

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



Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-016743
Article Type:	Protocol
Date Submitted by the Author:	07-Mar-2017
Complete List of Authors:	Bartoszko, Justyna; University of Toronto, Anesthesia Vorobeichik, Leon; University of Toronto, Anesthesia Jayarajah, Mohandas; Derriford Hospital, Anaesthesia Karkouti, K; Toronto General Hospital, University Health Network, University of Toronto, Anesthesia and Pain Management; University of Toronto Klein, Andrew; Papworth Hospital Lamy, Andre; McMaster University, Surgery Mazer, David; St. Michael's Hospital, Shuter Wing, Room 1-028e, 30 Bond Street, Toronto, Department of Anesthesia Murphy, Mike; John Radcliffe Hospital, NHS Blood and Transplant Richards, Toby; University College London, Division of Surgery & Interventional Surgery Englesakis, Marina; University Health Network, Library and Information Services Myles, Paul; Monash University, Anaesthesia and Perioperative Medicine; Monash University, Wijeyesundera, Duminda; St. Michael's Hospital, Li Ka Shing Knowledge Institute; Toronto General Hospital, University Health Network, University of Toronto, Anesthesia and Pain Management
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Surgery, Haematology (incl blood transfusion), Research methods
Keywords:	Clinical trials < THERAPEUTICS, Blood bank & transfusion medicine < HAEMATOLOGY, Blood loss, Anaesthesiology, Endpoints, Perioperative medicine

SCHOLARONE™
Manuscripts

Defining Clinically Important Perioperative Blood Loss and Transfusion for the Standardised Endpoints for Perioperative Medicine (StEP)

Collaborative: A Protocol for a Scoping Review

Justyna Bartoszko,¹ Leon Vorobeichik,¹ Mohandas Jayarajah,² Keyvan Karkouti,³ Andrew A. Klein,⁴ Andre Lamy,⁵ C. David Mazer,⁶ Mike Murphy,⁷ Toby Richards,⁸ Marina Englesakis,⁹ Paul S. Myles,¹⁰ Duminda N. Wijeyesundera¹¹

Author Affiliations

¹ University of Toronto; Toronto, Ontario, Canada

² Derriford Hospital; Plymouth, UK

³ Toronto General Hospital / University of Toronto; Toronto, Ontario, Canada

⁴ Papworth Hospital; Cambridge, UK

⁵ McMaster University; Hamilton, Ontario, Canada

⁶ St. Michael's Hospital / University of Toronto; Toronto, Ontario, Canada

⁷ Oxford University Hospitals / University of Oxford / NHS Blood & Transplant; Oxford, UK

⁸ University College London; London, UK

⁹ University Health Network; Toronto, Ontario, Canada

¹⁰ Alfred Hospital / Monash University; Melbourne, Victoria, Australia

¹¹ St. Michael's Hospital / Toronto General Hospital / University of Toronto; Toronto, Ontario, Canada

Version Date: 6 March 2017

Correspondence

Duminda N. Wijesundera, MD PhD

Li Ka Shing Knowledge Institute of St. Michael's Hospital

30 Bond Street, Toronto, Ontario, Canada M5B 1W8

Tel: 416-864-6060 (extension 7147)

Email: d.wijesundera@utoronto.ca

Word count (excluding title page, abstract, references, figures and tables)

2,248

Keywords

endpoints, clinical trials, anaesthesiology, perioperative medicine, transfusion, blood loss,
bleeding; surgery

Version Date: 6 March 2017

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 meta-analyses. 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, PubMed-not-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

Version Date: 6 March 2017

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

Version Date: 6 March 2017

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.

Version Date: 6 March 2017

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.¹ Subsequent adoption of CONSORT recommendations has been associated with improved clarity in the reporting of published trials.² 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.^{3,4} 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.⁵

Significant blood loss and transfusion are clinically relevant and prognostically important events in perioperative care.⁶ 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

Version Date: 6 March 2017

1
2
3 example, the Bleeding Academic Research Consortium (BARC) was established in 2010 to
4
5 standardise endpoint reporting in cardiovascular clinical trials.¹²
6
7

8 The 'Standardised Endpoints for Perioperative Medicine' (StEP) initiative is an
9
10 international multidisciplinary programme with an overarching goal of developing
11
12 comprehensive and standardised endpoint definitions for straightforward, clinically sensible and
13
14 valid application to clinical trials in perioperative medicine.¹³ The initiative will use
15
16 methodology adapted from existing guideline taskforces.¹⁴⁻¹⁶ It is comprised of a
17
18 multidisciplinary range of experts, who are themselves organised into several endpoint-specific
19
20 subgroups. Each subgroup will use a consensus-building process (e.g., Delphi or nominal group
21
22 methods) to define standardised definitions for endpoints within specific domains, such as
23
24 cardiovascular or respiratory complications. The Blood Loss and Transfusion subgroup of StEP
25
26 is composed of a range of content and methodology experts, including senior researchers with
27
28 expertise in anaesthesiology, surgery, transfusion medicine, haematology, multicentre clinical
29
30 trials, and clinical epidemiology. The subgroup is tasked with developing standardised
31
32 definitions for clinically significant blood loss or transfusion in the perioperative period. These
33
34 definitions will linked to recommendations regarding data collection in RCTs, such as how
35
36 perioperative blood loss and blood product transfusion should be measured.
37
38
39
40
41
42

43 To establish a baseline and inform the consensus-based development of these
44
45 standardised endpoint definitions, a systematic and thorough evaluation of the existing literature
46
47 is critical. A scoping review is an ideal approach for achieving this objective. Specifically,
48
49 scoping reviews are suited for mapping broad areas of the literature to gain an understanding of
50
51 the extent, range, and nature of research activity within a field.¹⁷⁻²³ As a prelude to developing
52
53
54
55
56
57
58
59
60

Version Date: 6 March 2017

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.
2. 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?

Version Date: 6 March 2017

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.¹⁴ 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.²¹⁻²³

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

Version Date: 6 March 2017

Stage 1: Identifying the Research Questions

Our aims are to (i) provide an understanding of the current extent of the published literature in perioperative medicine where blood loss and transfusion were reported as endpoints, (ii) map the types of definitions used, and (iii) 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 (e.g., platelets, plasma). The details of the three questions are presented in Table 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 sub-domains, 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 (i.e., 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 focussed on the association of blood loss or transfusion with intermediate- or long-term outcomes (i.e., more than 30-days after surgery).

