



# Interventions to reduce short term post-operative mortality in Low- and Middle-Income Countries: A Protocol for a systematic review of randomised controlled trials

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## Abstract

**Introduction:** Post-operative mortality is the third leading cause of death worldwide. Patients in low- and middle-income countries (LMIC) are at disproportionately increased risk, and it is likely that many deaths are avoidable and preventable. We aim to consolidate evidence on interventions tested in a randomised setting to reduce short term post-operative mortality following non-cardiac surgery in LMICs.

**Methods:** We will conduct a systematic review of all randomised controlled trials of interventions aimed at reducing short term post-operative mortality in Low- and Middle-Income countries. Short term mortality is defined as within 90 days of surgery. Trials will be included if they pertain to non-cardiac surgery in both elective and emergency settings and report mortality as their primary outcome. If trials are conducted across multiple countries, we will include them if we are able to extract the LMIC data separately. Our primary aim is to consolidate evidence on interventions tested in a randomised setting to reduce short term post-operative mortality. We will achieve this by several secondary outcomes which are to identify the number of RCTs of interventions tested in this context; describe the interventions, their components, and their timing on the patient pathway; the geographical location the trials were conducted and the adherence to the interventions. Finally, we will describe the impact on mortality of the interventions. Study selection will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Data on individual components of each intervention will be collected and thematically coded and grouped. We will use these groupings to map each intervention across the surgical pathway from the pre-operative phase and decision for surgery to postoperative rehabilitation. Formal ethical approval is not required as primary data will not be collected.

**Discussion:** Despite reductions in perioperative mortality globally in the last 50 years, post-operative mortality is the third leading cause of death, with 4.2 million people dying within 30 days of an operation each year. This systematic review will identify and discuss interventions tested in a randomised setting to reduce short-term post-operative mortality following non-cardiac surgery in LMICs. This will inform future trial design by identifying successful interventions or knowledge gaps in the patient pathway in which interventions have not been tested.

**Prospero registration number:** CRD42024604760

**Cite as:** Phelan, L. N., Sampaio-Alves, M., Agbeko, A. E., Haque, P. D., Zola, S., Nepogodiev, D., ... Glasbey, J. Interventions to reduce short term post-operative mortality in Low- and Middle-Income Countries: A Protocol for a Systematic Review of randomised controlled trials. *Impact Surgery*, 2(4), 134–138. <https://doi.org/10.62463/surgery.180>

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## Introduction

Mortality after surgery is the third leading cause of death worldwide<sup>1-3</sup>. It is recognised that patients in low- and middle-income countries (LMIC) are disproportionately affected, with two to three times increased risk of post-operative mortality (POM) compared to High Income countries (HIC)<sup>4, 5</sup>. Post-operative mortality is a complex, poorly understood area, but it is likely that many deaths after surgery in LMICs are avoidable and preventable.

The 2015 Lancet Commission for Global Surgery highlighted the increasing burden of morbidity and mortality of common surgical conditions in the world's poorest regions. Access to safe, timely and affordable surgical and anaesthetic care must be an integral part of national health systems to reduce premature death<sup>6</sup>.

Work has been done to try to reduce short term post-operative mortality. The most well-known intervention globally is likely the WHO Safer Surgery checklist. This is a complex perioperative intervention with multiple components which together contributed to a significant reduction in mortality and has been adopted by many centres globally<sup>7</sup>.

The FALCON trial assessed death after abdominal surgery in LMICs and showed almost three quarters were secondary to circulatory failure, with sepsis accounting for almost two-thirds. The variability of death highlighted opportunities to intervene along the patient's perioperative pathway to optimise outcomes<sup>8</sup>. ASOS-2 introduced a complex intervention to try to salvage patients who deteriorated post operatively. They highlighted complex interventions can be difficult to deliver and implement, particularly in resource limited settings and it is important to consider the fidelity of intervention implementation<sup>9</sup>.

The causal pathway for death is complex and likely multifactorial in origin. As such, it seems unlikely that a solitary intervention will make a colossal shift to reduce post-operative deaths in LMIC to offset the inequity in outcomes compared to high-income countries.

This systematic review will consolidate evidence on interventions that have been tested in a randomised setting within LMIC to reduce short term post-operative death and assess the success of their implementation. We hope that the information from this search will identify knowledge gaps which can be harnessed to support future trial design.

