Observed intervention effects for mortality in randomised clinical trials

a methodological study protocol

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Mathias Lühr Hansen ,[1,2] Caroline Kamp Jørgensen ,[2,3] Lehana Thabane ,[4,5] Eliana Rulli,[6] Elena Biagioli,[6] Maria Chiaruttini,[6] Lawrence Mbuagbaw ,[4,7] Ole Mathiesen,[8,9] Christian Gluud,[2,3] Janus Christian Jakobsen[2,3]

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For numbered affiliations see end of article.

Correspondence to
Dr Mathias Lühr Hansen; mathias.luehr.hansen@regionh.dk

ABSTRACT

Introduction It is essential to choose a realistic anticipated intervention effect when calculating a sample size for a randomised clinical trial. Unfortunately, anticipated intervention effects are often inflated, when compared with the 'true' intervention effects. This is documented for mortality in critical care trials. A similar pattern might exist across different medical specialties. This study aims to estimate the range of observed intervention effects for all-cause mortality in trials included in Cochrane Reviews, within each Cochrane Review Group.

Methods and analysis We will include randomised clinical trials assessing all-cause mortality as an outcome. Trials will be identified from Cochrane Reviews published in the Cochrane Database of Systematic Reviews. Cochrane Reviews will be clustered according to the registered Cochrane Review Group (eg, Anaesthesia, Emergency and Critical Care) and the statistical analyses will be conducted for each Cochrane Review Group and overall. The median relative risk and IQR for all-cause mortality and the proportion of trials with a relative all-cause mortality risk within seven different ranges will be reported (relative risk below 0.70, 0.70–0.79, 0.80–0.89, 0.90–1.09, 1.10–1.19, 1.20–1.30 and above 1.30). Subgroup analyses will explore the effects of original design, sample size, risk of bias, disease, intervention type, follow-up length, participating centres, funding type, information size and outcome hierarchy.

Ethics and dissemination Since we will use summary data from trials already approved by relevant ethical committees, this study does not require ethical approval. Regardless of our findings, the results will be published in an international peer-reviewed journal.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The design of this methodological study will rely on the principles of the published tutorial for the development of the Methodologlcal STudy reportlng Checklist.
⇒ A detailed description of the independent literature search and data extraction is presented in this protocol.
⇒ A detailed predefined statistical analysis plan including relevant subgroup analyses is described.
⇒ As trials reporting beneficial effects of interventions are more likely to be published, mortality estimates from our analyses will likely be exaggerated.
⇒ As data are extracted directly from the Cochrane Reviews instead of the trial publication, we will rely on the correctness of the Cochrane review authors' data extraction.

INTRODUCTION

Sample size and power estimations are pivotal elements when planning and designing randomised clinical trials.[1 2] To calculate a sample size, it is necessary to quantify an anticipated intervention effect. Large, anticipated intervention effects lead to relatively small sample sizes and small anticipated intervention effects lead to relatively large sample sizes. Different methods to estimate anticipated intervention effects are available, as described in the Difference ELicitation in TriAls reviews.[3 4] Anticipated intervention effects may be estimated based on what a minimal important difference would be, but this approach is problematic when assessing binary patient important outcomes such as mortality, where every event seems clinically important. A commonly used alternative approach is to estimate the anticipated intervention effect based on previous evidence, such as previous trial results or pilot trials, that is, estimate anticipated *realistic* intervention effects.[3 5 6] However, quantifications of intervention effects within most medical specialties have not previously been systematically assessed. It is problematic if the anticipated intervention effects are unrealistically large: (1) the sample sizes will be insufficient to detect smaller but more realistic intervention effects, even if still clinically relevant. This could potentially lead to false negative conclusions regarding the interventions' potential benefits[7]; (2) there is an increased

risk of showing misleading spurious intervention effects if too large intervention effects are anticipated[8–10]; and (3) relatively small randomised trials may not secure proper randomisation with good balance between the intervention groups of all important prognostic factors.[11] On the other hand, unrealistically small, anticipated intervention effects will lead to unnecessary large sample sizes and thereby excessive randomisations, which is unethical and a misuse of participants and resources.[12] Moreover, such 'overpowered' trials run the risks to demonstrate 'significant' findings of small irrelevant intervention effects.[13 14] If at all possible, quantifications of anticipated intervention effects that are far from the 'true' effect should be avoided.

