

## Patient-important outcomes other than mortality in recent ICU trials

### *Protocol for a scoping review*

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## **Patient-important outcomes other than mortality in recent ICU trials: protocol for a scoping review**

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## Abstract

**Background:** Randomised clinical trials (RCTs) conducted in intensive care units (ICUs) frequently focus on all-cause mortality, but other patient-important outcomes are increasingly used and recommended. Their use, however, is not straightforward: choices and definitions, operationalisation of death, handling of missing data, choice of effect measures, and statistical analyses for these outcomes vary greatly.

**Methods:** We will conduct a scoping review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews. We will search 10 selected general and speciality journals for RCTs conducted in adult ICU patients from 2018 and onwards reporting at least one patient-important outcome other than mortality (including days alive without life support/days alive and out of hospital-type outcomes, health-related quality of life, functional/cognitive/neurological outcomes and other general patient-important outcomes). We will summarise data on outcome measures and definitions, assessment time points, proportions and handling of death, proportions and handling of missing data, and effect measures and statistical methods used for analysis.

**Discussion:** The outlined scoping review will provide an overview of choices, definitions and handling of patient-important outcomes other than mortality in contemporary RCTs conducted in adult ICU patients. This may guide discussions with patients and relatives, the design of future RCTs, and research on optimal outcome choices and handling.

## Introduction

Randomised clinical trials (RCTs) conducted in critically ill patients in or outside the intensive care unit (ICU) often focus on all-cause mortality at single time-points,<sup>1</sup> while the use of other patient-important outcomes is limited.<sup>2</sup> Although mortality is intuitively important to patients and compelling due to its simplicity, its use is not without challenges and other outcomes may be equally important to patients. Due to its binary nature, mortality generally provides limited statistical information compared to continuous or ordinal outcomes,<sup>3-5</sup> consequently, RCTs must generally be substantially larger to be powered to detect differences in mortality. RCTs conducted in ICU patients are often neutral or inconclusive (i.e., unable to detect or exclude clinically important effects), in part due to sample size estimations based on unrealistically large effect sizes,<sup>1,6</sup> likely for economic and logistical reasons. There is empirical evidence that RCTs in ICU patients focusing on non-mortality outcomes more frequently reach statistical significance, even when evaluating other binary outcomes.<sup>1</sup> Consequently, there have been recent recommendations to focus on non-mortality outcomes in RCTs in ICU patients,<sup>7</sup> and there is increasing interest in other patient-important outcomes.<sup>8</sup>

Outcomes such as the proportion of ventilator-free days have previously been suggested,<sup>9</sup> and during the coronavirus disease 2019 (COVID-19) pandemic, several RCTs have used the number of days alive without different life supportive measures as the primary outcome.<sup>10-12</sup> Similar outcomes have previously been used in RCTs in the critically ill, however, often only as secondary outcomes.<sup>1,2,13-18</sup> These outcomes not only include mortality, but also measure ICU/hospital/healthcare resource use. In addition, longer hospital stays or longer periods on life support may be associated with worse longer-term outcomes and are thus likely patient-important as well. During the COVID-19 pandemic, there has been increased focus on other non-mortality outcomes, and the World Health Organisation (WHO) has recommended use of not only mortality, but also of an ordinal clinical outcome scale.<sup>19</sup>

Notwithstanding arguments in favour of patient-important outcomes other than mortality, these outcomes are often more difficult to operationalise and analyse<sup>7</sup> for at least four reasons. First, while several core outcome sets for specific populations of critically ill patients have been

developed, no such core outcome set exists for general ICU patients.<sup>20,21</sup> Thus, there is large variation in the choice of outcomes,<sup>1,2</sup> and definitions and handling of apparently similar outcomes often differ.<sup>22,23</sup> For example, days alive without life support or mechanical ventilation has been defined both as a total number of days and as a percentage of the total number of days alive.<sup>10-18</sup> Second, mortality can be operationalised differently: it can be a distinct outcome in a categorical encoding, the lowest value on a continuous scale, or even somewhere between the extreme values of continuous scales if some states are considered worse than dying, e.g. for health-related quality of life (HRQoL) schemes.<sup>10,12,17,23,24</sup> Worse, assessment of some patient-important outcomes is frequently limited to survivors only, which may bias results and hamper interpretation.<sup>25</sup> Third, the amount of missing data for longer-term outcomes is generally greater; this applies no less to patient-reported outcomes, including HRQoL, which are often collected with a substantial delay with respect to the index admission<sup>2</sup> and with missingness likely related to the actual outcome status.<sup>26</sup> Fourth, mortality is easy to analyse. Non-binary patient-important outcomes often have distributions that complicate analysis; consequently, different strategies including non-parametric methods, ordinal models, and multi-part models (e.g., zero-inflated, hurdle and mixture models) have been used or recommended,<sup>8,10,12,27-29</sup> each with different advantages and disadvantages.

