outcome is therefore a common way of combining two or more types of related clinical events into a single endpoint. However, it is limited in that it often categorises patients based on their first event, which is often of lower clinical importance. For example, consider a composite outcome of reintubation and death. If Patient A was extubated successfully after 5 days and did not require reintubation, but then died 2 weeks later, he/she may be considered as having a better outcome (due to the successful extubation) than Patient B who was extubated after 5 days, but required reintubation on day 6, even if Patient B survived. A hierarchical composite endpoint corrects for this by ranking the included outcomes such that the emphasis is on the event of most clinical importance. This ensures, in the example above, that the surviving patient (Patient B) is considered to have a better outcome than the one who died (Patient A).

### Aims and objectives

Our goal is to develop a standard set of outcomes for research studies on mechanically ventilated neurocritical care patients undergoing extubation. The primary aim of this study is to achieve international consensus on a COS, including definitions of outcomes and timing of measurements. The secondary aim is to reach consensus on a hierarchical composite endpoint for future research.

Our definition of neurocritical care patients for the purpose of this study includes adult patients with either traumatic or non-traumatic acute brain injury (including pathologies such as central nervous system infections and autoimmune encephalitis) admitted to the intensive care unit (ICU) and requiring invasive MV, as well as brain tumours requiring MV for more than 24 hours (Box 1). This excludes patients with spinal cord injuries, resuscitated after cardiac arrest, cerebral anoxia or patients with motor neuron disease (eg, amyotrophic lateral sclerosis) or neuromuscular disorders (eg, Guillain–Barre Syndrome, myasthenia gravis, myopathies), since these are not easily comparable to the group of patients with brain injury regarding their clinical trajectories and ventilation. While the types of brain injury included are heterogeneous and require different interventions regarding neurological management, there are also similarities among them (eg, regarding intracranial pressure control). As noted above, large epidemiological studies have demonstrated that these patients as a group are quite different from the general ICU population in terms of MV course and outcomes. We assume that for the aspects of airway and ventilation, the localisation and extent of the brain injury are more relevant than its nature of pathology. There seem to be no relevant differences within this group in the management of weaning from invasive MV. Given the current literature, it is reasonable to merge these
pathologies for the sake of developing a COS for use in the neurocritical care population; however, this certainly is a potential limitation. Future data may demonstrate that some subsets of patients are better served by certain outcomes than others.

**METHODS AND ANALYSIS**

This study will follow the guidelines from the Core Outcome Set-STAndards for Development (COS-STAR) for the design of COS studies, which offer guidance on the domains of scope specification, stakeholders involved and consensus process. We developed and structured the protocol in accordance with the Core Outcome Set-STAndardised Protocol Items (COS-STAP) (online supplemental appendix A). The COS development is registered with COMET.

The study will include a broadly representative, international panel of stakeholders as described below. It will involve four stages: (1) a scoping literature review to generate an initial list of outcomes, (2) an investigator meeting to review the outcomes for inclusion in the Delphi surveys, (3) four rounds of online Delphi consensus-building surveys and (4) online consensus meetings to finalise the COS and hierarchical composite endpoint. The study will be overseen by an expert in methodology and biostatistics. The study is planned to start in September 2023 and to be concluded approximately 18 months after it begins.

**Literature review**

**Search methods**

We will conduct a scoping review to evaluate the outcome measures reported in the current literature from studies involving subjects >18 years old hospitalised in the ICU with acute brain injury as defined in box 1 requiring invasive MV. Search terms (online supplemental appendix B) will be generated via collaboration between experts in critical care, brain injury and respiratory therapy. We will search MEDLINE, EMBASE and Web of Science for studies and filter the results to include randomised controlled trials and clinical trials. This scoping review will be performed in collaboration with a professional librarian experienced in research.

**Inclusion criteria**

We will include (1) randomised controlled trials and prospective observational studies specifically evaluating interventions for MV, weaning and extubation in adults with acute brain injury as well as (2) randomised controlled trials and prospective observational studies identified with these search terms that reported clinical outcomes related to MV involving this population but were not strictly testing MV interventions. Retrospective studies, case series, case reports and editorials will not be included. Both study protocols and reports of results will be eligible for inclusion. No language or publication date restrictions will be applied. The titles and abstracts of all studies identified by the query will be reviewed by two independent reviewers using the Rayyan web app for systematic review. A third reviewer will act as an arbitrator to resolve disputes, and the selected study manuscripts will be retrieved and again reviewed for inclusion.

