## BMJ Open Defining clinically important perioperative blood loss and transfusion for the Standardised Endpoints for Perioperative Medicine (StEP) collaborative: a protocol for a scoping review

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#### **ABSTRACT**

**Introduction** 'Standardised Endpoints for Perioperative Medicine' (StEP) is an international collaboration undertaking development of consensus-based consistent definitions for endpoints in perioperative clinical trials. Inconsistency in endpoint definitions can make interpretation of trial results more difficult, especially if conflicting evidence is present. Furthermore, this inconsistency impedes evidence synthesis and metaanalyses. The goals of StEP are to harmonise definitions for clinically meaningful endpoints and specify standards for endpoint reporting in clinical trials. To help inform this endeavour, we aim to conduct a scoping review to systematically characterise the definitions of clinically important endpoints in the existing published literature on perioperative blood loss and transfusion.

Methods and analysis The scoping review will be conducted using the widely adopted framework developed by Arksey and O'Malley, with modifications from Levac. We refined our methods with guidance from research librarians as well as researchers and clinicians with content expertise. The electronic literature search will involve several databases including Medline, PubMednot-Medline and Embase. Our review has three objectives, namely to (1) identify definitions of significant blood loss and transfusion used in previously published large perioperative randomised trials; (2) identify previously developed consensus-based definitions for significant blood loss and transfusion in perioperative medicine and related fields; and (3) describe the association between different magnitudes of blood loss and transfusion with postoperative outcomes. The multistage review process for each question will involve two reviewers screening abstracts, reading full-text articles and performing data extraction. The abstracted data will be organised and subsequently analysed in an iterative process. Ethics and dissemination This scoping review of

the previously published literature does not require research ethics approval. The results will be used to inform a consensus-based process to develop definitions

#### Strengths and limitations of this study

- ► This scoping review will use established research methodology, incorporate an electronic database search strategy developed by an experienced research librarian and benefit from the guidance of a multidisciplinary expert panel.
- The results of the scoping review will directly inform an international multidisciplinary programme to develop comprehensive and standardised endpoint definitions for perioperative clinical trials.
- Limitations include the exclusion of the grey literature and non-English papers. To minimise the impact of these limitations, we will consult content experts to ensure that relevant articles are not missed.
- While the review excludes articles published prior to 2005, this exclusion criterion will help focus the study on more contemporary evidence pertaining to clinically significant perioperative blood loss and transfusion.

of clinically important perioperative blood loss and transfusion. The results of the scoping review will be published in a peer-reviewed scientific journal.

#### INTRODUCTION

Concerns about the heterogeneous and inadequate reporting of randomised controlled trials (RCT) have led to the development of consensus-based reporting standards, an example being the Consolidated Standards of Reporting Trials (CONSORT) 2010 Consensus statement. Subsequent adoption of CONSORT recommendations has been associated with improved clarity in the reporting of published trials.<sup>2</sup> Nonetheless, there still remains considerable heterogeneity





with respect to important aspects of RCT design, a key example being how endpoints are defined in individual trials. Considerable variation in the definitions of important endpoints, either individual or composite, can make it difficult for readers to draw conclusions, especially when faced with studies that assessed similar interventions but had conflicting results. Such heterogeneity can also render evidence synthesis problematic and unreliable.<sup>34</sup> Growing recognition of this problem has led to initiatives to better standardise endpoint definitions in clinical trials, a key example being the Core Outcomes Measures in Effectiveness Trials (COMET) Initiative.<sup>5</sup>

Significant blood loss and transfusion are clinically relevant and prognostically important events in perioperative care. They are often reported as primary efficacy, secondary efficacy or safety endpoints in RCTs of surgical patients. Nonetheless, even a cursory evaluation of the surgical or anaesthesiology literature reveals considerable between-trial heterogeneity with respect to the definitions of clinically important blood loss and transfusion; the clinical relevance and prognostic importance of these definitions; and the extent to which detailed information on blood loss and transfusion is collected.7-11 In other fields of medicine, methodological attention has been paid towards standardising the definition of important blood loss and transfusion. For example, the Bleeding Academic Research Consortium (BARC) was established in 2010 to standardise endpoint reporting in cardiovascular clinical trials.<sup>12</sup>