In summary, the optimal choice, definition and operationalisation of patient-important outcomes other than all-cause mortality for RCTs in ICU populations remain unresolved, and practice varies greatly. We aim to conduct a scoping review focusing on the definition and operationalisation of patient-important outcomes other than mortality in recent RCTs conducted in adult ICU patients.

## Methods

This protocol has been prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P)<sup>30</sup> and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR)<sup>31</sup> statements (completed checklists available in the **supplement**). The protocol was submitted and accepted for publication prior to initiation of the scoping review.

### Context and research questions

This scoping review is conducted as part of the Intensive Care Platform Trial (INCEPT) research programme with the aim of informing outcome choices, definitions and statistical analysis plans for a future platform trial; however, the results of this scoping review will also be relevant for other RCTs in- and outside the ICU.

We aim to answer the following research questions:

- 1) Which patient-important outcomes other than mortality are used in recent RCTs conducted in adult ICU patients and how are they defined and prioritised?
- 2) Which assessment time points are used (e.g., in-hospital, 30-day, 90-day, 1-year, etc.), and is censoring/truncation/time-to-event considered?
- 3) What is the proportion of dead patients and how is death operationalised in the analyses?
- 4) What is the proportion of missing outcome data (not due to death) and how is this handled?
- 5) Which effect measures and statistical analyses/models are used?

### Search strategy and eligibility criteria

We will search for RCTs in 10 general and speciality journals: New England Journal of Medicine, JAMA, The Lancet, BMJ, The Lancet Respiratory Medicine, Intensive Care Medicine, American Journal of Respiratory and Critical Care Medicine, Chest, Critical Care Medicine, and Critical Care. The search will be conducted in PubMed and restricted to studies published from 2018 onward (online or in print). We will use the Cochrane Collaboration's highly sensitive search filter for RCTs;<sup>32</sup> the full search strategy is presented in the **supplement**.



We will include RCTs (including cluster- and quasi-RCTs but excluding cross-over-RCTs) conducted primarily in adult patients in the ICU. Adults will be defined as in the included RCTs; if no definition is provided or if an RCT includes both adult and non-adult patients, we will include it if the majority (>50%) of patients can reasonably be assumed to be  $\geq 18$  years of age based on available patient summary characteristics. We will include RCTs where the majority of patients were specified to be admitted to an ICU or similar high-dependency unit including critical care units and coronary care units. Additionally, we will assume that patients have been admitted to an ICU if they have received interventions typically restricted to the ICU (invasive mechanical ventilation, continuous use of vasopressors or inotropes, continuous renal replacement therapy, extracorporeal membrane oxygenation, etc.) and will include RCTs where the majority of patients can reasonably be assumed to be ICU patients based on available patient summary characteristics. We will exclude RCTs where the intervention primarily takes place outside the ICU, e.g., RCTs focusing on perioperative treatments, which may continue in the ICU but primarily takes place pre- or intraoperatively or primarily are assessing pre- or intraoperatively focused research questions, and RCTs randomising patients during ICU admission to post-ICU rehabilitation strategies or similar. Similarly, RCTs not reporting at least 1 patient-important outcome other than mortality (see definitions below) will be excluded. Only actual RCT reports will be included (including secondary publications reporting longer-term outcomes and similar); additional secondary, explorative or *post hoc* studies using data from RCTs and not primarily focused on the randomised treatment comparison will be excluded.

We will not search for RCTs elsewhere, but if an identified publication directly refers to other reports of results from the same RCT, these will be included and assessed in combination with the primary report as a single RCT. We will not include RCT protocol articles identified during the search or search trial registries, but we will use information from published protocols/trial registrations for included RCTs that directly refer to these. We do not plan to contact study authors for additional details. The search will be updated close to finalisation of the manuscript.

## **Outcomes**

The following patient-important outcomes other than mortality will be assessed:

1. “Days alive without...”-type outcomes: including days alive without life support, days alive without mechanical ventilation (often defined as “ventilator-free days”), days alive and out of hospital, etc.
2. HRQoL outcomes: any tool assessing HRQoL at or after ICU discharge.
3. Functional (including physical function)/cognitive/neurological outcomes, including frailty, dependency status and location-based outcomes if reported (e.g., number of patients in nursing homes, etc.) at or after ICU discharge.
4. Other relevant patient-outcomes, including ordinal outcomes similar to the previously mentioned WHO ordinal scale.<sup>19</sup>

