Progress on core outcomes sets for critical care research

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Title: Progress on core outcomes sets for critical care research

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Abstract

Purpose of the review: Appropriate selection and definition of outcome measures are essential for clinical trials to be maximally informative. Core outcome sets, an agreed, standardized collection of outcomes measured and reported in all trials for a specific clinical area, were developed due to established inconsistencies in trial outcome selection. This review discusses the rationale for, and methods of, core outcome set development as well as current initiatives in critical care.

Recent findings: Recent systematic reviews of reported outcomes and measurement instruments relevant to the critically ill highlight inconsistencies in outcome selection, definition, and measurement, thus establishing the need for core outcome sets. Current critical care initiatives include development of core outcome sets for trials aimed at reducing mechanical ventilation duration; rehabilitation following critical illness; long-term outcomes in acute respiratory failure; and epidemic and pandemic studies of severe acute respiratory infection.

Summary: Development and utilization of core outcome sets for studies relevant to the critically ill is in its infancy compared to other specialties. Notwithstanding, core outcome set development frameworks and guidelines are available, several sets are in various stages of development, and there is strong support from international investigator-led collaborations including the International Forum for Acute Care Trialists.

Key Words:

Core outcome sets; systematic reviews; critical care

Introduction

Clinical trial outcomes are defined as processes or events that are potentially modified by the intervention(1). Outcome measures are chosen by investigators to capture treatment effects that are not only important to the patient (death, morbidity, quality of life), but that will also provide better understanding about disease processes and the consequences of the intervention in the population studied. Consequently, appropriate selection and definition of outcome measures are critical for clinical trials to be maximally informative. Criteria to be considered in their selection include clinical importance, responsiveness to the intervention, precision of their definition and accuracy of measurement (1). In addition to appropriate selection, it is important that all trial outcomes are fully reported; yet we know that selective reporting occurs, generally to improve the chances of publication in peer reviewed literature, (2-4). As a result, there is considerable potential for bias and misinterpretation of the available evidence.

Inconsistency in measurement and reporting of trial outcomes has been recognised as a problem over many years. Despite strong recommendations from trial registries (CONSORT(5), the World Health Organization [WHO] registry(6)) and international guidelines (SPIRIT 2013(4)) that when registering trials investigators report for every outcome; the specific measurement variable; participant-level analysis metric (e.g. change from baseline, final value, time to

event); the method of aggregation (e.g. proportion, mean); and the time frame for each outcome measure, data suggest that these requirements are not being met (7). Missing outcome information constitutes avoidable research waste (Chan 2014) and a potential threat to the validity of the evidence (3). Inconsistency in outcome selection, measurement and reporting makes it difficult, sometimes impossible, to synthesise trial results in systematic reviews and meta-analyses and apply them in a meaningful way (8). There is an ethical imperative to ensure that trials, which are time consuming and costly to conduct, are maximally informative (9).

Disorder in selecting and measuring critical care outcomes

Evaluation of health status, an important patient-centred outcome, has led to the development of numerous measures of functional status and health related quality of life. In 2001, Black and colleagues conducted a review of studies published from 1970 to 1998 reporting impairment, functional and/or quality of life outcomes for patients following discharge from the intensive care unit (ICU) (10). They reviewed the outcome measurement properties (including responsiveness, reliability and validity) with a view to recommending appropriate measures for future research. However because of the large number of measures used and the poor quality of the measurement testing, they could not make strong recommendations. To permit a sizeable body of experience and evidence to be built up around a few measures, and to facilitate comparisons between studies, they called for agreement on a limited list of measures from which to select for any given study and a common time point for follow-up.

Over a decade later, problems in selection and measurement of outcomes in critical care research remain and have been exposed in recent *systematic reviews of interventions* such as protocolized weaning (11, 12) and exercise rehabilitation programmes (13) creating difficulties in the interpretation and synthesis of findings. Additionally, *systematic reviews of outcome measures* have exposed inconsistencies in: outcome selection and timing of assessment in mechanical ventilation trials for measuring duration of ventilation (14); instruments and clinimetric properties of outcomes measuring functional impairment and limitations in the critically ill (15); and a lack of data on an important patient-relevant outcome (chronic lung disease) in trials included in systematic reviews of critically ill neonates (16). These reviews highlight the need to ensure that critical care trial investigators measure outcomes that are the most important ones for patients and conditions examined; and that the right measure is used at the most appropriate time-point.