The 'Standardised Endpoints for Perioperative Medicine' (StEP) initiative is an international multidisciplinary programme with an overarching goal of developing comprehensive and standardised endpoint definitions for straightforward, clinically sensible and valid application to clinical trials in perioperative medicine. <sup>13</sup> The initiative will use methodology adapted from existing guideline task forces. 14-16 It is composed of a multidisciplinary range of experts, who are themselves organised into several endpoint-specific subgroups. Each subgroup will use a consensus-building process (eg, Delphi or nominal group methods) to define standardised definitions for endpoints within specific domains, such as cardiovascular or respiratory complications. The Blood Loss and Transfusion subgroup of StEP is composed of a range of content and methodology experts, including senior researchers with expertise in anaesthesiology, surgery, transfusion medicine, haematology, multicentre clinical trials and clinical epidemiology. The subgroup is tasked with developing standardised definitions for clinically significant blood loss or transfusion in the perioperative period. These definitions will be linked to recommendations regarding data collection in RCTs, such as how perioperative blood loss and blood product transfusion should be measured.

To establish a baseline and inform the consensus-based development of these standardised endpoint definitions, a systematic and thorough evaluation of the existing literature is critical. A scoping review is an ideal approach for achieving this objective. Specifically, scoping reviews are suited for mapping broad areas of the literature to gain an understanding of the extent, range and nature of research activity within a field.<sup>17–23</sup> As a prelude to developing consensus-based definitions for clinically significant perioperative blood loss and transfusion, we therefore plan to conduct a scoping review to answer three broad relevant questions:

- 1. What definitions for significant blood loss or transfusion have been previously successfully implemented in perioperative RCTs with reasonably large numbers of trial participants? Prior successful use in larger RCTs serves as supporting evidence showing the feasibility and practicability of implementing these endpoint definitions.
- What consensus-based definitions of significant blood loss or transfusion have been previously developed for application in perioperative medicine and related fields?
- 3. What is the association of different magnitudes of blood loss and transfusion with clinically important patient outcomes?

#### **METHODS AND ANALYSIS**

The scope of StEP encompasses perioperative medicine in adults, with perioperative medicine being defined as all aspects of anaesthesiology and perioperative care other than the surgical technique itself. Obstetrics, pain and critical care are included in contexts where they overlap with anaesthesiology and surgery. The aim of StEP is to harmonise standardised endpoints that can be used in clinical trials studying a range of interventions. With respect to the scope of work for the blood loss and transfusion subgroup of the StEP initiative, all endpoints within this domain that relate to blood loss and transfusion are of interest.

A thorough review of the existing literature is an important prerequisite for informing development of these consensus-based definitions. The overarching aim of this review is to answer the question 'What endpoints are currently used to measure blood loss and transfusion in the recent perioperative literature?' In conducting this scoping review, we will employ the widely used Arksey and O'Malley framework, with some modifications from Levac. <sup>21–23</sup>

In summary, all potentially relevant studies will be identified using a comprehensive electronic database search strategy that was developed with guidance from an experienced research librarian (ME) with expertise in scoping reviews. This list of relevant studies will be supplemented as needed by consulting content experts in the Blood Loss and Transfusion subgroup of StEP. Identification of the final pool of relevant studies will then be undertaken using a minimum two-step selection process involving two reviewers. Data from the final included studies will be collected and charted, and subsequently collated and summarised. The results of the scoping review will



#### Box 1 Research questions identified for scoping review

1. What endpoint definitions for significant blood loss and transfusion are currently used in perioperative randomised trials? *Population:* adults (≥18 years) participating in a randomised controlled trial with an overall study sample size ≥500 participants. These patients must have undergone surgical procedures, anaesthetic procedures, minimally invasive procedures or interventions offered as part of an admission to a surgical intensive care unit. To help ensure that the number of potentially relevant trials is maintained in a reasonable range, we will exclude trials focused on interventional cardiology and interventional radiology procedures.

