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# The use of adaptive analysis for late phase randomised controlled trials in intensive care with mortality outcomes

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## Introduction

Randomised controlled trials (RCTs) in intensive care settings that use mortality as the primary endpoint and include heterogeneous populations require large sample sizes (1,2).

Adaptive trials that undertake interim monitoring may identify futility or efficacy with smaller sample sizes, and be especially valuable for trials in Intensive Care.

We undertook a systematic review to ascertain:

- **how frequently and when adaptive designs are being used for large-scale intensive care trials,**
- **what adaptive elements do they include,**
- **what statistical methods are employed in ongoing monitoring.**

## Methods

We searched for RCTs published between **January 2017** and **December 2021**, using electronic databases, including **MEDLINE (via Ovid), Embase (via Ovid), Web of Science and Scopus,** using the following terms:

1) "randomized controlled trial" (2) "intensive care"; (3)" intensive care unit"; (4) "critical illness" (5) "mortality" and (6) "survival".

Included studies were RCTs of patients managed in a critical care unit using any clinical treatments with mortality as a primary outcome. We excluded:

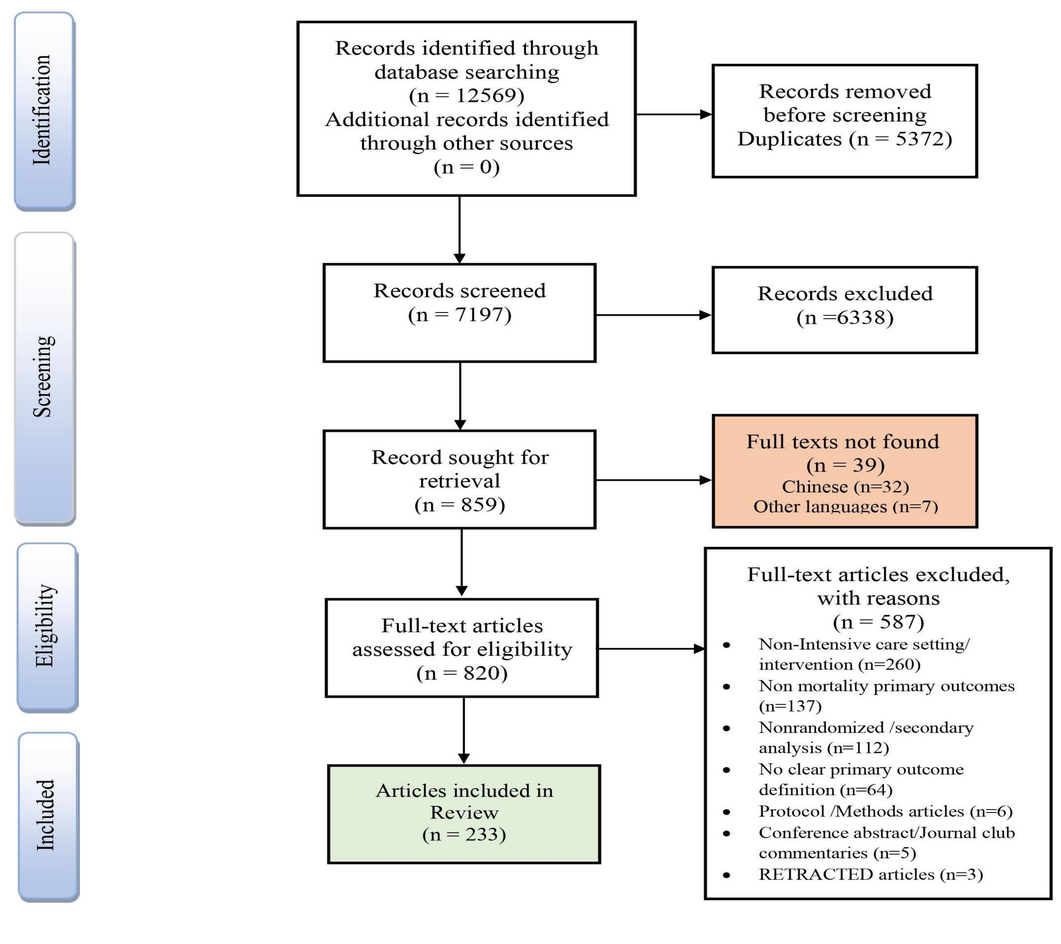
- Cluster-randomised trials including, stepped wedge designs
- Pilot and feasibility trials
- Behavioural & psychological treatments

Screening was done independently by two authors using COVIDENCE. Any disagreements were resolved by consensus or through arbitration by a third reviewer where necessary.

## Results

The search identified **12,569** records. After removing duplicates, **7197** records were imported to COVIDENCE for screening. **859** articles were sought for retrieval, of which full texts were not available for **39** records. **820** full texts were assessed for eligibility, **233** of which met our inclusion criteria and were included in our review [**Figure 1**].

Figure 1) PRISMA follow diagram




**Data extraction is ongoing, but a number of challenges have been encountered whilst undertaking this review, including:**

a. We aimed to include trials with mortality as a primary outcome but found many scales and assessment tools where death is included as a composite outcome.

b. We found many trials in which the primary outcome was not clearly defined.

c. It is challenging to distinguish Emergency and general Surgical settings from Intensive Care settings.

d. In COVID-19 trials, a mixed population of moderate, severe and critical patients were included, which made it difficult to clearly identify the population and setting.

**After data extraction is complete, we will report the following:**

- Trial and population characteristics, type of intervention and disease
- The array of adaptive designs used, including the types of adaptive elements, number and type of interim monitoring with statistical methods used
- The proportion of trials stopped early with reasons, the planned and actual sample size, proportion and type of trials with adaptive designs by pandemic status (before and during the pandemic).

**For further information please scan the QR code.**

## Potential Relevance & Impact

During the COVID-19 pandemic, the adaptive design framework provided flexibility to critical care treatment trials in order to obtain timely results.

Adaptive trials that undertake ongoing monitoring offer an opportunity to identify futility or efficacy with smaller sample sizes and thus improve the efficiency of clinical trials in intensive care. **We need to understand how often and how well they are being used.**

1. Harhay MO, Wagner J, Ratcliffe SJ, Bronheim RS. et al. Outcomes and statistical power in adult critical care randomized trials. Am J Respir Crit Care Med. 189(12) 2014.
2. François, B., Clavel, M., Vignon, P. et al. Perspective on optimizing clinical trials in critical care: how to puzzle out recurrent failures. j intensive care 4: 67 2016.

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