

A Core Outcome Set for Critical Care Ventilation Trials

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Objectives: Our objective was to obtain international consensus on a set of core outcome measures that should be recorded in all clinical trials of interventions intended to modify the duration of ventilation for invasively mechanically ventilated patients in the ICU.

Design: A two-stage consensus process was undertaken between December 2015 and January 2018. Stage 1 included an online three-round Delphi study and three consensus meetings. Stage 2 included three consensus meetings.

Setting: The setting was international, including Europe, North and South America, Australia, Asia, and Africa.

Participants: Organization members representing intensive care survivors and carers; nursing, allied health professionals, and critical care physicians; clinical trials groups and trial investigators; and industry.

Interventions: None.

Measurements and Main Results: Delphi study outcomes were scored by participants from one (least important) to nine (most important). Consensus criteria for including the outcome in the core set were more than 70% of responses rating the outcome above seven and not more than 15% rating the outcome less than 3. From 222 participants, 183 from 38 organizations in 27 countries contributed to the consensus process. Stage 1: Delphi response rates from 200 participants ranged from 89% to 90% across three rounds. Forty-seven outcomes were ranked as follows: 19 met consensus criteria for inclusion and were considered at three consensus meetings (33 participants). Six outcomes were agreed for the core set as follows: extubation, reintubation, duration of mechanical ventilation, length of stay, health-related quality of life, and mortality. Stage 2: Three consensus meetings (37 participants) agreed on the measures for each outcome.

Conclusions: We used rigorous and well-established methods to develop a core outcome set for use in all clinical trials evaluating interventions intended to modify duration of mechanical ventilation. This core outcome set will inform the design of future trials in this field by strengthening methodological quality and improving comparability across trials. (*Crit Care Med* 2019; 47:1324–1331)

Key Words: clinical trials; critical care outcomes; Delphi technique; intensive care; mechanical ventilation

Clinical trials provide evidence for best clinical practice, but comparisons of findings across trials are difficult because of differences in the selection and reporting of trial outcomes. The resulting inability to compare findings not only diminishes our ability to synthesize evidence and address knowledge gaps but wastes research resources (1). Several Cochrane Reviews of trials evaluating ventilator weaning protocols spanning 2 decades have highlighted substantial variation in outcome selection, definition, measurement, and reporting (2–4). More recently, we (B.B., M.C., J.C.M., L.R., D.F.M.) have shown in a review of 66 trials that inconsistency in ventilation outcome reporting in critical care trials remains problematic: among the 66 trials, only 12 (25%) provided a definition and 16 different definitions of duration of mechanical ventilation were used (5). Ideally, trials focused on the same health condition and intervention should assess the same clinically meaningful outcomes and measure them in a similar fashion to facilitate more appropriate comparisons.

Standardization in selection and measurement of a core outcome set (COS) has been proposed as a method of addressing problems of inconsistency. A COS is defined as the minimum set of outcomes that should be measured and reported in all clinical trials of a specific condition (6). Using a COS ensures that trials collect the same outcomes in standard ways, which increases availability of the most important and relevant information for meta-analyses. The Core Outcome Measures in Effectiveness Trials (COMET) initiative, a resource repository for COS researchers and users, summarizes the current methodological approach for COS development (7). The recommended multistage process advocates obtaining consensus on “what” outcomes should be in the COS, before addressing “how” and “when” these outcomes should be measured (7). Within critical care, the effort to drive COS development forward is championed by the International Forum for Acute Care Trialists (InFACT) and is receiving widespread attention by the critical care research community (8). COS for cardiac arrest (9) and long-term outcomes in acute respiratory failure are already completed (10), with others relating to physical rehabilitation (11), delirium (12), and subarachnoid hemorrhage (13) are at different stages of development.