The evolution of core outcomes in critical care research

Over the last 10 years, many international critical care organisations have advocated for appropriate selection and measurement of clinical and patient-relevant outcomes. The European Society of Intensive Care Medicine, the American Thoracic Society, and the Society of Critical Care Medicine held a consensus conference to discuss the necessity for research to address valid long term outcome measures of ICU survivors (17). While recognising that short term outcomes (e.g. hospital mortality) were important, patients are more likely to rate functional and cognitive status in the long term of higher importance than death. The conference participants recommended that all future clinical trials of critical care therapies

should include a set of long term outcome measures with a minimum follow-up of 6 months within the domains of survival, quality of life, morbidity, functional status, and costs of care. Subsequent appeals for a standardized format for reporting methods, endpoints, and a standard set of outcome measures have come from: the International Sepsis Forum colloquium on outcome measures for clinical research in sepsis (1); the Division of Lung Diseases of the National Heart, Lung and Blood Institute workshop on acute lung injury (18); the Society of Critical Care Medicine stakeholder conference on post-ICU care (19); and the inter-agency Pediatric Traumatic Brain Injury (TBI) Outcomes Workgroup for age-relevant outcome measures for TBI research (20).

One solution for the problems outlined above is to select a standard set of outcomes that are considered to be 'core' outcomes (7). A core outcome set (COS) is defined as an "agreed, standardized collection of outcomes measured and reported in all trials for a specific clinical area" (8). Using a COS does not prevent investigators from measuring other outcomes of interest; rather, as a small set of outcomes standardized across similar trials, it enables transparent comparisons of findings.

The Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Group formed in 1992 was one of the first collaborative groups to formally address problems caused by disparity of outcome selection through the development of a COS (21). A recent systematic review identified 70% uptake of the core outcome sets in rheumatoid arthritis trials since the original set was published demonstrating the success of the OMERACT's approach to COS development

(22). Although there are obvious differences between rheumatology and critical care, the success of the approach used by OMERACT as used by other medical specialties (maternity care (23); childhood asthma (24); otitis media (25); ulcerative colitis (26)), suggests that the basic principles encapsulated by OMERACT can be generalised and successfully applied to critical care.

Mechanisms for developing COS

A number of supportive mechanisms exist for assisting COS development that include collaborative initiatives and conceptual frameworks.

The COMET Initiative

The COMET (Core Outcome Measures in Effectiveness Trials) Initiative, launched in 2010, has been instrumental in assisting with the development and application of COS across health and social care (27). Its website contains guidelines on core outcome set selection and seeks to facilitate collaboration among researchers developing COS. The COMET repository includes a unique collection of more than 306 studies that are registered to develop a COS (28). The COMET initiative has received widespread international support from many organizations, including OMERACT (29) and, in relation to critical care, the International Forum for Acute Care Trialists (InFACT) (30). InFACT is a network of investigator-led clinical research consortia that aims to promote international collaboration in critical care research and address barriers in undertaking trials; it is currently the major driving force behind the advancement of creating COS for critical care trials.

The standard process for development of a COS relies upon a combination of literature searches and expert group consensus, although methods of obtaining consensus and the stakeholders invited are variable. A systematic review of COS development studies has highlighted this variation with methods comprising unstructured group discussion, the Delphi technique, consensus conferences, surveys and the Nominal Group Technique (31). Participants in consensus panels were mainly clinical experts and non-clinical research experts; relatively few studies reported public involvement, although this is an important recommendation by COMET and OMERACT (27, 29).

Conceptual Frameworks

A scoping review by Idzerda and colleagues from the OMERACT group identified five conceptual frameworks (in addition to the OMERACT framework) that have been used to guide the development of COS (32). These include: the WHO tripartite definition of health; the 5 Ds (discomfort, disability, drug toxicity, dollar cost, and death); the International Classification of Functioning (ICF); PROMIS (Patient-Reported Outcomes Measurement System); and the Outcomes Hierarchy. Of these, only the 5 Ds and ICF frameworks had been systematically used in COS development and many COS development studies have not used a framework. Up until 2014, the OMERACT group largely followed the 5-Ds framework, although this framework does not include measurement of pathophysiology, an important consideration for understanding if an intervention has worked as intended. In 2014, OMERACT revised their conceptual

framework (33, 34). Given its relevance to emerging work in developing critical care COS, it is described here in more detail.