Mortality is a frequently used and patient-relevant outcome in randomised clinical trials within all medical specialties.[15–17] Inflated, anticipated intervention effects for mortality are already well documented in critical care trials.[18 19] It is likely that a similar trend exists across different medical specialties. Knowledge on observed intervention effects for mortality within different medical specialties could aid trialists in choosing realistic anticipated intervention effects in the trial design phase. Such knowledge could also be used by funding agencies to determine whether an anticipated intervention effect for a proposed trial is realistic.

METHODS AND ANALYSIS

Aim

The aim of this methodological study is to estimate the range of observed intervention effects for all-cause mortality in randomised clinical trials included in Cochrane Reviews within each Cochrane Review Group and overall.[20] Additionally, we will conduct subgroup analyses to explore the effects of various methodological factors on the observed intervention effects for all-cause mortality.

Study design

We will conduct a descriptive, cross-sectional, methodological study. According to our knowledge, no sufficient reporting guidelines are available yet for methodological studies or adjacent protocols. Authors of the protocol for the development of the MethodologIcal STudy reportIng Checklist, a work-in-progress reporting checklist for methodological studies,[21] have published a tutorial that provides an overview of the key aspects of methodological studies.[22] The design and conduct of this methodological study rely on the principles from this tutorial.[22]

Eligibility criteria

Cochrane Reviews and randomised clinical trials will be selected according to the criteria below.

Types of studies

We will include randomised clinical trials, included in Cochrane Reviews from inception and until the date of the literature search.[20] Cochrane Reviews will be identified by using the search string described below under 'search strategy'. A Cochrane Review is considered eligible, if it includes at least one randomised clinical trial reporting on all-cause mortality. Eligible trials in the Cochrane Reviews must either assess all-cause mortality as a separate outcome or as part of a composite outcome where the number of participants and mortality events in both intervention groups are reported separately. Trials of factorial design will be included as well, but each separate comparison will be considered as one trial in the data analyses. Cluster randomised trials will not be included, as the unit of intervention and analysis method differs from ordinary randomised trials.[23] Cross-over randomised trials will not be included, as the design is inappropriate when measuring longer-term outcomes such as mortality.[23] Adaptive randomised trials will not be included, as the number of intervention groups or the sample size is modifiable during the trial conduct.[24] Quasirandomised studies will not be included due to their lack of random group assignment.[25]

Types of participants

We will include participants of all ages, irrespectively of comorbidities and sex.

Types of interventions

We will include randomised clinical trials evaluating all types of interventions, including complex interventions.[26] The type of intervention will be noted for all included trials and categorised as below:

- Drug.
- Medical device.
- Surgical procedure.
- Complex intervention.
- Other interventions.

Outcomes

The primary and sole outcome in this methodological study is all-cause mortality at longest follow-up, as reported in the Cochrane Review. Thus, if more than one mortality outcome is reported for a meta-analysis within the Cochrane Review, we will extract data based on the mortality outcome with the longest follow-up (eg, death up until 30 days from discharge will be prioritised over death before discharge).

Search strategy

Within each Cochrane Review Group, we will identify potentially eligible Cochrane Reviews by conducting a systematic search in the Cochrane Database of Systematic Reviews (https://www.cochranelibrary.com/advanced-search). The search string will be as follows: "Title Abstract Keyword: 'mortality' or 'death' or 'survival'" and will include 'search word variations'. The following search limits will be imposed: 'Cochrane reviews', 'all dates', 'all years'.

Data collection and analysis

Selection of studies

Within each Cochrane Review Group, all identified Cochrane Reviews will be uploaded to EndNote (Clarivate, Philadelphia, Pennsylvania, USA) and duplicates will be removed. Two authors will independently screen titles and abstracts of identified reviews. If necessary, the full Cochrane Review reports will be assessed for eligibility. If disagreement between the two authors regarding eligibility of a Cochrane Review, a third author will be presented to the disagreement and make a final decision regarding inclusion or exclusion of the Cochrane Review. Once the eligible Cochrane Reviews have been identified, trials published in the Cochrane Reviews will be assessed for eligibility according to the eligibility criteria defined in this protocol.