Stage 2: Search Strategy

Version Date: 6 March 2017

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 pre-specified inclusion and exclusion criteria are presented in Table 2. 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, DNW) that included a research librarian. The primary search terms were 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 to 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 Appendix. Once the final search strategy is implemented, the results

Version Date: 6 March 2017

(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 multi-stage process with at least two reviewers. For Questions 2 and 3, two reviewers (JB, 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 3. A PRISMA flow diagram will be used to report the conduct of this search strategy.²⁴

Stage 4: Charting the Data

An initial set of data categories to be abstracted are presented in Table 3. These initial data categories were identified based on their relevance to the goals of the StEP initiative.¹⁴ 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, LV). Their data extraction results will be compared, and any

Version Date: 6 March 2017

disagreements 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 (e.g., presence of transfusion, changes in haemoglobin values, 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 a framework similar to that used in prior scoping reviews applied to questions in critical care, anaesthesiology, and health policy.¹⁷⁻²⁴

Version Date: 6 March 2017

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.

Version Date: 6 March 2017

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.

Version Date: 6 March 2017

REFERENCES

1. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
2. Plint AC, Moher D, Morrison A, *et al.* Does the CONSORT Checklist improve the quality of reports of randomized controlled trials? A systematic review. *Med J Aust* 2006;185:263-7.
3. Koreshetz W. A core set of trial outcomes for every medical discipline? *BMJ* 2015;350:h85.
4. Williamson PR, Altman DG, Blazeby JM, *et al.* Developing core outcome sets for clinical trials: issues to consider. *Trials* 2012;13:132.
5. Gorst SL, Altman DG, Blazeby JM, *et al.* COMET V Meeting Summary. *Trials* 2015;16(Suppl 3):A1.
6. Wu WC, Smith TS, Henderson WG, *et al.* Operative blood loss, blood transfusion, and 30-day mortality in older patients after noncardiac surgery. *Ann Surg* 2010;252:11-7.
7. Martin RCG, Brennan MF, Jaques DP. Quality of complication reporting in the surgical literature. *Ann Surg* 2002; 235: 803-13.
8. Rahbari NN, Garden OJ, Padbury R, *et al.* Post-hepatectomy hemorrhage: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *HPB (Oxford)* 2011;13:528-35.

Version Date: 6 March 2017

- 1
2
3 9. Wente MN, Veit JA, Bassi C, *et al.* Postpancreatectomy hemorrhage (PPH): an
4
5 International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery*
6
7 2007;142:20-5.
8
9
- 10 10. Opondo D, Gravas S, Joyce A, *et al.* Standardization of outcomes reporting in
11
12 percutaneous nephrolithotomy. *J Endourol* 2014;28:767-74.
13
14
- 15 11. Dyke C, Aronson S, Dietrich W, *et al.* Universal definition of perioperative bleeding in
16
17 adult cardiac surgery. *J Thorac Cardiovasc Surg* 2014; 147: 1458-63.
18
19
- 20 12. Mehran R, Rao S, Bhatt DL, for the Bleeding Academic Research Consortium.
21
22 Standardized bleeding definitions for cardiovascular clinical trials. *Circulation*
23
24 2011;123:2736-47.
25
26
- 27 13. Boney O, Moonesinghe SR, Myles PS, Grocott MPW. Standardizing endpoints in
28
29 perioperative research. *Can J Anaesth* 2016;63:159-68.
30
31
- 32 14. Myles PS, Grocott MP, Boney O, Moonesinghe SR, on behalf of the COMPAC-StEP
33
34 Group. Standardizing end points in perioperative trials: towards a core and extended
35
36 outcome set. *Br J Anaesth* 2016;116:586-9.
37
38
- 39 15. Prinsen CA, Vohra S, Rose MR, *et al.* Core Outcome Measures in Effectiveness Trials
40
41 (COMET) initiative: protocol for an international Delphi study to achieve consensus on
42
43 how to select outcome measurement instruments for outcomes included in a 'core
44
45 outcome set'. *Trials* 2014;15:247
46
47
- 48 16. Bellera CA, Pulido M, Gourgou S, *et al.* Protocol of the Definition for the Assessment of
49
50 Time-to-Event Endpoints in CANcer Trials (DATECAN) project: formal consensus
51
52 method for the development of guidelines for the standardized time-to-event endpoints'
53
54 definitions in cancer clinical trials. *Eur J Cancer* 2013;49:769-81.
55
56
57
58
59
60

Version Date: 6 March 2017

17. Brien SE, Lorenzetti DL, Lewis S, Kennedy J, Ghali WA. Overview of a formal scoping review on health system report cards. *Implement Sci* 2010;5:2.
18. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *Int J Evid Based Healthc* 2015; 13:141-6.
19. Duffett M, Choong K, Hartling L, *et al.* Randomized controlled trials in pediatric critical care: a scoping review. *Crit Care* 2013;17:R256.
20. Halas G, Schultz ASH, Rothney J, Goertzen L, Wener P, Katz A. A scoping review protocol to map the research foci trends in tobacco control over the last decade. *BMJ Open* 2015;5:e006643.
21. Arksey H, O'Malley L. Scoping Studies: Towards a methodological framework. *Int J Soc Res Methodol* 2005;8:19-32.
22. Levac D, Colquhoun H, O'Brein K. Scoping studies: advancing the methodology. *Implement Sci* 2010;5:69.
23. Daudt HML, van Mossel C, Scott SJ. Enhancing the scoping review methodology: a large, inter-professional team's experience with Arksey and O'Malley's framework. *BMC Med Res Methodol* 2013;13:48.
24. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic Reviews and meta analyses: the PRISMA Statement. *PLoS Med* 2009;6:e1000097.

Version Date: 6 March 2017

ACKNOWLEDGEMENTS

DNW and KK are supported in part by Merit Awards from the Department of Anesthesia at the University of Toronto. PSM is supported by an Australian National Health and Medical Research Council (NHMRC) Practitioner Fellowship. DNW is supported in part by a New Investigator Award from the Canadian Institutes of Health Research (CIHR).

For peer review only

Version Date: 6 March 2017

CONTRIBUTORS

1
2
3
4
5
6
7
8
9
10 JB, LV, ME, PSM and DNW contributed to the conception and design of the study. JB wrote the
11 first draft of the protocol. JB, LV, MJ, KK, AAK, AL, CDM, MFM, TR, ME, PSM, and DNW
12 revised the protocol critically for important intellectual content. DNW is the guarantor. All
13 authors have read and approved the final version of the manuscript to be published.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Version Date: 6 March 2017

FUNDING STATEMENT

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Version Date: 6 March 2017

COMPETING INTERESTS STATEMENT

AAK has received support for research and/or honoraria from Pharmacosmos, Vifor Pharma, CSL Behring, Brightwake Ltd and Fisher Paykel. TR has received support for research and/or honoraria from Pharmacosmos, Vifor Pharma, Acelity, and Libresse/Bodyform. TR is a director of the Iron Clinic Ltd (London, UK), director of Veincare London Ltd (London, UK), and Vascular Surgery lead for 18-Week Support Ltd (London, UK). The remaining authors have no competing interests or conflicts to declare.