We sought to develop a COS for trials testing any intervention intended to modify mechanical ventilation duration in critical care. In recognizing that trial outcomes should include health results most relevant to patients, our specific objectives were to engage relevant participants in identifying important core outcomes for these trials and to obtain agreement on how they should be defined, measured, and reported. This COS is intended for use in randomized trials of interventions for invasively mechanically ventilated adults in critical care, but would also be suitable for nonrandomized studies.

MATERIALS AND METHODS

This Core Outcomes in Ventilation Trials (COVenT) study used a two-stage, mixed methods, consensus approach (Fig. 1). COVenT Stage I determined “what” outcomes to include. COVenT Stage II determined “how” the agreed outcomes

should be measured. Methods included systematic reviews of published (5), unpublished (J Friedrich and J Marshall, InFACT February 29, 2016, personal communication); Ringrow et al (14) and online information sources (Improve Long-Term Outcome COS www.improvelto.com); a three-round, online Delphi study supported by a bespoke e-management system (DelphiManager, Version 1.0 2014, University of Liverpool, United Kingdom); webinar and face-to-face consensus meetings. For more details on methods, see **eAppendix 1** and **eAppendix 2** for the Delphi questionnaire (Supplemental Digital Content 1, <http://links.lww.com/CCM/E744>).

To recruit Delphi participants, we contacted a broad range of international organizations representing: ICU survivor and carer support groups; nursing, allied health professional (AHP), and medical critical care societies; critical care clinical trials groups and trial investigators; and industries involved with ventilation equipment. Organization leads either notified members about the study for self-selection or identified member representatives. Consensus meeting participants were recruited from Delphi respondents completing all three rounds. Additionally, we purposively invited a cohort of non-Delphi participants, including a statistician, health economist, two critical care journal, and social media editors and others to provide specific methodological expertise. Names and affiliations of COVenT participants are listed in **eAppendix 3** (Supplemental Digital Content 1, <http://links.lww.com/CCM/E744>).

COVenT was registered on the COMET database, and the study protocol was published (15, 16). The COVenT study was ethically approved by Queen’s University Belfast, School of Medicine Ethics Committee (reference: 14.34v2; October 3, 2014). Findings are reported according to accepted standards for reporting COS development (17).

RESULTS

In total, 222 participants were recruited and 183 contributed to the final consensus process. The final 183 included 161 participants that completed all three rounds of the Delphi study and an additional 22 non-Delphi participants. **Table 1** shows the stakeholder composition and geographical spread of the 183 participants.

COVenT Stage I Results

The Delphi study was conducted from December 2015 to March 2016 and 200 participants participated in round one. Subsequently, 178 of 200 (89%) completed round two and 161 of 178 (90%) completed round three (Fig. 1). The proportions of panel participants were 9% ICU survivors/carers; 50% nurses, AHP, and physicians; 35% trials group members and investigators; and 6% industry. Participant stakeholder groups and geographical locations are shown in **eTable 1** (Supplemental Digital Content 1, <http://links.lww.com/CCM/E744>).

Round one contained 24 outcomes and Delphi participants recommended 23 additional outcomes that were added to round two (47 outcomes in total) (see **eAppendix 2** for the questionnaire, Supplemental Digital Content 1,