For each Cochrane Review Group, a flowchart of the literature search and study selection, including reasons for ineligibility, will be completed and included with the publication of the results. The flowchart will be based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.[27]

Data extraction and management

For each eligible trial, the following data will be extracted directly from the Cochrane Reviews:

1. Trial characteristics: Cochrane Review Group, Cochrane Review title, trial authors and year of publication, original design (superiority, non-inferiority or equivalence trial design), industry funding or conflicts of interest (yes or no) as evaluated and reported by the Cochrane authors, number of participating centres (total number and categorised as 1 centre; 2–4 centres; less than 5 centres; 5–10 centres; or more than 10 centres), sample size (total number of participants and categorised as trials with less than 50 participants; 50–200 participants; or more than 200 participants), intervention type (specific intervention and categorised as drug; medical device; surgical procedure; complex intervention; or other interventions), disease area (specific disease area), factorial design (yes or no), method for risk-of-bias assessment (RoB or RoB V.2), RoB (high; unclear or of some concerns; or low) as evaluated and reported by the Cochrane authors, follow-up time on all-cause mortality (number of days and categorised as 14 days of follow-up; from 14 to 60 days of follow-up; from 61 to 90 days of follow-up; or more than 90 days follow-up), all-cause mortality as the primary outcome (yes or no), method ascertaining and validating death (eg, registry data, clinical records, direct contacts with relatives).
2. Results: observed intervention effect for mortality (in relative risk, odds ratio, hazard ratio etc with 95% CIs), number of participants in the experimental group in the mortality analysis (n), number of mortality events in the experimental group in the mortality analysis (n), number of participants in the control group in the mortality analysis (n), number of mortality events in the control group in the chosen mortality analysis (n).

The data extraction will be conducted independently by two authors and entered into a specific data extraction form designed for this study. If any disagreements in data extractions between the two authors, a third author will make the final decision.

Assessment of RoB for all-cause mortality in the included studies

The RoB assessment conducted by the Cochrane authors and reported in the Cochrane Review will be used to determine the RoB for each trial.

Original RoB tool

If the Cochrane authors used the Cochrane Collaboration's original RoB tool[28] in the Cochrane Review, we will consider a trial to be at low RoB, if the authors have judged all domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, other bias) to be at low RoB. We will consider a trial to be at unclear RoB, if one or more domains have been judged as unclear RoB, but no domains judged as high RoB. We will consider a trial to be at high RoB if one or more domains have been judged as high RoB.

RoB V.2 tool

If the Cochrane authors used the Cochrane Collaboration's RoB V.2 tool, we will rely on the overall RoB judgement for the mortality outcome (low RoB, of some concerns or high RoB).[29]

Publication bias

To assess the risk of publication bias, we will create a funnel plot for all-cause mortality at longest follow-up including all eligible trials. The funnel plot will be visually inspected for asymmetry and the asymmetry will be evaluated by the Harbord test.[30]

Statistical analyses

The statistical analyses below will be conducted within each Cochrane Review Group. Thus, the analyses will be based on eligible trials from Cochrane Reviews within each Cochrane Review Group.

Primary analysis

In the primary analysis, we will estimate the median relative risk and IQR for all-cause mortality at longest follow-up. Additionally, we will present the median follow-up time and IQR in days for all-cause mortality at longest follow-up. Within each trial, the relative risk for all-cause mortality will be estimated based on the reported number of participants and number of mortality events in each arm (table 1).