The OMERACT framework (33, 34)

The structure of the conceptual framework outlined by OMERACT consists of two overarching concepts: impact of health conditions and pathophysiological manifestations. Relating to these concepts are four *core areas* of outcome: death, life impact, pathophysiological manifestations and resource use (Figure 1). Within each core area are *domains of interest* for particular conditions. Stakeholders should determine at least one domain as a core outcome within the core area, thus there will be a minimum of four core outcomes in a COS; termed the *core domain set*. Within each core domain, at least one validated instrument should be selected resulting in a *core outcome measurement* set. This set should be included in all trials addressing the condition for which it was developed in addition to other outcomes of interest to the investigators undertaking the trial.

The OMERACT process of defining the core outcome measurement set broadly involves two key steps to determine the 'what' and 'how' to measure. Each step should be preceded by a systematic review of relevant literature to identify the domains of interest and the instruments for measuring them, followed by a consensus activity involving full participation of all stakeholders (including patients). The first key step will involve establishing 'what' the domains of interest are within the four core areas: the product of this step will be the *core domain set*.

The second step will involve ascertaining 'how' to measure each outcome in the core domain set; the product of this step will be the *core outcome measurement set*.

The terms *core domain sets* and *core measurement outcome sets* provide a clearer understanding of the original COS definition in that they separate the steps in generating the completed COS.

Current initiatives in critical care

As of June 2015, six critical care projects are registered for COS development: studies aiming to reduce duration of ventilation (35); cardiac arrest clinical trials (36); rehabilitation following critical illness (37); long-term outcomes in acute respiratory failure (38); epidemic and pandemic studies of severe acute respiratory infection (39); and early phase trials in mechanically ventilated patients (40). As with most COS development projects (31), all are using systematic reviews and a form of expert consensus including the Delphi technique and consensus meetings. Needham's study (38) is guided by the OMERACT framework and the others are broadly following this process, as a critical care framework does not yet exist. Investigators involved in these studies have been communicating with the InFACT Outcome Measures Working Group as it works towards establishing a framework for critical care research.

Outcome measurement in the critically ill poses some unique challenges. For example, survival may not be the most important outcome for patients for whom critical illness is a complicating

process as the end of life. Additionally, as critically ill patients are often sedated or comatose and therefore unaware of the course of their illness, the family and loved ones bear a disproportionate burden, and so become a constituency whose perspective must be considered when establishing a COS. Therefore an early priority of the InFACT Outcome Measures Working Group will be to create a developmental framework that encompasses these challenges.

In an effort to promote greater rigour in outcome measurement in critical illness, InFACT has established an Outcome Measures Working Group that has three core objectives:

1. To create core outcome measure sets in multiple areas of research focus in critical care
2. To understand the strengths, limitations, and performance characteristics of outcome measures used for critical care research
3. To develop novel measures to meet unmet needs for outcome measures relevant to the study of the critically ill.

InFACT's goal in undertaking this work is to develop approaches that will be maximally inclusive, and so maximally generalizable. InFACT member groups come from every continent, and represent middle income as well as upper income countries. Therefore the focus of the InFACT Outcome Measures Working Group incorporate measures relevant to areas where resources for critical care are limited as well as measures relevant to resource rich countries.

Conclusion

Inconsistency in outcome selection, definition and measurement has been established in critical care trials. Several frameworks for core outcome set development exist and assistance and guidelines are available from collaborations such as COMET and OMERACT. Development and utilization of core outcome sets for studies relevant to the critically ill is in its infancy compared to other specialties. Notwithstanding, several core outcome sets are in various stages of development, and there is strong leadership and support from international investigator-led collaborations such as the InFACT.

Key Points

- Inconsistency in outcome selection, measurement and reporting of critical care outcomes creates major problems in synthesising trial results in systematic reviews and meta-analyses and applying them in a meaningful way.
- Core outcome sets which are agreed, standardized collections of outcomes measured and reported in all trials for specific conditions have been proposed to minimise outcome selection and reporting bias and ensure that critical care trials are maximally informative.
- Supportive mechanisms for assisting core outcome set development include the COMET (Core Outcome Measures in Effectiveness Trials) Initiative and the International Forum for Acute Care Trialists (InFACT) Outcome Measures Working Group and there are exciting opportunities ahead for making progress in improving critical care trial outcomes.

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Conflicts of interest

None.

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Figure Legend

Figure 1. The OMERACT conceptual model

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