**Data collection**

Data extraction will be made in duplicate using Redcap by investigators and clinicians experienced in research. Data to be extracted from eligible studies include: publication date, years in which the trial was conducted, country, clinical setting, intervention and outcomes measured (including definitions and timing of measurement). From these data, we will assemble a list of relevant outcomes and the frequency with which they are reported in the literature. Outcomes together with their definitions will be reviewed and cross-checked. Any disputes will be resolved via a third reviewer.

**Delphi survey**

**Stakeholders**

This project was initiated by the ENIO (Exubration strategies and in Neuro-Intensive care unit patients and associations with Outcomes) working group. The ENIO working group consists of investigators who care for neurocritical care patients in 73 ICUs in 18 countries. Centres were recruited through the national and international intensive care and neurocritical care networks and site investigators (mailing lists and websites) of the PROtective VENTilation network, the European Society of Intensive Care Medicine, the Society of Critical Care Medicine, the Colegio Mexicano de Medicina Critica, the Atlântica group and the Société Française d’Anesthésie-Réanimation-SFAR research network. The investigators are primarily critical care physicians. The core investigator group for this study will consist of five critical care physicians representing four countries.

In the absence of clear guidelines for optimal sample size to achieve stable consensus in Delphi studies, panel size is usually dictated by practical considerations such as the availability of experts and resources. Hence, we will purposively sample approximately 50 critical care physicians, 30 critical care nurses and 30 respiratory therapists using the ENIO network. We will target clinicians with at least 2 years of clinical experience caring for this population. We will also recruit 15 patients or caregivers through patient support groups and via the providers in the ENIO network. A plain language summary of the study objectives (based on COMET patient resources) will be prepared so that non-researchers can clearly understand what the study aims to accomplish and its importance.

We will collect demographic information for each participating healthcare worker, including age, primary specialty, country, years of experience, field of interest, current position, type of institution (teaching vs non-teaching) and primary type of patients (brain injury vs other) to characterise the panel. For patients and caregivers, we will also gather relevant demographic information.
Table 1 Description of the iterative process to reach consensus on core outcome set and hierarchical composite endpoint

<table>
<thead>
<tr>
<th>Core outcome set</th>
<th>Hierarchical composite endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator meeting</td>
<td>Meeting of core investigator group to determine what outcomes will be included in Delphi Round 1 Survey</td>
</tr>
<tr>
<td>Round 1</td>
<td>Respondents rank outcomes using GRADE scale and propose new outcomes</td>
</tr>
<tr>
<td>Round 2</td>
<td>Respondents rerank outcomes from Round 1 as well as additional outcomes suggested during Round 1</td>
</tr>
<tr>
<td>Round 3</td>
<td>All outcomes from Round 2 are reranked by respondents</td>
</tr>
<tr>
<td>Round 4</td>
<td>Respondents rerank only outcomes for which consensus was not met in Round 3</td>
</tr>
<tr>
<td>Consensus meetings</td>
<td>Stakeholders will finalise the core outcome set</td>
</tr>
<tr>
<td>GRADE, Grading of Recommendations Assessment, Development and Evaluations.</td>
<td>Stakeholders will finalise the hierarchical composite endpoint</td>
</tr>
</tbody>
</table>

Information, including age, relationship to patient with brain injury, type of brain injury, length of intubation, length of ICU stay and recovery status. Participants will be assigned a unique identification number to track their responses across rounds and responses will be fully anonymised.

We will ask investigators and participants to disclose any relevant conflicts of interest. People with conflicts of interest pertinent to the study goals will be removed from the panel.

Delphi process
The iterative Delphi process to reach consensus on the COS and the composite endpoint is described in Table 1.

Investigator meeting
After completion of the scoping review, the core investigator group will meet to examine and discuss the results of the literature review, determine the list of outcomes for the first Delphi round and generate a list of questions to be addressed by the panel. We plan to include outcomes identified from the literature review in the Delphi survey, as well as outcomes from the COS for critical care ventilation trials8 for the general ICU population in case these are deemed relevant by stakeholders to the neurocritical care population. Investigators will determine whether to combine similar outcomes or keep only one (eg, if multiple studies measure the same outcome at different time points) based on what is most common in the literature, expert opinion and discussion. Due to the paucity of research in the neurocritical care subpopulation, the core investigator group may also add other relevant outcomes as appropriate. In addition to the formal outcome definitions, each outcome will be presented in plain language to ensure that patients and caregivers are fully able to participate in the process. These simple definitions will be reviewed for clarity by patient representatives prior to Round 1.