Optimal information size

For each included trial, we will also calculate the 'optimal information size'. The calculation of the optimal

Table 1 Median relative risks and IQRs for all-cause mortality in the primary analysis and in subgroup analyses excluding disease area subgroups.

	n (%) of total included trials	Median relative risk and IQR
Primary analysis of all-cause mortality at the longest follow-up		
All trials		
Follow-up time		*
Subgroup analyses of all-cause mortality		
Original design		
Superiority		
Non-inferiority		
Equivalence		
Sample size of participants		
Less than 50		
50–200		
More than 200		
Risk of bias		
Low		
Unclear or of some concerns		
High		
Intervention type		
Drug		
Medical device		
Surgical procedure		
Complex intervention		
Other interventions		
Length of follow-up for all-cause mortality		
Less than 14 days		
14–60 days		
61–90 days		
More than 90 days		
Number of participating centres		
1		
2–4		
5–10		
More than 10		
Funding type		
Industry funded or conflicts of interest		
No industry funding and no conflicts of interest		
Optimal information size		
Less than 50% of the optimal information size		
50%–99% of the optimal information size		
More than 99% of the optimal information size		
Outcome hierarchy for all-cause mortality		
Defined as primary outcome		
Defined as any other outcome		

*Median days and IQR.
n, number of trials included in the analysis.

Table 2 Number and percentage of trials with a relative risk within seven different ranges.

Relative risk	Number and percentage of trials, n (%)
Below 0.70	
0.70–0.79	
0.80–0.89	
0.90–1.09	
1.10–1.19	
1.20–1.30	
Above 1.30	

information size will be based on the observed proportion of all-cause mortality events in the control group in the relevant Cochrane Review, a relative risk reduction of 25%, a 5% risk of type I error and a 20% risk of type 2 error.[31]

Secondary analyses

As secondary analyses, we will estimate the proportion of trials with a relative risk for all-cause mortality in the following ranges (table 2):

- Relative risk below 0.70.
- Relative risk between 0.70 and 0.79.
- Relative risk between 0.80 and 0.89.
- Relative risk between 0.90 and 1.09
- Relative risk between 1.10 and 1.19.
- Relative risk between 1.20 and 1.30.
- Relative risk above 1.30.

Subgroup analyses

Additionally, we will estimate the median relative risk with IQR for all-cause mortality in the following subgroups (tables 1 and 3):

1. Trials of superiority design, non-inferiority design or equivalence design.
2. Trials with less than 50 randomised participants, 50–200 randomised participants or more than 200 randomised participants.
3. Trials at low RoB, unclear RoB or of some concern or high RoB, as reported in the Cochrane Review.
4. Trials within specific disease areas (eg, abdominal surgery, cardiac surgery, orthopaedic surgery in Anaesthesia trials).
5. Trials evaluating a drug intervention, a medical device intervention, a surgical procedure, a complex intervention or other interventions.
6. Trials with less than 14 days of follow-up, from 14–60 days of follow-up, from 61–90 days of follow-up or more than 90 days follow-up on all-cause mortality.
7. Trials with only 1 centre, 2–4 centres, 5–10 centres or more than 10 centres.
8. Trials with less than 50% of the optimal information size, 50%–99% of the optimal information size or more than 99% of the optimal information size.
9. Trials where all-cause mortality is defined as the primary outcome or defined as any other outcome.
10. Trials with and without industry support or conflicts of interest, as reported in the Cochrane Review.
11. Trials published per decade.

Patient and public involvement statement

No patients involved.

DISCUSSION

This methodological study will provide important and clinically relevant information on the range of observed intervention effects for all-cause mortality in randomised clinical trials across different medical specialties. We believe this information can aid trialists in choosing a realistic, anticipated intervention effect when planning a randomised clinical trial. This will decrease the risk of initiating trials that are unable to detect smaller, but realistic and still clinically relevant, intervention effects.

The most important weakness of this methodological study is the risk of publication bias affecting our mortality estimates.[32] It is likely that trials reporting a 'positive result' (a beneficial effect) of the intervention are more likely to be published than trials reporting a 'neutral' or 'negative result' (no benefit).[33–35] Such publication bias skews the accrued literature towards benefit of interventions. In accumulated analyses of trial results, this may lead to exaggerated intervention effects. Therefore, it

Table 3 Median relative risks and interquartile ranges for all-cause mortality in subgroup analysis of trials within specific disease areas (examples on disease areas for the manuscript on the Cochrane Review Group 'Anaesthesia').