Version Date: 6 March 2017

Table 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 focussed 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 consensus-based 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 (i.e., within 30 days or less after surgery) outcome including complications (e.g., myocardial infarction, stroke, acute kidney injury), death, and hospital length of stay

Version Date: 6 March 2017

Table 2. Inclusion and exclusion criteria used to identify potentially relevant studies

Inclusion Criteria	Exclusion Criteria
<ol style="list-style-type: none"> 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) 6.) Research targeting patients undergoing surgery, anaesthetic procedures, and minimally invasive interventions, as well as patients who have been admitted to a post-surgical critical care unit 	<ol style="list-style-type: none"> 1.) Journal articles that were not original research or systematic reviews (e.g., case reports, case series, opinion pieces, commentaries, or editorials)

Version Date: 6 March 2017

Table 3. Inclusion criteria and data extraction fields by stage of article processing

Article Processing Stage	Inclusion Criteria and Domains to be Extracted		
	Question 1	Question 2	Question 3
Initial Title and Abstract Screen	<ul style="list-style-type: none"> • Randomised controlled trials • Systematic reviews or meta-analyses will be excluded 	<ul style="list-style-type: none"> • Research including adults • Consensus-based criteria or systematic review of clinical trials that included a pre-specified definitions of major blood loss or transfusion as a study endpoint 	<ul style="list-style-type: none"> • Evaluates dose-response association between transfusion or blood loss with patient outcomes • Surgical, anaesthesiology or perioperative disciplines only (obstetrics or trauma literature excluded)
Second Abstract Screen and Full Text Evaluation	<ul style="list-style-type: none"> • Study design confirmed as randomised controlled trial • Major blood loss or transfusion reported as an endpoint • ≥ 500 participants • Within fields of perioperative medicine, anaesthesiology or surgery 	<ul style="list-style-type: none"> • Consensus-based statement, guideline, or recommendation for defining significant blood loss or transfusion endpoints • Systematic review or evidence synthesis that refers to a consensus-based definition of major blood loss or transfusion 	<ul style="list-style-type: none"> • Study pertains to surgery, anaesthesiology, or perioperative medicine • Reports dose-response association between transfusion or blood loss with patient outcomes
Data Extraction	<ul style="list-style-type: none"> • Sample size • Intervention and control being compared • Endpoint definition for major blood loss or transfusion 	<ul style="list-style-type: none"> • Name of organisations and/or panels involved • Definition of significant blood loss or transfusion • Patient 	<ul style="list-style-type: none"> • Patient sample in which the outcome was measured • Type of study (e.g., retrospective cohort study) • Number of patients included • Exposure

Version Date: 6 March 2017

		<p>population to which definition applies</p> <ul style="list-style-type: none"> • Interventions to which definition applies 	<p>definition and how it was measured (e.g., >500 mL blood loss identified from anaesthetic record)</p> <ul style="list-style-type: none"> • Definition of outcome and how it was measured (e.g., 30-day all-cause mortality)
--	--	---	---

For peer review only

Appendix

APPENDIX

A. Literature Search (Question 1)

The databases to be searched are:

- a. Medline
- b. Medline In-Process
- c. Embase
- d. Pubmed-NOT-Medline

(a) Medline Search Strategy

#	Search Terms
1	Blood Loss, Surgical/
2	Endotamponade/ [new MeSH as of 2011]
3	(blood loss* adj3 significan*).mp,kw.
4	(blood loss* adj3 substantial*).mp.
5	(blood loss* adj3 acute*).mp.
6	(blood loss* adj3 considerabl*).mp.
7	(blood loss* adj3 excess*).mp.
8	(blood loss* adj3 major).mp.
9	(blood loss* adj3 massive).mp.
10	(blood loss* adj5 serious*).mp.
11	(blood loss* adj3 (severe or severely)).mp.
12	(blood loss* adj3 appreciab*).mp.
13	(blood loss* adj3 greater than).mp.
14	(blood loss* adj3 ml).mp.
15	(blood lost adj3 significan*).mp.
16	(blood lost adj3 substantial*).mp.
17	(blood lost adj3 considerabl*).mp.
18	(blood lost adj3 excess*).mp.
19	(blood lost adj3 major).mp.
20	(blood lost adj3 massive).mp.
21	(blood lost adj3 serious*).mp.
22	(blood lost adj3 (severe or severely)).mp.
23	(blood lost adj3 greater than).mp.
24	(blood lost adj3 ml).mp.

Appendix

25	(bleed* adj3 significan*).mp.
26	(bleed* adj3 substantial*).mp.
27	(bleed* adj3 considerabl*).mp.
28	(bleed* adj3 acute*).mp.
29	(bleed* adj3 excess*).mp.
30	(bleed* adj3 major).mp.
31	(bleed* adj3 massive).mp.
32	(bleed* adj3 serious*).mp.
33	(bleed* adj3 (severe or severly)).mp.
34	(bleed* adj3 greater than).mp.
35	(bleed* adj3 ml).mp.
36	Hemorrhage/ and (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*).mp.
37	(h?emorrhag* adj3 (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*)).mp.
38	(massive adj3 transfusion?).mp,kw.
39	(massively adj3 transfuse?).mp,kw.
40	or/1-39 [Massive / Acute Blood Loss]
41	exp surgical procedures, operative/
42	su.fs.
43	exp perioperative care/
44	exp perioperative period/
45	intraop*.mp,kw.
46	intra-op*.mp,kw.
47	periop*.mp,kw.
48	operative*.mp,kw.
49	operation?.mp,kw.
50	(surgery or surgeries or surgical*).mp,kw.
51	Surgeon/
52	exp Specialties, Surgical/
53	Anesthesiology/
54	exp "Anesthesia and Analgesia"/
55	an?esth*.mp,kw.
56	or/41-55 [Surgery OR Perioperative OR Anesthesia]

Appendix

57	40 and 56
58	40 and 56 [** Massive Blood Loss + Sx/Periop/Anesth **]
59	limit 58 to english language
60	limit 59 to humans
61	limit 60 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")
62	limit 61 to yr="2005 -Current"
63	exp Randomized Controlled Trial/
64	exp Randomized Controlled Trials as Topic/
65	(pragmatic adj6 (trial or trials or study or studies)).mp,kw.
66	(randomi#ed adj6 (trial or trials or study or studies)).mp,kw.
67	or/63-66
68	62 and 67 [** Massive Blood Loss + Sx/Periop/Anesth + RCTs (w Limits) **]
69	remove duplicates from 68