Round 1
Core outcome set
The modified iterative Delphi survey will be electronically administered via a web-based interface.25 26 The outcomes will be presented in a random order to each participant. Participants will be instructed to score each outcome using the Grading of Recommendations Assessment, Development and Evaluations (GRADE) scale.27 The scale ranges from 1 to 9, with 1 being least important to include and 9 being most important to include. In analyses, we will summarise responses by noting the number and percentage of responses in each of the following categories: 1–3=not important for inclusion; 4–6=important but not critical; 7–9=critical for inclusion. There will also be an option for ‘unable to score’. Additionally, participants will have the opportunity to suggest additional outcomes for inclusion in the second round.

For each round, participants will have 3 weeks to complete the survey with reminders sent at the 1-week and 2-week marks.

Round 2
Core outcome set
Before starting round 2, the core investigator group will review additional outcomes suggested in Round 1 to determine that they are (1) within the scope of the COS and (2) not already represented in the list of outcomes. Outcomes that meet these criteria will be added to the survey for Round 2. All outcomes from Round 1 will be carried forward. All participants who completed the Round 1 survey will be invited to participate in Round 2.

In the Round 2 survey and subsequent rounds, we will provide participants with the following feedback: (1) a summary of responses from the entire panel, (2) a summary of responses by each stakeholder group and (3) their own response from the prior round for comparison. Using the GRADE scale, we will ask them to rescore the importance of each outcome given this information and give an initial score to new items.

Hierarchical composite endpoint
In this round, respondents will also note whether each outcome should be included in the hierarchical composite outcome. Each respondent will be allowed to choose up
to 10 outcomes for inclusion. Respondents will then be asked to rank their choices in order of importance for inclusion in the composite outcome.

**Round 3**

**Core outcome set**
Participants will be asked to rerank all outcomes using the GRADE scale from Round 2 given the feedback provided.

**Hierarchical composite endpoint**
Investigators will create a preliminary composite endpoint based on Round 2 responses. They will use the top three ranked items that are independent enough to be included together in one composite endpoint. Respondents will then be asked to rank the items by clinical importance within this endpoint.

**Round 4**

**Core outcome set**
Participants will rerank only outcomes for which consensus (see below definition) has not yet been reached by round 3 to minimise respondent burden.

**Hierarchical composite endpoint**
If there is not consensus on the order of clinical importance of items within the endpoint (>70% agreement on rankings), investigators will present case vignettes to determine the hierarchy among endpoints. We will describe example patients who have different experiences of the components of the composite outcome and participants will be asked to choose which patient has the most favourable outcome. For example, to determine whether successful extubation (avoiding reintubation) or ventilator-free days (shorter duration of MV) represents a more desirable clinical outcome, we could ask respondents to choose which is most desirable: (1) patient who was intubated for 15 days, but extubated successfully on day 16 or (2) patient who was intubated for 6 days, but reintubated within 48 hours for another 5 days. This exercise can clarify which outcomes are valued more by stakeholders.  

**Analysis**
The objective will be to reach consensus and not agreement, meaning that the final choice of the group may not be the first choice of an individual member who, according to cooperative behaviour, should adopt whenever possible a stand-aside position. No blocking positions will be permitted.

The analysis of voting results will be performed by a non-voting methodologist. We will determine whether there is consensus on each item for inclusion in the COS according to the following definition: >70% of responses rating the outcome ≥7 (critical for inclusion) and not more than 15% of responses rating the outcome ≤3 (not important for inclusion).  

We will report the number of participants and response rate (total number of respondents who completed the survey as a percentage of those who were initially invited to do so) by round. The potential for selection bias due to attrition will be assessed by, for example, comparing scores from Round 1 for those who completed all rounds with those who completed only Round 1. We will also examine distributions of scores by stakeholder group and present these visually at the consensus meeting.

**Consensus meetings**
The final step in the consensus process will be two online meetings (due to the international nature of the panel). The meetings will be chaired by the principal investigators. All participants who complete all the Delphi surveys will be invited to attend. We will use a range of functions to facilitate the online meeting, including breakout rooms for small group discussions, polls and chat as needed. Patients and caregivers will be encouraged to participate in discussions and voting along with all other stakeholders.

During the first meeting, we will finalise the COS outcomes, definitions and measurement times. Results from each round of the Delphi survey will be presented. Consensus will be finalised through discussion and voting. Participants will ratify the outcomes that meet the consensus criteria for inclusion in the COS.

During the second meeting, we will create a final version of the hierarchical composite endpoint. Results from each step of the process in creating the hierarchical composite endpoint will be presented, including respondent voting on which outcomes should be included in the endpoint and rankings of clinical importance. Consensus will be finalised through discussion and voting. Participants will then ratify the final hierarchical composite endpoint.