Disease area	n (%) of total included trials	Median relative risk and IQR
Abdominal surgery		
Cardiac surgery		
Abdominal aortic surgery		
Thoracic non-cardiac surgery		
Brain surgery		
Spinal surgery		
Orthopaedic surgery		
Gynaecological surgery		

is plausible that the mortality estimates from our analyses are larger than the 'true' intervention effects. To address this potential issue, we will create funnel plots and evaluate any asymmetry by visual inspection and the Harbord test.[30] In general, bias due to poor methodology can lead to an exaggeration of the intervention effect in single randomised clinical trials, which can also affect accumulated analyses.[15 36] To evaluate the effect of bias on our observed intervention effects for mortality, we will conduct subgroup analyses stratified per the RoB level of the trials. Extracting trial data directly from the Cochrane Reviews instead of the trial publication could also be identified as a methodological weakness, since we will rely on the correctness of the Cochrane Review authors' data extraction. However, Cochrane Reviews are based on solid methodology and data extraction is done by multiple persons to minimise random errors.[37] Therefore, we believe that the available data in the Cochrane Reviews can be trusted. Additionally, extracting data directly from Cochrane Reviews allows us to identify and extract data from a larger number of trials, than if each eligible trial ought to be identified in a systemic search from various databases (eg, PubMed, EMBASE), followed by data extraction from the trial publication. Thus, we can reach a larger sample size and greater statistical power in our mortality effect estimates in a shorter period. Cochrane reviews also include randomised clinical trials regardless of quality, sample size and 'news value'. This will give our observed mortality effect estimates a higher external validity and generalisability, than if the estimates were based on trial data from, for example, the top-five high impact journals. An alternative method to derive mortality data from randomised clinical trials is to extract data directly from the databases of regulating authorities, such as the US Food and Drug Administration Resources on Drugs and Devices and the European Union Drug Regulating Authorities Clinical Trials Database. This has been done for multiple disease entities in a previously published methodological study.[38] However, these databases do not include RoB assessments as opposed to the Cochrane Reviews and therefore, this methodology is not feasible for the purpose of our present study.

Even though this methodological study has weaknesses, we still believe that it will provide valuable information for trialists. With limited available funding for investigator-initiated trials,[39 40] it is important that trials succeeding in obtaining the necessary funding are based on sound methodology, including a sample size that is large enough to evaluate a realistic intervention effect with sufficient statistical power. In the future, it would be relevant to determine the range of observed intervention effects for various, frequently used trial outcomes.

ETHICS AND DISSEMINATION

Ethics

As this methodological study does not include any data from individual persons, ethical approval is not required.

DISSEMINATION

The results will be reported separately for each Cochrane Review group. Thus, we intend to write one manuscript for each Cochrane Review Group, starting with one manuscript for the Cochrane Review group 'Anaesthesia' followed by one manuscript for the Cochrane Review Group 'Emergency and Critical Care'. Once the results have been reported for each Cochrane Review groups, we intend to write a manuscript based on the results from the overall analysis including trials across each Cochrane Review group. Regardless of the findings, the results will be published in an international peer-reviewed journal. We plan to conduct the search and initiate data collection for the first study on the Cochrane Review Group 'Anaesthesia' by 1 September 2023. Expected date for submission of the adjacent manuscript is 1 December 2023.

Author affiliations
[1]Department of Neonatology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark
[2]Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark
[3]Department of Regional Health Research, The Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark
[4]Department of Health Research Methods, Evidence, and Impact, McMaster University, and St Joseph's Healthcare, Hamilton, Ontario, Canada
[5]Faculty of Health Sciences, University of Johannesburg, Johannesburg, South Africa
[6]Methodology for Clinical Research Laboratory, Oncology Department, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy
[7]Centre for Development of Best Practices in Health (CDBPH), Yaoundé Central Hospital, Yaoundé, Cameroon
[8]Department of Clinical Medicine, Copenhagen University, Copenhagen, Denmark
[9]Centre for Anaesthesiological Research, Department of Anaesthesiology, Zealand University Hospital, Køge, Denmark

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Competing interests None declared.

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ORCID iDs
Mathias Lühr Hansen http://orcid.org/0000-0003-1957-7005
Caroline Kamp Jørgensen http://orcid.org/0000-0002-7756-4694
Lehana Thabane http://orcid.org/0000-0003-0355-9734
Lawrence Mbuagbaw http://orcid.org/0000-0001-5855-5461

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