(b) Medline In-Process Search Strategy

#	Search Terms
1	Blood Loss, Surgical/
2	Endotamponade/ [new MeSH as of 2011]
3	(blood loss* adj3 significan*).mp,kw.
4	(blood loss* adj3 substantial*).mp.
5	(blood loss* adj3 acute*).mp.
6	(blood loss* adj3 considerabl*).mp.
7	(blood loss* adj3 excess*).mp.
8	(blood loss* adj3 major).mp.
9	(blood loss* adj3 massive).mp.
10	(blood loss* adj5 serious*).mp.
11	(blood loss* adj3 (severe or severely)).mp.
12	(blood loss* adj3 appreciab*).mp.
13	(blood loss* adj3 greater than).mp.
14	(blood loss* adj3 ml).mp.
15	(blood lost adj3 significan*).mp.

Appendix

16	(blood lost adj3 substantial*).mp.
17	(blood lost adj3 considerabl*).mp.
18	(blood lost adj3 excess*).mp.
19	(blood lost adj3 major).mp.
20	(blood lost adj3 massive).mp.
21	(blood lost adj3 serious*).mp.
22	(blood lost adj3 (severe or severely)).mp.
23	(blood lost adj3 greater than).mp.
24	(blood lost adj3 ml).mp.
25	(bleed* adj3 significan*).mp.
26	(bleed* adj3 substantial*).mp.
27	(bleed* adj3 considerabl*).mp.
28	(bleed* adj3 acute*).mp.
29	(bleed* adj3 excess*).mp.
30	(bleed* adj3 major).mp.
31	(bleed* adj3 massive).mp.
32	(bleed* adj3 serious*).mp.
33	(bleed* adj3 (severe or severely)).mp.
34	(bleed* adj3 greater than).mp.
35	(bleed* adj3 ml).mp.
36	Hemorrhage/ and (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*).mp.
37	(h?emorrhag* adj3 (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*)).mp.
38	(massive adj3 transfusion?).mp,kw.
39	(massively adj3 transfuse?).mp,kw.
40	or/1-39 [Massive / Acute Blood Loss]
41	exp surgical procedures, operative/
42	su.fs.
43	exp perioperative care/
44	exp perioperative period/
45	intraop*.mp,kw.
46	intra-op*.mp,kw.

Appendix

47	periop*.mp,kw.
48	operative*.mp,kw.
49	operation?.mp,kw.
50	(surgery or surgeries or surgical*).mp,kw.
51	Surgeon/
52	exp Specialties, Surgical/
53	Anesthesiology/
54	exp "Anesthesia and Analgesia"/
55	an?esth*.mp,kw.
56	or/41-55 [Surgery OR Perioperative OR Anesthesia]
57	40 and 56 [** Massive Blood Loss + Sx/Periop/Anesth **]
58	exp Randomized Controlled Trial/
59	exp Randomized Controlled Trials as Topic/
60	(pragmatic adj6 (trial or trials or study or studies)).mp,kw.
61	(randomi#ed adj6 (trial or trials or study or studies)).mp,kw.
62	or/58-61
63	57 and 62
64	remove duplicates from 63
65	limit 64 to yr="2005 -Current"

(c) Embase Search Strategy

#	Search Terms
1	operative blood loss/
2	endotamponad*.mp,kw.
3	(blood loss* adj3 significan*).mp,kw.
4	(blood loss* adj3 substantial*).mp.
5	(blood loss* adj3 acute*).mp.
6	(blood loss* adj3 considerabl*).mp.
7	(blood loss* adj3 excess*).mp.
8	(blood loss* adj3 major).mp.
9	(blood loss* adj3 massive).mp.
10	(blood loss* adj5 serious*).mp.
11	(blood loss* adj3 (severe or severely)).mp.

Appendix

12	(blood loss* adj3 appreciab*).mp.
13	(blood loss* adj3 greater than).mp.
14	(blood loss* adj3 ml).mp.
15	(blood lost adj3 significan*).mp.
16	(blood lost adj3 substantial*).mp.
17	(blood lost adj3 considerabl*).mp.
18	(blood lost adj3 excess*).mp.
19	(blood lost adj3 major).mp.
20	(blood lost adj3 massive).mp.
21	(blood lost adj3 serious*).mp.
22	(blood lost adj3 (severe or severely)).mp.
23	(blood lost adj3 greater than).mp.
24	(blood lost adj3 ml).mp.
25	(bleed* adj3 significan*).mp.
26	(bleed* adj3 substantial*).mp.
27	(bleed* adj3 considerabl*).mp.
28	(bleed* adj3 acute*).mp.
29	(bleed* adj3 excess*).mp.
30	(bleed* adj3 major).mp.
31	(bleed* adj3 massive).mp.
32	(bleed* adj3 serious*).mp.
33	(bleed* adj3 (severe or severly)).mp.
34	(bleed* adj3 greater than).mp.
35	(bleed* adj3 ml).mp.
36	bleeding/ and (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*).mp.
37	(h?emorrhag* adj3 (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*)).mp.
38	(massive adj3 transfusion?).mp,kw.
39	(massively adj3 transfuse?).mp,kw.
40	or/1-39 [Massive / Acute Blood Loss]
41	exp surgery/
42	su.fs.
43	exp perioperative care/

Appendix

1	
2	
3	
4	44 exp perioperative period/
5	45 intraop*.mp,kw.
6	46 intra-op*.mp,kw.
7	47 periop*.mp,kw.
8	48 operative*.mp,kw.
9	49 operation?.mp,kw.
10	50 (surgery or surgeries or surgical*).mp,kw.
11	51 Surgeon/
12	52 anesthesiological procedure/
13	53 Anesthesiology/
14	54 exp anesthesia/
15	55 exp analgesia/
16	56 an?esth*.mp,kw.
17	57 or/41-56 [Surgery OR Perioperative OR Anesthesia]
18	58 40 and 57 [** Massive Blood Loss + Sx/Periop/Anesth **]
19	59 randomized controlled trial/
20	60 "randomized controlled trial (topic)"/
21	61 ct.fs. [Clinical Trial subheading]
22	62 (pragmatic adj6 (trial or trials or study or studies)).mp,kw.
23	63 (randomi#ed adj6 (trial or trials or study or studies)).mp,kw.
24	64 or/59-63
25	65 58 and 64 [** Massive Blood Loss + Sx/Periop/Anesth + RCTs**]
26	66 limit 65 to yr="2005 -Current"
27	67 limit 66 to human
28	68 limit 67 to english language
29	69 limit 68 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
30	70 68 not 69
31	71 limit 68 to (adult <18 to 64 years> or aged <65+ years>)
32	72 70 or 71
33	73 limit 72 to (book or book series or conference abstract or conference proceeding or "conference review")
34	74 72 not 73
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	
60	