## Methods

### *Aims and Objectives*

Our primary aim is to consolidate evidence on interventions tested in a randomised setting to reduce short term post-operative mortality. We will achieve this by five specific aims to discuss the literature:

1. Identify the number of randomised controlled trials that have tested interventions to reduce short term post-operative mortality following non-cardiac surgery
2. Describe the interventions, their components, and their timing in the patient pathway
3. Assess the geographical location the trials were conducted
4. Assess the adherence to the interventions
5. Assess the impact on mortality of the described interventions

### *Inclusion criteria*

This review will include randomised trials that describe any intervention to reduce short term post-operative mortality as its primary aim. The intervention can be in any part of the patient pathway and data will be collected on the intervention key components and their timings. Patients can be of any age, gender or ethnicity and be undergoing non-cardiac surgery in either an elective or emergency setting. The studies must report short term mortality, defined as 90 days or less following the operation, as a primary outcome to be included. We will not include time limitations in our search criteria to ensure we find all relevant publications.

### *Exclusion criteria*

Studies reporting overall survival, progression free survival or disease-free survival as their primary outcome will be excluded. If the papers discuss both LMIC and high-income countries (HIC), these will be included providing we are able to separately extract the data that pertains to the LMIC only. Additionally, if an intervention has been discussed on both surgical and medical patients, we will include the data relevant to the surgical cohort if we are able to extract this from the paper in question separately. Papers comparing non-operative vs operative approaches will be excluded as the conservative group are not exposed to a surgical intervention. Endoscopic or luminal interventions in vasculature will be excluded (e.g., Transarterial Chemoembolisation, TACE) as they are not



deemed to be operations or surgery. We will include only randomised studies and therefore exclude observational studies, reviews, study protocols, abstracts, editorial, systematic reviews, meta-analyses and opinion pieces. Studies in animals will be excluded. The inclusion criteria are summarised in Table 1.

**Table 1: PICO Inclusion Criteria**

Populations	Patients undergoing non-cardiac surgery in Low- and Middle-Income Countries. All ages, genders, and ethnicity
Interventions	Interventions to reduce short term post-operative mortality (defined as 90 days or less) tested in a randomised setting
Comparators	Control group within each study
Outcomes	Impact on short term post-operative mortality (defined as 90 days or less) as a primary outcome

### Information sources

A comprehensive search will be conducted in PubMed, EMBASE via OVID, Science citation index and ESCI (Web of Science), Cochrane Library, Global Health (EBSCO) and the Virtual Health Library. The reference list of included publications will also be reviewed.

### Search strategy

The search strategy will incorporate a combination of population terms, condition terms, and geographic terms. An example of the proposed Pubmed search terms are summarised in Supplement 1.

### Data management

Search results and references will be stored and managed through a combination of EndNote, Microsoft Excel (Microsoft Office, Redmond, USA) and Covidence.

Data will be extracted from included studies and stored in a Microsoft Excel (Microsoft Office, Redmond, USA) document. Data will be extracted from the included studies using a data collection sheet that captures key information including study characteristics, population details, intervention details and outcomes. The results of these will be cross checked between independent reviewers. We will extract verbatim the individual components of included interventions and then in the synthesis and analysis stages thematically code and group these. Data will be extracted using a data collection sheet, included variables are listed in Table 2.

**Table 2: Data extraction plan**

Category	Variables to be extracted
Basic descriptive information	Author, year, country, publication reference World bank income rating of country
Participant characteristics	Age, gender Number of patients Speciality of surgery Timing of surgery – elective/emergency/both
Intervention characteristics	Extracted verbatim and later grouped into themes in the data synthesis/analysis stage
Outcomes	Primary outcome: Consolidate evidence on interventions tested in a randomised setting to reduce short term post-operative mortality. We will achieve this by five specific aims to discuss the literature: 1. Identify the number of randomised controlled trials that have tested interventions to reduce short term post-operative mortality following non-cardiac surgery. 2. Describe the interventions, their components, and their timing on the patient pathway. 3. Assess the geographical location the trials were conducted. 4. Assess the adherence to the interventions. 5. Assess the impact on mortality of the described interventions.