*Intervention/comparators:* any intervention that justifies the inclusion of blood loss or transfusion as a study endpoint.

*Outcome:* the primary or secondary endpoint of the study should be significant blood loss or blood product transfusion.

# 2. What are the existing consensus definitions for significant blood loss or transfusion in perioperative medicine and related fields?

Population: adults (≥18 years) undergoing surgical procedures, anaesthetic procedures, minimally invasive procedures or interventions offered as part of an admission to a surgical intensive care unit. Interventional cardiology and interventional radiology procedures will be considered.

*Interventions or comparators:* any intervention that justifies the use of blood loss or transfusion as a study endpoint.

Study content requirement: the study must report a consensusbased definition for reporting blood loss or transfusion. Systematic reviews will be included to identify any cases where the authors who synthesised evidence adopted any established consensus definitions.

### 3. What elements of blood loss and transfusion are associated with clinically important patient outcomes?

Population: adults (≥18 years) included in a (prospective or retrospective) cohort study or randomised controlled trial. Relevant evidence synthesis, such as meta-analysis, can be included. These patients must have undergone a surgical procedure, anaesthetic, minimally invasive procedure or intervention offered as part of an admission to a surgical intensive care unit (most procedures conducted by interventional cardiology or interventional radiology will be excluded).

Exposure of interest: administration of blood products or blood loss. *Outcome:* any short-term postoperative (ie, within 30 days or less after surgery) outcome including complications (eg, myocardial infarction, stroke and acute kidney injury), death and hospital length of stay.

be reported to the StEP Blood Loss and Transfusion subgroup. The details of each step are presented below.

#### Stage 1: identifying the research questions

Our aims are to (1) provide an understanding of the current extent of the published literature in perioperative medicine where blood loss and transfusion were reported as endpoints, (2) map the types of definitions used and (3) understand the extent to which elements of existing definitions of blood loss and transfusion are related to other patient outcomes. For this review, 'transfusion' refers to transfusion of red blood cells, either in isolation or in combination with other blood components (eg, platelets and plasma). The details of the three questions are presented in box 1. With guidance of a research

librarian, we iteratively refined our electronic database search strategy to identify potentially relevant studies. To further categorise the identified studies into manageable subdomains, we subdivided our overarching search question into three components, namely identification of definitions of significant blood loss and transfusion used in perioperative randomised trials of significant size, identification of previously published consensus-based definitions of significant blood loss and transfusion in perioperative medicine and related fields, and identification of studies describing the dose-response association between different magnitudes of blood loss and transfusion with important short-term postoperative outcomes (ie, within 30 days or less after surgery). We defined trials of significant size a priori as those recruiting 500 or more participants. This threshold was selected because it has face validity, impacted the feasibility of the conducting the review and confirmed the practicability of implementing these endpoint definitions in clinical trials. In developing harmonised definitions of clinically significant blood loss and transfusion, we do not plan to include literature focused on the association of blood loss or transfusion with intermediate or long-term outcomes (ie, more than 30 days after surgery). Notably, perioperative blood loss and transfusion can plausibly have important intermediate and long-term effects on patients' health; however, most perioperative randomised trials focus on measuring the effects of interventions on shorter term outcomes, typically within 30 days after surgery. Hence, the demonstration of a dose-response association between different magnitudes of blood loss and transfusion with short-term postoperative outcomes will help support the criterion validity of any endpoint definition recommended by the StEP Blood Loss and Transfusion subgroup.

#### Stage 2: search strategy

Given the volume and extent of the literature addressing blood loss and transfusion in perioperative medicine, we will exclude the grey literature since it is highly likely that almost all relevant information is already captured by the indexed published literature. In addition, the literature search will be restricted to English-language articles published in a contemporary period, which is defined as 2005 onwards.

#### **Eligibility criteria for studies**

The prespecified inclusion and exclusion criteria are presented in table 1. These criteria were used to guide development of the electronic database search and help establish an initial abstract screening form.