Appendix

75	from 74 keep 1-4999
76	remove duplicates from 75
77	from 74 keep 5000-9331
78	remove duplicates from 77
79	76 or 78

(d) PubMed-NOT-Medline Search Strategy

Search	Query
#5	Search (((((((blood loss OR hemorrhage OR blood transfusion)) AND (hemoglobin OR hemoglobins OR haemoglobin OR haemoglobins))) AND (surgery OR surgeries OR surgical OR surgeon OR surgeons OR operation OR operations OR operative OR perioperative OR peroperative OR intraoperative OR anesthesia OR anaesthesia OR anesthesiology OR anaesthesiology OR anesthetic OR anesthetics))) AND (random OR randomly OR randomized OR randomised OR randomization OR randomisation OR pragmatic OR placebo OR placebos OR double-blind OR double-blinds OR double-blinded OR double-blinding))) NOT medline [sb] Sort by: PublicationDate
#4	Search medline [sb] Sort by: PublicationDate
#3	Search (((((((blood loss OR hemorrhage OR blood transfusion)) AND (hemoglobin OR hemoglobins OR haemoglobin OR haemoglobins))) AND (surgery OR surgeries OR surgical OR surgeon OR surgeons OR operation OR operations OR operative OR perioperative OR peroperative OR intraoperative OR anesthesia OR anaesthesia OR anesthesiology OR anaesthesiology OR anesthetic OR anesthetics))) AND (random OR randomly OR randomized OR randomised OR randomization OR randomisation OR pragmatic OR placebo OR placebos OR double-blind OR double-blinds OR double-blinded OR double-blinding) Sort by: PublicationDate
#2	Search random OR randomly OR randomized OR randomised OR randomization OR randomisation OR pragmatic OR placebo OR placebos OR double-blind OR double-blinds OR double-blinded OR double-blinding Sort by: PublicationDate
#1	Search (((((blood loss OR hemorrhage OR blood transfusion)) AND (hemoglobin OR hemoglobins OR haemoglobin OR haemoglobins))) AND (surgery OR surgeries OR surgical OR surgeon OR surgeons OR operation OR operations OR operative OR perioperative OR peroperative OR intraoperative OR anesthesia OR anaesthesia OR anesthesiology OR anaesthesiology OR anesthetic OR anesthetics) Sort by: PublicationDate

Appendix

B. Literature Search (Question 2)

The databases to be searched are:

- a. Medline

(a) Medline Search Strategy

#	Search Terms
1	Blood Loss, Surgical/
2	Endotamponade/ [new MeSH as of 2011]
3	(blood loss* adj3 significan*).mp,kw.
4	(blood loss* adj3 substantial*).mp.
5	(blood loss* adj3 acute*).mp.
6	(blood loss* adj3 considerabl*).mp.
7	(blood loss* adj3 excess*).mp.
8	(blood loss* adj3 major).mp.
9	(blood loss* adj3 massive).mp.
10	(blood loss* adj5 serious*).mp.
11	(blood loss* adj3 (severe or severely)).mp.
12	(blood loss* adj3 appreciab*).mp.
13	(blood loss* adj3 greater than).mp.
14	(blood loss* adj3 ml).mp.
15	(blood lost adj3 significan*).mp.
16	(blood lost adj3 substantial*).mp.
17	(blood lost adj3 considerabl*).mp.
18	(blood lost adj3 excess*).mp.
19	(blood lost adj3 major).mp.
20	(blood lost adj3 massive).mp.
21	(blood lost adj3 serious*).mp.
22	(blood lost adj3 (severe or severely)).mp.
23	(blood lost adj3 greater than).mp.
24	(blood lost adj3 ml).mp.
25	(bleed* adj3 significan*).mp.
26	(bleed* adj3 substantial*).mp.
27	(bleed* adj3 considerabl*).mp.
28	(bleed* adj3 acute*).mp.

Appendix

29	(bleed* adj3 excess*).mp.
30	(bleed* adj3 major).mp.
31	(bleed* adj3 massive).mp.
32	(bleed* adj3 serious*).mp.
33	(bleed* adj3 (severe or severely)).mp.
34	(bleed* adj3 greater than).mp.
35	(bleed* adj3 ml).mp.
36	Hemorrhage/ and (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*).mp.
37	(h?emorrhag* adj3 (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*)).mp.
38	(massive adj3 transfusion?).mp,kw.
39	(massively adj3 transfuse?).mp,kw.
40	bleed???.mp. and (definition or definitions or defined or define or defines).ab. /freq=2
41	(bleed??? and (definition or definitions or defined or define)).ti.
42	(bleed* adj6 (criteria or criterion)).mp,kw.
43	(bleed??? adj3 classifi*).mp,kw.
44	or/1-43 [Massive / Acute Blood Loss]
45	exp Consensus Development Conference/ or exp Consensus/
46	consensus.mp,kw.
47	exp Guideline/
48	exp Guidelines as Topic/
49	guideline?.mp,kw.
50	Clinical Protocols/
51	Critical Pathways/
52	protocol*.mp,kw.
53	((critical or clinical) adj2 pathway?).mp,kw.
54	Taskforce??.af.
55	Task force??.af.
56	(systematic adj3 (review or reviews or overview?)).mp,kw.
57	Meta-Analysis/
58	Meta-Analysis as Topic/
59	meta-anal*.mp,kw.
60	metaanal*.mp,kw.