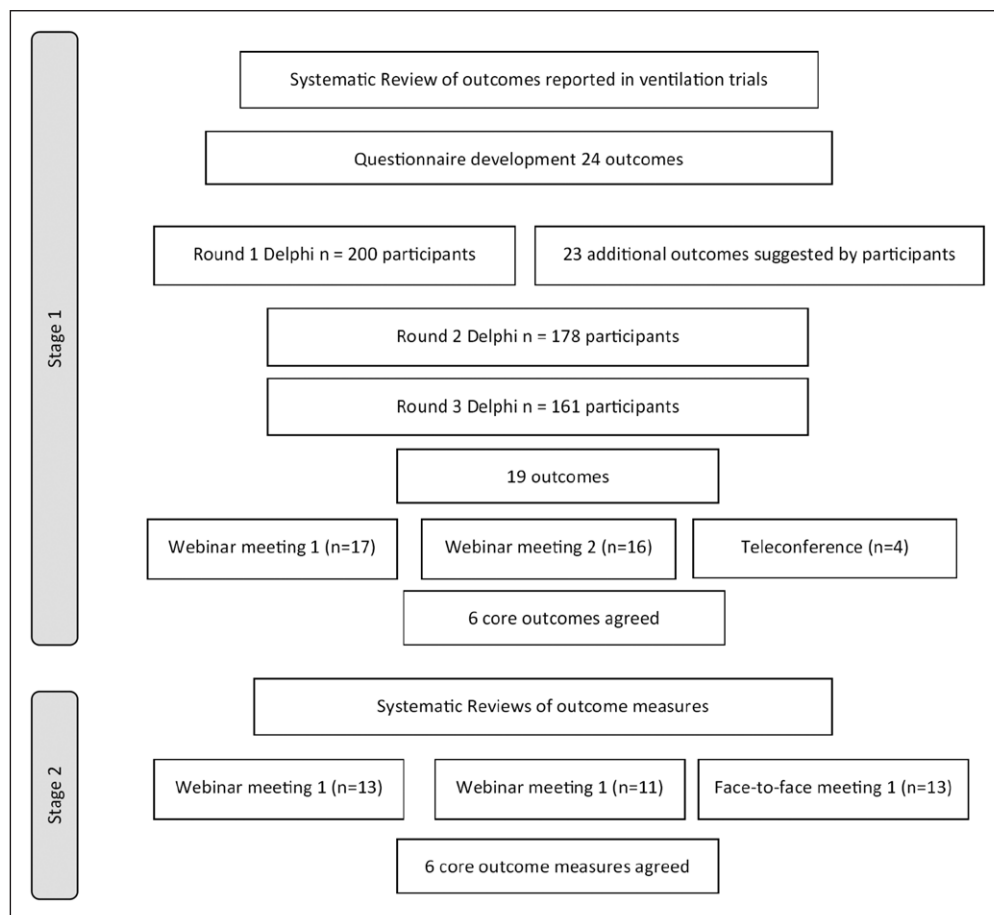


Figure 1. Core Outcomes in Ventilation Trials study flow diagram.

<http://links.lww.com/CCM/E744>). After round three, 19 outcomes met consensus criteria (> 70% participants scoring the outcome as critical and not more than 15% rating the outcome not critical). We classified outcomes using the COMET taxonomy structure into categories of death; physiologic/clinical; life impact; resource use; and adverse events (18) (eTable 2, Supplemental Digital Content 1, <http://links.lww.com/CCM/E744>). The research team (authors) considered the taxonomy and noted overlapping similarities in outcomes within categories (e.g., mortality and survival). Furthermore, 19 outcomes were considered too large for a COS; therefore, these were taken forward for further discussion and voting “in,” “out,” or “unsure” at three consensus meetings: two webinar meetings (October 11, 2016, and October 17, 2016; $n = 33$ participants); and a follow-up teleconference with ICU survivors and family carers (October 25, 2016; $n = 4$). Webinar voting details are presented in eTables 3 and 4 (Supplemental Digital Content 1, <http://links.lww.com/CCM/E744>).

From the consensus meetings, nine outcomes were voted in as “core” (Table 2), but only six were universally agreed by all. These six form the COS are as follows: extubation, reintubation, duration of mechanical ventilation, length of stay, health-related quality of life (HRQOL), and mortality. The three outcomes not universally agreed were survival, pulmonary complications, and delirium.