**ETHICS AND DISSEMINATION**
This study was approved by the French Society of Anaesthesia and Critical Care Medicine Institutional Review Board (CERAR-IRB 00010254-2023-029).

At the beginning of the online survey, we will ask for consent for participation and to store contact information for future Delphi rounds and invitation to consensus meetings. We will highlight that participation is voluntary and participants are free to withdraw at any stage. We will underscore that survey responses will be anonymised.

**Patient and public involvement**
Patient and public were not involved in designing or drafting the protocol but will be involved in the study.

**Data management**
Data generated as part of this study will be downloaded and stored on encrypted devices in compliance with the University of California, San Francisco Minimum Security Standards for Electronic Information Resources. All systems used to store, process or analyse data will meet these standards, and access to data will be granted only to authorised individuals with approved access and a business need to know.
Dissemination

We will disseminate the results of this work following the Core Outcome Set-STDAndards for Reporting (COS-STAR) guidelines through publication in a peer-reviewed journal on study completion. Results may also be presented at international conferences. Plain language results will also be communicated to all study participants, including nurses, respiratory therapists, patients and caregivers.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES
# Appendices

## Appendix A. Core Outcome Set-STAndardised Protocol Items Checklist

<table>
<thead>
<tr>
<th>Core Outcome Set-STAndardised Protocol Items</th>
<th>Page and Line Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TITLE/ABSTRACT</strong></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1a Identify in the title that the paper describes the protocol for the planned development of a COS</td>
</tr>
<tr>
<td>Abstract</td>
<td>1b Provide a structured abstract</td>
</tr>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td></td>
</tr>
<tr>
<td>Background and objectives</td>
<td>2a Describe the background and explain the rationale for developing the COS, and identify the reasons why a COS is needed and the potential barriers to its implementation</td>
</tr>
<tr>
<td></td>
<td>2b Describe the specific objectives with reference to developing a COS</td>
</tr>
<tr>
<td>Scope</td>
<td>3a Describe the health condition(s) and population(s) that will be covered by the COS</td>
</tr>
<tr>
<td></td>
<td>3b Describe the intervention(s) that will be covered by the COS</td>
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<tr>
<td></td>
<td>3c Describe the context of use for which the COS is to be applied</td>
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<tr>
<td><strong>METHODS</strong></td>
<td></td>
</tr>
<tr>
<td>Stakeholders</td>
<td>4 Describe the stakeholder groups to be involved in the COS development process, the nature of and rationale for their involvement and also how the individuals will be identified; this should cover involvement both as members of the research team and as participants in the study</td>
</tr>
<tr>
<td>Information sources</td>
<td>5a</td>
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<tr>
<td></td>
<td>5b</td>
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<tr>
<td>Consensus process</td>
<td>6</td>
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<tr>
<td>Consensus definition</td>
<td>7a</td>
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<tr>
<td></td>
<td>7b</td>
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</tbody>
</table>

### ANALYSIS

| Outcome scoring/feedback | 8  | Describe how outcomes will be scored and summarised, describe how participants will receive feedback during the consensus process | Page 7, Lines 323-328, Page 8, Lines 349-353 |
|--------------------------|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|__________________________________________|
| Missing data             | 9  | Describe how missing data will be handled during the consensus process | Page 9, Lines 409-412 |

### ETHICS and DISSEMINATION

| Ethics approval/informed consent | 10 | Describe any plans for obtaining research ethics committee/institutional review board approval in relation to the consensus process and describe how informed consent will be obtained (if relevant) | Page 10, Lines 457-462 |
|---------------------------------|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|__________________________________________|
| Dissemination                  | 11 | Describe any plans to communicate the results to study participants and COS users, inclusive of methods and timing of dissemination | Page 10, Lines 472-476 |

### ADMINISTRATIVE INFORMATION

| Funders                      | 12 | Describe sources of funding, role of funders | NA |
Appendix B. List of key search terms.

("brain injury" OR stroke OR "subarachnoid hemorrhage" OR "intracerebral hemorrhage" OR meningitis OR encephalitis OR "acute ischemic stroke" OR "status epilepticus") AND (cerebral OR head OR skull OR neurological OR neurologic OR neurosurgery OR neurosurgical) AND (injury OR damage OR "neurocritical care" OR "neurointensive care" OR "neuroscience ICU") AND (ventilation OR mechanical OR intubat* OR extubat* OR tracheostomy)