Appendix

61	metanal*.mp,kw.
62	(practi#e adj1 parameter).mp,kw.
63	statement?.ti.
64	or/45-63 [Consensus or Guideline or Protocol or Taskforce or Systematic Review]
65	44 and 64 [Massive / Acute Blood Loss + Consensus or Guideline or Protocol or Taskforce or Systematic Review]
	<i>Limits applied:</i>
66	limit 65 to english language
67	limit 66 to humans
68	limit 67 to yr="2005 -Current"
69	remove duplicates from 68

Appendix

C. Literature Search (Question 3)**The databases to be searched are:**

- a. Medline
- b. Medline In-Process
- c. Embase
- d. Pubmed-NOT-Medline

(a) Medline Search Strategy

#	Search Terms
1	Blood Loss, Surgical/
2	Endotamponade/ [new MeSH as of 2011]
3	(blood loss* adj3 significan*).mp,kw.
4	(blood loss* adj3 substantial*).mp.
5	(blood loss* adj3 acute*).mp.
6	(blood loss* adj3 considerabl*).mp.
7	(blood loss* adj3 excess*).mp.
8	(blood loss* adj3 major).mp.
9	(blood loss* adj3 massive).mp.
10	(blood loss* adj5 serious*).mp.
11	(blood loss* adj3 (severe or severely)).mp.
12	(blood loss* adj3 appreciab*).mp.
13	(blood loss* adj3 greater than).mp.
14	(blood loss* adj3 ml).mp.
15	(blood lost adj3 significan*).mp.
16	(blood lost adj3 substantial*).mp.
17	(blood lost adj3 considerabl*).mp.
18	(blood lost adj3 excess*).mp.
19	(blood lost adj3 major).mp.
20	(blood lost adj3 massive).mp.
21	(blood lost adj3 serious*).mp.
22	(blood lost adj3 (severe or severely)).mp.
23	(blood lost adj3 greater than).mp.
24	(blood lost adj3 ml).mp.
25	(bleed* adj3 significan*).mp.

Appendix

26	(bleed* adj3 substantial*).mp.
27	(bleed* adj3 considerabl*).mp.
28	(bleed* adj3 acute*).mp.
29	(bleed* adj3 excess*).mp.
30	(bleed* adj3 major).mp.
31	(bleed* adj3 massive).mp.
32	(bleed* adj3 serious*).mp.
33	(bleed* adj3 (severe or severly)).mp.
34	(bleed* adj3 greater than).mp.
35	(bleed* adj3 ml).mp.
36	Hemorrhage/ and (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*).mp.
37	(h?emorrhag* adj3 (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*)).mp.
38	(massive adj3 transfusion?).mp,kw.
39	(massively adj3 transfuse?).mp,kw.
40	or/1-39 [Massive / Acute Blood Loss]
41	exp HEMOGLOBINS/
42	hemoglobin*.mp,kw.
43	haemoglobin*.mp,kw.
44	or/41-43 [Hemoglobins]
45	40 and 44 [Massive / Acute Blood Loss + Hemoglobins]
46	exp surgical procedures, operative/
47	su.fs.
48	exp perioperative care/
49	exp perioperative period/
50	intraop*.mp,kw.
51	intra-op*.mp,kw.
52	periop*.mp,kw.
53	operative*.mp,kw.
54	operation?.mp,kw.
55	(surgery or surgeries or surgical* or surgeon?).mp,kw.
56	Surgeon/
57	exp Specialties, Surgical/

Appendix

58	Anesthesiology/
59	exp "Anesthesia and Analgesia"/
60	an?esth*.mp,kw.
61	or/46-60 [Surgery OR Perioperative OR Anesthesia]
62	45 and 61 [** Massive Blood Loss + Hemoglobins + Sx/Periop/Anesth **]
63	exp cohort studies/
64	exp prognosis/
65	exp morbidity/
66	exp mortality/
67	exp survival analysis/
68	exp models, statistical/
69	prognos*.tw.
70	predict*.tw.
71	course*.tw.
72	diagnosed.tw.
73	cohort*.tw.
74	death.tw.
75	or/63-74
76	62 and 75 [** Massive Blood Loss + Hemoglobins + Sx/Periop/Anesth + M/M/Prognosis **]
77	limit 76 to english language
78	limit 77 to humans
79	limit 78 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")
80	limit 79 to yr="2005 -Current"
81	remove duplicates from 80
82	blood transfusion/ or blood component transfusion/ or erythrocyte transfusion/
83	(blood adj3 transfus*).mp,kw.
84	prbc.mp,kw.
85	packed red blood cell?.mp,kw.
86	(erythrocyte? adj2 transfus*).mp,kw.
87	(red blood cell? adj2 transfus*).mp,kw.
88	(rbc adj2 transfus*).mp,kw.
89	or/82-88 [Blood Transfusion & related terms]

Appendix

90	61 and 75 and 89
91	44 and 90
92	limit 91 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")
93	limit 92 to (english language and humans)
94	limit 93 to yr="2005 -Current"
95	remove duplicates from 94
96	81 or 95
97	96 not 81 [Blood Transfusion related citations]

(b) Medline In-Process Search Strategy

#	Search Terms
1	Blood Loss, Surgical/
2	Endotamponade/ [new MeSH as of 2011]
3	(blood loss* adj3 significan*).mp,kw.
4	(blood loss* adj3 substantial*).mp.
5	(blood loss* adj3 acute*).mp.
6	(blood loss* adj3 considerabl*).mp.
7	(blood loss* adj3 excess*).mp.
8	(blood loss* adj3 major).mp.
9	(blood loss* adj3 massive).mp.
10	(blood loss* adj5 serious*).mp.
11	(blood loss* adj3 (severe or severely)).mp.
12	(blood loss* adj3 appreciab*).mp.
13	(blood loss* adj3 greater than).mp.
14	(blood loss* adj3 ml).mp.
15	(blood lost adj3 significan*).mp.
16	(blood lost adj3 substantial*).mp.
17	(blood lost adj3 considerabl*).mp.
18	(blood lost adj3 excess*).mp.
19	(blood lost adj3 major).mp.

Appendix

20	(blood lost adj3 massive).mp.
21	(blood lost adj3 serious*).mp.
22	(blood lost adj3 (severe or severely)).mp.
23	(blood lost adj3 greater than).mp.
24	(blood lost adj3 ml).mp.
25	(bleed* adj3 significan*).mp.
26	(bleed* adj3 substantial*).mp.
27	(bleed* adj3 considerabl*).mp.
28	(bleed* adj3 acute*).mp.
29	(bleed* adj3 excess*).mp.
30	(bleed* adj3 major).mp.
31	(bleed* adj3 massive).mp.
32	(bleed* adj3 serious*).mp.
33	(bleed* adj3 (severe or severly)).mp.
34	(bleed* adj3 greater than).mp.
35	(bleed* adj3 ml).mp.
36	Hemorrhage/ and (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*).mp.
37	(h?emorrhag* adj3 (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*)).mp.
38	(massive adj3 transfusion?).mp,kw.
39	(massively adj3 transfuse?).mp,kw.
40	blood transfusion/ or blood component transfusion/ or erythrocyte transfusion/
41	(blood adj3 transfus*).mp,kw.
42	prbc.mp,kw.
43	packed red blood cell?.mp,kw.
44	(erythrocyte? adj2 transfus*).mp,kw.
45	(red blood cell? adj2 transfus*).mp,kw.
46	(rbc adj2 transfus*).mp,kw.
47	or/1-46 [Massive / Acute Blood Loss / Blood Transfusion]
48	exp HEMOGLOBINS/
49	hemoglobin*.mp,kw.
50	haemoglobin*.mp,kw.
51	or/48-50 [Hemoglobins]