COVenT Stage II Results

We convened two webinar meetings (November 13, 2017, and November 17, 2017) and a face-to-face meeting (February 6, 2018) including 37 participants to determine definitions and measures for the six core outcomes. At the meetings we presented a set of preliminary definitions and measures derived from the aforementioned systematic reviews and based on four recommended components for defining an outcome (specific variable, analysis metric, aggregation method, and time point) (19) (preliminary list detailed in eTable 5, Supplemental Digital Content 1, <http://links.lww.com/CCM/E744>). Consensus was gained through discussion and voting. Webinar participants reached agreement on definitions and measures for four outcomes (duration of mechanical ventilation, length of stay, HRQOL, and mortality), but did not reach consensus on two (extubation and reintubation). The

remaining two outcomes were discussed and agreed in the final face-to-face meeting (eTable 5, Supplemental Digital Content 1, <http://links.lww.com/CCM/E744>).

Table 3 presents the final core outcome measurement set detailing how the outcomes should be specifically defined and measured and, where necessary, provides additional clarification and recommendations. Table 4 details the study variable fields that investigators can insert into an electronic case report form for a clinical trial.

DISCUSSION

This large, international consensus study, including participants from 38 organizations in 27 countries has established a COS for critical care trials of interventions intended to modify mechanical ventilation duration. The six core outcomes are extubation, reintubation, duration of mechanical ventilation, length of stay, HRQOL, and mortality. Additionally, this study provides the specific measurement variable; analysis metric; aggregation method; and measurement time-point for each outcome. All outcome data should be reported for survivors and, where appropriate, nonsurvivors. This COS represents the minimum number of outcomes. Additional outcomes and measurement time points can be added at the investigators’ discretion. To our knowledge, this study is the first to develop

TABLE 1. Characteristics of Core Outcomes in Ventilation Trials Participants

Composition	n (%)
Stakeholder	
Clinicians	82 (45)
Researchers	76 (41.5)
ICU survivors/carers	15 (8)
Industry	10 (5.5)
Geographical	
Europe	116 (63)
United Kingdom (52), Ireland (3), Germany (4), Italy (7), Spain (3), Greece (6), Sweden (6), Israel (1), Netherlands (4), France (5), Turkey (5), Austria (3), Malta (1), Slovenia (3), Poland (4), Croatia (1), Switzerland (7), Belarus (1)	
North America	45 (25)
United States (31), Canada (14)	
Australasia	15 (8)
Australia (13), New Zealand (2)	
Asia	3 (2)
Singapore (1), India (1), Philippines (1)	
South Africa	3 (2)
South America (Brazil)	1 (1)

a COS for ventilation trials, as such, this represents important new insight for critical care investigators.

The validity of this COS is strengthened by following a robust development process, including a Delphi study and consensus meetings that enabled wide representation and engagement. The sample size for consensus processes is not determined by achieving statistical power, rather the main consideration is maximizing representation from key stakeholder groups (7). We achieved this through broad geographical and stakeholder composition. The importance of a wide stakeholder group in COS development is not to be underestimated in achieving agreement on outcomes that are relevant and important to patients, clinicians, and researchers.

Duration of mechanical ventilation and length of stay outcomes relate to successful medical management and prompt liberation from mechanical ventilation. Although they are commonly used in ventilation trials, they are inconsistently defined and measured (5); therefore, their appearance in the COS was not unexpected. Likewise, extubation and reintubation, while less frequently measured in trials (20), influence ventilation duration and length of stay and thus require clinically meaningful definitions. Conversely, outcomes important to patients, such as HRQOL are not generally profiled in trials. Indeed, a recent systematic review of critical care trials found

TABLE 2. Outcomes Agreed at Each Consensus Meeting and the Final Core Outcome Set (Bold)

Webinar 1	Webinar 2	Teleconference
Outcomes agreed and reaching consensus by all three meeting groups		
Successful extubation	Successful extubation	Successful extubation
Reintubation	Reintubation	Reintubation
Duration IMV	Duration IMV	Duration IMV
LOS (hospital)	LOS (ICU)	LOS (hospital)
HRQOL	HRQOL	HRQOL
Mortality	Mortality	Mortality
Outcomes agreed and reaching consensus by one or two meeting groups		
	Survival	Survival
Pulmonary complications		Pulmonary complications
		Delirium
<i>n</i> = 7	<i>n</i> = 7	<i>n</i> = 9

HRQOL = health-related quality of life, IMV = invasive mechanical ventilation, LOS = length of stay.