## **Selection process**

Two authors will independently review the results of the database search. Articles will be included or excluded following screening of their titles and abstracts. For any article where it is unclear from the title and abstract alone it will be carried forward into the full paper review process. The full papers of all included articles from the above process will be sourced and independently reviewed to ensure they meet the inclusion criteria. Following this the independent reviewers will meet to discuss all included articles to finalise inclusion. Any disputed articles will be reviewed by a third independent author who holds the final decision regarding inclusion. We will also review the reference list of included papers to assess for any that meet our inclusion criteria. The record selection process will be summarised in a PRISMA flowchart.

## **Outcomes and prioritisation**

Given the disproportionate increase in post-operative mortality in LMICs compared to HICs, our primary outcome is to consolidate evidence on interventions tested in a randomised setting to reduce short term post-operative mortality.

## **Risk of bias assessment**

The risk of bias will be assessed by two independent reviewers using Cochrane Risk of Bias tool 2 (ROB2) for assessment of randomised controlled trials. Discrepancies in assessments will be resolved through discussion with a third, senior reviewer.

## **Data synthesis**

After extraction of the individual components of the included interventions we will thematically code and group these. We will use these groupings to map each intervention strategy across the surgical pathway from the pre-operative phase and decision for surgery to postoperative rehabilitation. We will extract adherence data for the intervention and assess the implementation strategies used for the interventions. Finally, we will assess the impact on mortality of each of the tested interventions. In addition to the above, we will analyse subgroups based on urgency of surgery (planned/unplanned/both), World Bank Economic ranking (UMIC/LMIC/LIC/all) and indication for surgery (cancer/benign/trauma/all). We do not intend to conduct any meta-analyses.

## **Discussion**

Despite reductions in perioperative mortality globally in the last 50 years, post-operative mortality is the third leading cause of death, with 4.2 million people dying within 30 days of an operation each year<sup>2,3</sup>. Despite a lower risk profile and fewer complications, patients in LMIC are twice as likely to die after surgery than patients in High income countries (HIC)<sup>10</sup>. Some estimates suggest those in some LMICs have up to 100-fold increase in death after caesarean delivery and 40-fold increase following inguinal hernia repair or appendectomy compared to HIC<sup>11</sup>. While there have been some interventions that have proved successful in reducing surgical mortality globally, notably the WHO Safer Surgery checklist, little is known about what interventions have been designed and tested in LMIC to combat preventable post-operative mortality.

Death after surgery is complex and likely multifactorial in its causality. The WHO checklist is a complex perioperative intervention with multiple components which together contribute to a significant reduction in mortality (pre-intervention 1.5% vs post intervention 0.8%  $p=0.003$ )<sup>7</sup>. We intend to use key descriptors of the simple and complex interventions and explore the effective components of each intervention to assess its impact on death in our review.

Data shows an increase in postoperative mortality following cancer surgery in LMIC, which is not fully explained by patients presenting with later stages of disease, where failure to rescue may reduce preventable surgical deaths<sup>11</sup>. ASOS-2, conducted in 28 African countries, implemented a package of five interventions to enhance postoperative surveillance to identify the deteriorating surgical patient and therefore 'rescue' them. Although they did not demonstrate a significant reduction in post-operative mortality, they did highlight the complexities of introducing a complex intervention into clinical practice. Only 16.1% and 13.2% of high-risk patients received all five interventions in their package on day 0 and day 1 respectively<sup>9</sup>. We intend to explore the adherence to interventions in our review, its relation to reduction in post-operative mortality and methods of improving implementation of complex interventions.

We hope this systematic review highlights positive areas in the delivery of surgical care in LMIC, but also highlight knowledge gaps and periods of the patient pathway that are deficient in the implementation of interventions. This information will allow the design of future trials that seek to reduce death, particularly in high-risk surgical patients,



for example those undergoing emergency laparotomy. Additionally, the data could help support prospective studies aiming to understand the mechanisms of post-operative mortality.

**Funding:** This study was supported by NIHR Global Health Research Unit Grant (NIHR133364) and NIHR Green Group Grant (NIHR156087). The funders had no role in study design or writing of this report. The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR or the UK Department of Health and Social Care.

**Conflicts of interest:** The authors have no conflicts of interest to declare.

**GAIT statement<sup>1</sup> for Generative AI use:** Generative AI was used solely for minor language editing in this manuscript. No content generation, data analysis, or substantive rewriting was performed. The authors take full responsibility for the accuracy and integrity of the work.

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