Appendix

1	
2	
3	
4	52 47 and 51 [Massive / Acute Blood Loss + Hemoglobins]
5	53 exp surgical procedures, operative/
6	54 su.fs.
7	55 exp perioperative care/
8	56 exp perioperative period/
9	57 intraop*.mp,kw.
10	58 intra-op*.mp,kw.
11	59 periop*.mp,kw.
12	60 operative*.mp,kw.
13	61 operation?.mp,kw.
14	62 (surgery or surgeries or surgical* or surgeon?).mp,kw.
15	63 Surgeon/
16	64 exp Specialties, Surgical/
17	65 Anesthesiology/
18	66 exp "Anesthesia and Analgesia"/
19	67 an?esth*.mp,kw.
20	68 or/53-67 [Surgery OR Perioperative OR Anesthesia]
21	69 52 and 68 [** Massive Blood Loss + Hemoglobins + Sx/Periop/Anesth **]
22	70 exp cohort studies/
23	71 exp prognosis/
24	72 exp morbidity/
25	73 exp mortality/
26	74 exp survival analysis/
27	75 exp models, statistical/
28	76 prognos*.tw.
29	77 predict*.tw.
30	78 course*.tw.
31	79 diagnosed.tw.
32	80 cohort*.tw.
33	81 death.tw.
34	82 or/70-81
35	83 69 and 82 [** Massive Blood Loss + Hemoglobins + Sx/Periop/Anesth + M/M/Prognosis **]
36	84 remove duplicates from 83
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	
60	

Appendix

(c) Embase Search Strategy

#	Search Terms
1	operative blood loss/ [Embase]
2	[endotamponade - has a different meaning in Embase; do not use]
3	(blood loss* adj3 significan*).mp,kw.
4	(blood loss* adj3 substantial*).mp.
5	(blood loss* adj3 acute*).mp.
6	(blood loss* adj3 considerabl*).mp.
7	(blood loss* adj3 excess*).mp.
8	(blood loss* adj3 major).mp.
9	(blood loss* adj3 massive).mp.
10	(blood loss* adj5 serious*).mp.
11	(blood loss* adj3 (severe or severely)).mp.
12	(blood loss* adj3 appreciab*).mp.
13	(blood loss* adj3 greater than).mp.
14	(blood loss* adj3 ml).mp.
15	(blood lost adj3 significan*).mp.
16	(blood lost adj3 substantial*).mp.
17	(blood lost adj3 considerabl*).mp.
18	(blood lost adj3 excess*).mp.
19	(blood lost adj3 major).mp.
20	(blood lost adj3 massive).mp.
21	(blood lost adj3 serious*).mp.
22	(blood lost adj3 (severe or severely)).mp.
23	(blood lost adj3 greater than).mp.
24	(blood lost adj3 ml).mp.
25	(bleed* adj3 significan*).mp.
26	(bleed* adj3 substantial*).mp.
27	(bleed* adj3 considerabl*).mp.
28	(bleed* adj3 acute*).mp.
29	(bleed* adj3 excess*).mp.
30	(bleed* adj3 major).mp.

Appendix

31	(bleed* adj3 massive).mp.
32	(bleed* adj3 serious*).mp.
33	(bleed* adj3 (severe or severely)).mp.
34	(bleed* adj3 greater than).mp.
35	(bleed* adj3 ml).mp.
36	exp bleeding/ and (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*).mp.
37	(h?emorrhag* adj3 (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*)).mp.
38	(massive adj3 transfusion?).mp,kw.
39	(massively adj3 transfuse?).mp,kw.
40	blood transfusion/ or blood component therapy/ or erythrocyte transfusion/
41	erythrocyte concentrate/
42	(blood adj3 transfus*).mp,kw.
43	prbc.mp,kw.
44	packed red blood cell?.mp,kw.
45	(erythrocyte? adj2 transfus*).mp,kw.
46	(red blood cell? adj2 transfus*).mp,kw.
47	(rbc adj2 transfus*).mp,kw.
48	or/1-47 [Massive / Acute Blood Loss / Blood Transfusion]
49	exp hemoglobin/
50	hemoglobin*.mp,kw.
51	haemoglobin*.mp,kw.
52	or/49-51 [Hemoglobins]
53	48 and 52 [Massive / Acute Blood Loss + Hemoglobins]
54	exp surgery/
55	su.fs.
56	exp peroperative care/
57	exp perioperative period/
58	intraop*.mp,kw.
59	intra-op*.mp,kw.
60	perio*.mp,kw.
61	operative*.mp,kw.
62	operation?.mp,kw.

Appendix

63	(surgery or surgeries or surgical* or surgeon?).mp,kw.
64	Surgeon/
65	exp anesthetic agent/
66	Anesthesiology/
67	exp anesthesia/ or exp analgesia/
68	an?esth*.mp,kw.
69	or/54-68 [Surgery OR Perioperative OR Anesthesia]
70	53 and 69 [** Massive Blood Loss + Hemoglobins + Sx/Periop/Anesth **]
71	exp cohort analysis/
72	exp prognosis/ or prognostic assessment/
73	exp morbidity/
74	exp mortality/
75	exp survival/
76	statistical model/
77	prognos*.tw.
78	predict*.tw.
79	course*.tw.
80	diagnosed.tw.
81	cohort*.tw.
82	death.tw.
83	or/71-82
84	70 and 83 [** Massive Blood Loss + Hemoglobins + Sx/Periop/Anesth + M/M/Prognosis **]
85	limit 84 to english
86	(exp animals/ or exp animal experimentation/ or nonhuman/) not ((exp animals/ or exp animal experimentation/ or nonhuman/) and exp human/)
87	85 not 86
88	limit 85 to human
89	87 or 88
90	limit 89 to yr="2005 -Current"
91	limit 90 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
92	90 not 91
93	limit 90 to (adult <18 to 64 years> or aged <65+ years>)
94	92 or 93

Appendix

95	remove duplicates from 94
96	limit 95 to (book or book series or conference abstract or conference proceeding or "conference review")
97	95 not 96