LOS was retained as a core outcome for consideration of the measurement time point in Core Outcomes in Ventilation Trials stage II.

only 22% (160/713) reported patient-important outcomes with HRQOL accounting for only 3% (*n* = 22 trials) (20). The inclusion of less commonly reported, but nevertheless, clearly important outcomes in the COS serves to show the value of engaging patients in COS development.

This COS defines randomization as the measurement start point for the time-related outcomes, duration of mechanical ventilation, and length of stay. Participants considered randomization a more reliable start point as it marks commencing delivery of the experimental or control intervention to modify an outcome. However, for research designs where randomization does not signal commencement of intervention delivery, the COS recommends that alternative start point should be clearly justified and defined.

The recommended endpoint for extubation and duration of mechanical ventilation is defined as “successful extubation” and “unassisted breathing,” respectively, at 48 hours. A previous round table conference on weaning defined 48 hours as the time-point measure of success, but this is now more than 10 years old (21). In the light of newer practices incorporating noninvasive ventilation as a weaning strategy or to treat post extubation respiratory distress, arguably identification of success of extubation should be at a more distal time-point (22). However, although there is no evidence for adopting the 48-hour period to define success, in the current study, participant expert opinion upheld 48 hours because any subsequent need for intubation and ventilation would likely be related to

TABLE 3. Final Core Outcome Measurement Set for All Clinical Trials Evaluating Interventions Intended to Modify Duration of Mechanical Ventilation**Extubation**

Definition: Time from randomization to first successful extubation.

Measurement: Mean and median time (hr) to establishment of natural airway (meaning all tube extubation) with a follow-up to 60 d from randomization (censor at hospital discharge).

Clarifications: Extubation is defined as free from all tubes, endotracheal tube, and tracheostomy. Success is defined as remaining free from tubes at 48 hr. Time does not include the 48-hr success period. If discharged from hospital before the 48-hr success period, assume extubation is successful.

Reintubation

Definition: Reintubation of endotracheal tube after an extubation that was planned.

Measurement: All reintubation events with date/time. Report as total number of reintubations after a planned extubation in each group and the average number of reintubation events/patient in each group. Time to follow-up 60 d from randomization (censor at hospital discharge).

Clarifications: Excludes “reinsertion for procedure only,” i.e., temporary elective reintubations.

Duration of mechanical ventilation

Definition: Time from randomization until first successful unassisted breathing or death.

Measurement: Mean and median time (hr). Follow-up to 60 d from randomization (censor at hospital discharge).

Clarifications: Unassisted breathing defined as no inspiratory support or extracorporeal lung support. Success defined as remaining to breathe unassisted at 48 hr. Measure time by calculating date/time of start and stop; do not include the 48-hr success period. Record date/time of all periods of ventilation up to day 60. Present data for survivors and nonsurvivors.

Duration includes time receiving extracorporeal lung support, invasive mechanical ventilation and noninvasive ventilation delivering volume or pressure support ventilation; excludes high-flow oxygen therapy and continuous positive airway pressure.

Duration of stay

Definition: Time from randomization until patient first leaves the relevant facility or death.

Measurement: Mean and median time (hr). Follow-up to 60 d from randomization (censor at discharge).

Clarifications: Can include “critical care length of stay,” “hospital length of stay,” or both. Define censoring points. “Hospital” and “critical care” must be clearly defined a priori in the study protocol. Definition should ideally include information on country, type of hospital, type of ICU (open/closed model), ICU staff to patient ratios, payment system, and access to long-term ventilator facilities.

Mortality

Definition: Confirmation of death.

Measurement: Number of events in each group reported as the mortality rate. Follow-up to 60 d from randomization.