#### **Databases**

The electronic databases to be searched are Medline, Medline In-Process, Embase, and PubMed-NOT-Medline.

#### Search strategy

The electronic search strategy was developed iteratively by a team of three authors (JB, ME and DNW) that included a research librarian. The primary search terms were



#### Table 1 Inclusion and exclusion criteria used to identify potentially relevant studies

#### Inclusion criteria

#### 1. Published in the English language

- 2. Published in a peer-reviewed journal
- 3. Human subjects
- 4. Publication date from 2005 onwards
- 5. Limited to adults (≥18 years)
- Research targeting patients undergoing surgery, anaesthetic procedures and minimally invasive interventions as well as patients who have been admitted to a postsurgical critical care unit

#### **Exclusion criteria**

 Journal articles that were not original research or systematic reviews (eg, case reports, case series, opinion pieces, commentaries or editorials)

focused on variations of blood loss and transfusion, with secondary search terms including various terms related to significant or clinically important bleeding. These terms were combined using Boolean operators with other terms to capture relevant fields (perioperative medicine and related fields), consensus-based endpoint definitions or postoperative outcomes. These search results were filtered to include English-language studies in adult humans from 2005 onwards. In iterative steps, we evaluated 200-400 abstracts identified by successive versions of this search strategy to determine if further refinement of the strategy was required. The final version of the search strategy is presented in the online supplementary appendix 1. Once the final search strategy is implemented, the results (after elimination of any duplicates) will be uploaded into DistillerSR (2016, Evidence Partners, Ottawa, Ontario, Canada) to facilitate further article screening and selection. This list of potentially relevant studies will be supplemented as needed by consulting content experts in the Blood Loss and Transfusion subgroup of StEP.

#### Stage 3: study selection

Study screening and selection will involve a multistage process with at least two reviewers. For questions 2 and 3, two reviewers (JB and LV) will conduct screening of titles or abstracts and full-text review of selected articles. All disagreements will be resolved by discussion and, where necessary, involvement of a third reviewer (DNW). Due to the large volume of potentially relevant articles identified for question 1, a modified study selection process will take place. In the first step, a single reviewer (JB) will screen abstracts to identify any potentially relevant studies. To maximise sensitivity in this additional first step, any study with uncertain relevance will be retained for consideration in the next screening stage. The remaining steps in the screening and selection process will be identical to those employed for questions 2 and 3. The full inclusion and exclusion criteria applied for each stage of study screening and evaluation are presented in table 2. A Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) flow diagram will be used to report the conduct of this search strategy.<sup>24</sup>

#### Stage 4: charting the data

An initial set of data categories to be abstracted are presented in table 2. These initial data categories were identified based on their relevance to the goals of the StEP initiative. Based on the types of interventions, outcomes and patient samples encountered in the abstract screening stages, these domains may be further refined. As with study selection, all data extraction will be performed by two reviewers (JB and LV). Their data extraction results will be compared, and any disagreements will be resolved through discussion or involvement of a third reviewer (DNW). We do not plan to contact study authors to obtain any further information or data that were not published in peer-reviewed manuscripts.

#### Stage 5: collating, summarising and reporting the Results

Once data extraction is completed, we will organise the included studies into categories that are meaningful for the StEP subgroup. For question 1, we will group the published literature by the categories of endpoint definitions used in existing trials, attempting to identify how endpoints used in published perioperative trials are related to existing consensus-based definitions of significant blood loss or transfusion. For question 2, we will organise consensus-based statements and guidelines based on the interventions and patient subgroups to which they were designed for application. For question 3, studies will be organised broadly based on how blood loss or transfusion were characterised (eg, presence of transfusion, changes in haemoglobin values and estimated surgical blood loss during the operation) and how these exposures were associated with patient outcomes. We will look for themes in how various predictors consistently relate to patient outcomes. 23 24 Interim reviews will be undertaken during the data processing to seek feedback from the StEP Blood Loss and Transfusion working group. Consultation with content experts in the working group will inform any required changes in the organisational structure used to classify the literature. Additionally, these content experts will help identify any relevant studies that were not initially identified in the electronic database search. Importantly, they will add insight into the relevance of the findings and which context the findings should be interpreted. 21-24 The final results will be reported using