These categories are partly based on the definition on Gaudry and colleagues;<sup>2</sup> their definition does not include “days alive without...”-type outcomes. Instead, they comment on outcomes such as duration of ventilation and do not consider this outcome patient-important. In this scoping review, we consider “days alive without...”-type outcomes to be patient-important, as long as they assess the duration during which the patient is out of the hospital or free of certain interventions, as they can be considered composite outcomes including both mortality and setting or status of the patient. We assume that most patients prefer being free of highly invasive treatments and prefer being at home compared to at the hospital. We do not include similar outcomes that solely focus on the *duration* of treatments/hospital/ICU admission, etc., without considering mortality as patients who die early may then appear to have favourable outcomes (e.g., shorter ICU length of stay for patients that die early). If death is considered by assigning dead patients the worst possible value or similar, these outcomes will be eligible. We will only include outcomes applicable to general ICU populations and not outcomes only relevant for specific diseases or subsets of patients. Relevant outcomes will be included regardless of the data collection method (self-reported, interview, cognitive testing, etc.). Similar outcomes assessed at multiple time points will be considered separate outcomes. Of note, while mortality is certainly patient-important, it is not included in this review, as there is less uncertainty about how it should be measured and analysed.

## Study selection

We will use Covidence ([www.covidence.org](http://www.covidence.org)) for study selection. Titles and abstracts of identified

studies will be assessed independently and in duplicate; potentially eligible studies will similarly be assessed in full-text independently and in duplicate. Any disagreements will be resolved by discussion and, if necessary, by involvement of a third author.

### **Data extraction**

Data extraction will be performed independently and in duplicate. The following data will be extracted from each included RCT: digital object identifier, journal, author/trial acronym, year, countries included, number of centres, number of patients, intervention types (drug/management/medical device, as previously defined<sup>33,34</sup>), interventions, full protocol available and included with/referenced in publication (yes/no); and for each outcome, the outcome, definition/tool used, outcome prioritisation ((co-)primary outcome (yes/no)), prioritisation of outcomes containing multiple components (e.g., HRQoL-tools consisting of multiple domains), assessment time points including censoring/truncation/time-to-event, proportion of dead patients, operationalisation of death, missing data proportion and handling, effect measure(s) used and statistical analysis used. Data will be extracted using a standardised spreadsheet form (**supplement**); the form will be pilot tested on the first 10 studies by at least two authors and revised as necessary before data is extracted for the remaining studies.

### **Data synthesis**

We will summarise data using descriptive statistics (medians with interquartile ranges (IQRs) for numeric data, numbers and percentages for categorical data), and present separate data according to intervention types and outcome types. No assessment of risk of bias or certainty of evidence will be conducted, as this is not relevant for this scoping review.<sup>31</sup>

### **Ethics and dissemination**

No ethics approval is required as only data already available in the public domain are collected and summarised. The results of this scoping review will be reported in an international peer-reviewed journal regardless of findings. If any protocol amendments or deviations are necessary, they will be described with reasonings in the final report.

## Discussion

The outlined scoping review will provide important insights into the choices, definitions and operationalisation of patient-important outcomes other than mortality in contemporary ICU RCTs. This will help inform outcome selection and handling in future RCTs in- and outside the ICU. It will also provide an overview of the different statistical approaches to these outcomes, allowing direct comparison of methods using actual and simulated RCT data.

The outlined scoping review comes with several strengths, including adherence to recommendations for conducting systematic- and scoping reviews<sup>30,31</sup> and publication of the protocol prior to commencement. The outlined project comes with limitations, too. First, the search is limited in time and to 4 high-impact general journals and 6 high-impact speciality journals, which might exclude potentially relevant RCTs. The restriction to select journals limits the number of irrelevant hits and, along with the limited temporal scope, ensures that results are representative for contemporary practice. Second, our definition of patient-important outcomes does not completely match the previous definition of patient-important outcomes in critically ill patients by Gaudry and colleagues.<sup>2</sup> The primary discrepancy is due to our expanding the definition to include “days alive...”-type outcomes; these outcomes are frequently used, and although they may not be as patient-important as mortality or HRQoL, we believe that they are relevant for most patients. Of note, “days at home” has previously been evaluated as a patient-important outcome in surgical patients.<sup>35</sup> Further, these outcomes can be considered composite outcomes also including mortality, which is generally considered patient-important.<sup>2</sup> Third, we focus on the most central questions related to definitions and handling of these outcomes; additional details could be relevant, and some of these are currently being assessed for HRQoL-outcomes for a longer time period in a separate systematic review.<sup>26</sup>

In conclusion, the outlined scoping review will provide an overview of contemporary choices, definitions and handling of patient-important outcomes other than mortality in contemporary RCTs conducted in adult ICU patients. This may guide discussions with patients and relatives and help inform planning, execution and analysis of future RCTs and other research on optimal outcome choice and handling.

**Authors' contributions:** Study design: all authors. Drafting of protocol: AG. Revision of protocol for critically important intellectual content: all authors. Guarantor: MHM. All authors approved the final version of the protocol.

**Conflicts of interest:** The Department of Intensive Care at Rigshospitalet has received funding for other projects from The Novo Nordisk Foundation, Pfizer, Ferring and Fresenius Kabi.

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