Recommendation: Recording date/time of randomization and death will enable survival analysis to be undertaken (if required).

Health-related quality of life

Definition: EQ-5D-5L as a quality of life tool.

Measurement: Distribution of responses for each dimension level reported as the number and % of responses and the mean visual analog scale score. Follow-up to 6 mo from randomization.

Clarification: EQ-5D-5L should be reported as the distribution of responses rather than a health utility score.

EQ-5D-5L = EuroQol 5 dimensions 5 levels.

General recommendations: Report all outcome data for survivors and, where appropriate, nonsurvivors. This core outcome set represents the minimum number of outcomes. Additional outcomes and measurement time points can be added at the investigators' discretion.

a new clinical event. Additionally, the endpoint for duration of mechanical ventilation, “unassisted breathing,” is defined as a patient being free from invasive ventilation, including extracorporeal lung support and noninvasive ventilation delivering volume or pressure support. Although we recognize that continuous positive airway pressure and high-flow oxygen therapy

may not be truly “unassisted,” these modes of ventilation were excluded from the definition of assisted breathing. Further, high-flow oxygen therapy devices technically only modify percentage of oxygen delivery and rate of gas flow rather than assisted support as provided by the other forms of mechanical ventilation (23).

TABLE 4. Case Report Form Items

Extubation
Date/time of randomization; date/time of extubation; date/time to establishment of natural airway.
Reintubation
Date/time of planned extubation; date/time of each reintubation event.
Duration of mechanical ventilation
Date/time of randomization; date/time of first successful unassisted breathing; date/time of death.
Duration of stay
Date/time of randomization; date/time patient leaves critical care unit; date/time patient leaves hospital; date/time of death.
Mortality
Date/time of randomization; dead/alive at day 60; date/time of death.
Health-related quality of life
Response for each dimension: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.
0–100 visual analog scale.

Participants recognized that achieving standardized measures of length of stay was challenging due to international differences in healthcare provision. Length of stay is generally used as a benchmark to assess healthcare systems, with shorter stays typically associated with system efficiency (24) and for this reason, it was deemed important for the COS. Although length of stay may reflect important progress in a patient's trajectory of recovery, structural and process factors may impact its standardization. The average length of stay, in both ICU and hospital, varies considerably between countries, with nonclinical factors, such as professional or cultural settings, differing public and private healthcare reimbursement schemes, and access to long-term care and ventilator facilities contributing to international variability (25, 26). Given the influence of these factors on duration of stay and challenges in modifying them, the COS recommends that investigators clearly define the setting (hospital and/or critical care facility) and any censoring points in their study protocol to facilitate understanding of comparisons and generalizability.

The reported mortality endpoint in critical care trials has varied from 28 to 90 days and, in some trials, up to 1 year (5). In selecting a pragmatic mortality time-point for the COS, participants considered a number of important reasons for agreeing on 60 days. First, measuring ICU and hospital mortality was considered limiting due to potential variability in duration of stay as a result of factors unrelated to the patient's condition. Second, the time-point should be stable and realistically capture the full effects of the intervention. Although a

short time-point (e.g., 28 d) might capture immediate survival impact, the mortality rate could be manipulated by delaying clinical decisions (e.g., withdrawal of treatment); therefore, participants considered a more distal time-point preferable. The 60-day choice was informed by a systematic review of trials reporting mortality at three or more time-points that showed significant incremental risk difference between treatment arms to at least 60 days after randomization (J. Friedrich and J. Marshall, personal communication, 2016). A third reason for choosing 60 days was that the time-point should not substantially increase the burden of follow-up.

Defining the HRQOL outcome measure was greatly assisted because the Improve Long-Term Outcome group had already completed a COS that included HRQOL measures. The group recommended the EuroQol 5 dimensions 5 levels (EQ-5D-5L) measurement tool at a 6-month time point (<https://www.improvelto.com/>) (10). A number of COVenT participants had also participated in the Improve Long-Term Outcome project, and so agreement was readily reached that it was appropriate for the COVenT COS.