Article	Inclusion criteria and data extraction fields by stage of article processing           Article         Inclusion criteria and domains to be extracted	ticle processing	
processing stage	Question 1	Question 2	Question 3
Initial title and abstract screen	<ul> <li>▶ Randomised controlled trials</li> <li>▶ Systematic reviews or meta-analyses will be excluded</li> </ul>	<ul> <li>▶ Research including adults</li> <li>▶ Consensus-based criteria or systematic review of clinical trials that included a prespecified definitions of major blood loss or transfusion as a study endpoint</li> </ul>	<ul> <li>▶ Evaluates dose-response association between transfusion or blood loss with patient outcomes</li> <li>▶ Surgical, anaesthesiology or perioperative disciplines only (obstetrics or trauma literature excluded)</li> </ul>
Second abstract screen and full- text evaluation	Second abstract ► Study design confirmed as randomised screen and full-controlled trial text evaluation ► Major blood loss or transfusion reported as an endpoint ► ≥500 participants ► ≥500 participants anaesthesiology or surgery	<ul> <li>▶ Consensus-based statement, guideline or recommendation for defining significant blood loss or transfusion endpoints</li> <li>▶ Systematic review or evidence synthesis that refers to a consensusbased definition of major blood loss or transfusion</li> </ul>	<ul> <li>Consensus-based statement, guideline or recommendation for defining significant blood loss or transfusion endpoints</li> <li>Systematic review or evidence synthesis that refers to a consensusbased definition of major blood loss or transfusion</li> <li>Study pertains to surgery, anaesthesiology or perioperative medicine</li> <li>Peports dose-response association between transfusion or blood loss or transfusion</li> </ul>
Data extraction	<ul> <li>Sample size</li> <li>Intervention and control being compared</li> <li>Endpoint definition for major blood loss or transfusion</li> </ul>	<ul> <li>Name of organisations and/or panels involved involved</li> <li>Definition of significant blood loss or transfusion</li> <li>Patient population to which definition applies</li> <li>Interventions to which definition applies</li> </ul>	<ul> <li>▶ Patient sample in which the outcome was measured</li> <li>▶ Type of study (eg, retrospective cohort study)</li> <li>▶ Number of patients included</li> <li>▶ Exposure definition and how it was measured (eg, &gt;500 mL blood loss identified from anaesthetic record)</li> <li>▶ Definition of outcome and how it was measured (eg, 30-day all-cause mortality)</li> </ul>



a framework similar to that used in prior scoping reviews applied to questions in critical care, anaesthesiology and health policy.  $^{17-24}$ 

#### **ETHICS AND DISSEMINATION**

As a scoping review of the previously published literature, this study does not require research ethics approval. The results of the scoping review will be presented at relevant national and international conferences as well as published in a peer-reviewed scientific journal. As indicated previously, we will use the results of this review to inform the StEP consensus-based process to develop definitions of clinically important perioperative blood loss and transfusion. The results of this consensus-based endpoint definition process will be published separately in a peer-reviewed scientific journal.

#### CONCLUSIONS

This protocol details the methodology for the conduct of a large comprehensive scoping review with the aim of informing the Blood Loss and Transfusion subgroup of StEP. This review will encompass a wide variety of research material, including observational studies, clinical trials and evidence synthesis. The methodology is further strengthened by continual feedback from stakeholders and content experts as well as early involvement of an experienced research librarian. As researchers and clinicians increasingly recognise the limitations of widely disparate endpoint definitions in clinical trials, we expect more collaborations to be formed within various fields to help standardise endpoint reporting. Scoping reviews, such as the one presented in this protocol, will be an integral part of the process to develop standardised, pragmatic and clinically relevant endpoint definitions for clinical trials.

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