At the end of stage I, three outcomes (survival, pulmonary complications, and delirium) reached inclusion criteria for the COS by one or more consensus groups, but as they were not universally agreed by all groups, they were excluded from the COS. Nevertheless, these outcomes may be captured in other ways. For the mortality outcome measure, the COVenT COS recommends documenting date and time of randomization and death which would enable a survival analysis to be undertaken. Pulmonary complications can be documented and reported alongside other trial adverse events. Delirium is being addressed in a separate COS development study (12); therefore, ventilation studies that also want to incorporate standardized delirium outcomes could add these, when they become available, to their trial measures.

A limitation of our study was the low number of patient participants, a challenge that has been experienced in other COS development studies (27). We planned to recruit from ICU support groups, but accessing these proved difficult as they are not well established internationally. Given the importance of patient involvement in research (28), we asked clinical trials groups and the European Federation of Critical Care Nurses associations for contact details of support groups in their countries, but received no suggestions highlighting a need for more work to encourage patient and carer engagement in research. ICU survivors and family carers in our study were recruited from Canada and a U.K. charity (<https://icusteps.org/>).

We also experienced challenges in engaging participants representing research funding organizations. U.K. funders were concerned about the potential for exponential requests to participate in Delphi studies due to the growing interest in this field of research. However, the role of funding organizations in the overall COS development process may be more valuable for subsequent promotion and dissemination through mandating their use in funding applications. This is the case in the United Kingdom, where the National Institute for Health

Research, Health Technology Assessment guidance documents encourage applicants to use established COS among the list of outcomes where these are available (29). As a result, it is likely that we will see a rising tide of COS development and use in future trials.

Moving forward, we plan to disseminate the COS through the COVenT participants and their organizations, conference presentations, social media, research funders, and relevant Cochrane Review Groups. We will monitor the uptake of the COVenT COS with a planned cohort study that aims to identify if participation in the COVenT COS development effects uptake by individual researchers over the next decade (16).

CONCLUSIONS

Using rigorous and well-established methods, we reached international consensus on the COVenT COS that should be reported in all future trials of interventions designed to modify the duration of invasive mechanical ventilation in critical care. The set comprises standardized definitions and measures for six outcome measures (extubation, reintubation, duration of mechanical ventilation, length of stay, HRQOL, and mortality). We are confident that by standardizing these outcomes, this COS will benefit future research in this field. We recommend that trialists and systematic reviewers use this COS to enable cross-study comparisons, minimize outcome reporting bias, and ensure that their research findings provide information deemed important by patients, clinicians, and policy makers.

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Society; Pediatric Acute Lung Injury and Sepsis Investigators (PALISI); Queens University Belfast (QUB); Réseau européen de Recherche en ventilation Artificielle (REVA); Scandinavian Critical Care Trials Group; Scandinavian Society of Anaesthesiology and Intensive Care; Scottish Intensive Care Society of Critical Care Medicine; The Clinical Trials Network for the Prevention and Early Treatment of Acute Lung Injury (PETAL Network); The United States Critical Illness and Injury Trials Group (USCIITG); United Kingdom Critical Care research Forum (UKCCRF); United Kingdom Intensive Care Society (ICS); United Kingdom Intensive Care Society Clinical Trials Group (UK ICS CTG); and World Federation of Physical Therapy. We thank Melanie Harper-Jones, Duncan Appelbe, and Paula Williamson from the University of Liverpool for on-line Delphi development and management; and members of Centre Cochrane Français (Amelie Yavchitz and Philippe Ravaud) for conducting the PubMed search to identify clinical trial investigators. We also thank Professor David Harrison (Head Statistician, Intensive Care National Audit & Research Centre, London, United Kingdom) for assistance with defining outcome analysis metrics and aggregation methods.

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