(d) PubMed-NOT-Medline Search Strategy

Search	Query
#9	Search (((((((blood loss OR hemorrhage OR blood transfusion)) AND (hemoglobin OR hemoglobins OR haemoglobin OR haemoglobins))) AND (surgery OR surgeries OR surgical OR surgeon OR surgeons OR operation OR operations OR operative OR perioperative OR peroperative OR intraoperative OR anesthesia OR anaesthesia OR anesthesiology OR anaesthesiology OR anesthetic OR anesthetics))) AND (morbidity OR mortality OR prognosis OR survival OR cohort OR predict OR prediction OR course OR courses OR diagnosed OR death OR deaths))) AND (((publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR inprocess[sb] OR pubmednotmedline[sb] OR oldmedline[sb] OR ((pubstatusnihms OR pubstatuspmcsd) AND publisher[sb]))) Sort by: PublicationDate
#8	Search (((publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR inprocess[sb] OR pubmednotmedline[sb] OR oldmedline[sb] OR ((pubstatusnihms OR pubstatuspmcsd) AND publisher[sb]))) Sort by: PublicationDate
#7	Search (((((((blood loss OR hemorrhage OR blood transfusion)) AND (hemoglobin OR hemoglobins OR haemoglobin OR haemoglobins))) AND (surgery OR surgeries OR surgical OR surgeon OR surgeons OR operation OR operations OR operative OR perioperative OR peroperative OR intraoperative OR anesthesia OR anaesthesia OR anesthesiology OR anaesthesiology OR anesthetic OR anesthetics))) AND (morbidity OR mortality OR prognosis OR survival OR cohort OR predict OR prediction OR course OR courses OR diagnosed OR death OR deaths) Sort by: PublicationDate
#6	Search morbidity OR mortality OR prognosis OR survival OR cohort OR predict OR prediction OR course OR courses OR diagnosed OR death OR deaths Sort by: PublicationDate
#5	Search (((((blood loss OR hemorrhage OR blood transfusion)) AND (hemoglobin OR hemoglobins OR haemoglobin OR haemoglobins))) AND (surgery OR surgeries OR surgical OR surgeon OR surgeons OR operation OR operations OR operative OR perioperative OR peroperative OR intraoperative OR anesthesia OR anaesthesia OR anesthesiology OR anaesthesiology OR anesthetic OR anesthetics) Sort by: PublicationDate
#4	Search surgery OR surgeries OR surgical OR surgeon OR surgeons OR operation OR operations OR operative OR perioperative OR peroperative OR intraoperative OR anesthesia OR anaesthesia OR anesthesiology OR anaesthesiology OR anesthetic OR anesthetics Sort by: PublicationDate
#3	Search ((blood loss OR hemorrhage OR blood transfusion)) AND (hemoglobin OR hemoglobins OR haemoglobin OR haemoglobins) Sort by: PublicationDate
#2	Search hemoglobin OR hemoglobins OR haemoglobin OR haemoglobins Sort by: PublicationDate

Appendix

#1	Search blood loss OR hemorrhage OR blood transfusion Sort by: PublicationDate
----	---

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2017-016743 on 30 June 2017. Downloaded from <http://bmjopen.bmj.com/> on April 27, 2024 by guest. Protected by copyright.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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



Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-016743.R1
Article Type:	Protocol
Date Submitted by the Author:	29-May-2017
Complete List of Authors:	Bartoszko, Justyna; University of Toronto, Anesthesia Vorobeichik, Leon; University of Toronto, Anesthesia Jayarajah, Mohandas; Derriford Hospital, Anaesthesia Karkouti, K; Toronto General Hospital, University Health Network, University of Toronto, Anesthesia and Pain Management; University of Toronto Klein, Andrew; Papworth Hospital Lamy, Andre; McMaster University, Surgery Mazer, David; St. Michael's Hospital, Shuter Wing, Room 1-028e, 30 Bond Street, Toronto, Department of Anesthesia Murphy, Mike; John Radcliffe Hospital, NHS Blood and Transplant Richards, Toby; University College London, Division of Surgery & Interventional Surgery Englesakis, Marina; University Health Network, Library and Information Services Myles, Paul; Monash University, Anaesthesia and Perioperative Medicine; Monash University, Wijeyesundera, Duminda; St. Michael's Hospital, Li Ka Shing Knowledge Institute; Toronto General Hospital, University Health Network, University of Toronto, Anesthesia and Pain Management
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Surgery, Haematology (incl blood transfusion), Research methods
Keywords:	Clinical trials < THERAPEUTICS, Blood bank & transfusion medicine < HAEMATOLOGY, Blood loss, Anaesthesiology, Endpoints, Perioperative medicine

SCHOLARONE™
Manuscripts

Defining Clinically Important Perioperative Blood Loss and Transfusion for the Standardised Endpoints for Perioperative Medicine (StEP)

Collaborative: A Protocol for a Scoping Review

Justyna Bartoszko,¹ Leon Vorobeichik,¹ Mohandas Jayarajah,² Keyvan Karkouti,³ Andrew A. Klein,⁴ Andre Lamy,⁵ C. David Mazer,⁶ Mike Murphy,⁷ Toby Richards,⁸ Marina Englesakis,⁹ Paul S. Myles,¹⁰ Duminda N. Wijeyesundera¹¹

Author Affiliations

¹ University of Toronto; Toronto, Ontario, Canada

² Derriford Hospital; Plymouth, UK

³ Toronto General Hospital / University of Toronto; Toronto, Ontario, Canada

⁴ Papworth Hospital; Cambridge, UK

⁵ McMaster University; Hamilton, Ontario, Canada

⁶ St. Michael's Hospital / University of Toronto; Toronto, Ontario, Canada

⁷ Oxford University Hospitals / University of Oxford / NHS Blood & Transplant; Oxford, UK

⁸ University College London; London, UK

⁹ University Health Network; Toronto, Ontario, Canada

¹⁰ Alfred Hospital / Monash University; Melbourne, Victoria, Australia

¹¹ St. Michael's Hospital / Toronto General Hospital / University of Toronto; Toronto, Ontario, Canada

Version Date: 6 March 2017

Correspondence

Duminda N. Wijesundera, MD PhD

Li Ka Shing Knowledge Institute of St. Michael's Hospital

30 Bond Street, Toronto, Ontario, Canada M5B 1W8

Tel: 416-864-6060 (extension 7147)

Email: d.wijesundera@utoronto.ca

Word count (excluding title page, abstract, references, figures and tables)

2,322

Keywords

endpoints, clinical trials, anaesthesiology, perioperative medicine, transfusion, blood loss,
bleeding; surgery

Version Date: 6 March 2017

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 meta-analyses. 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, PubMed-not-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

Version Date: 6 March 2017

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

Version Date: 6 March 2017

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.

Version Date: 6 March 2017

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.¹ Subsequent adoption of CONSORT recommendations has been associated with improved clarity in the reporting of published trials.² 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.^{3,4} 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.⁵

Significant blood loss and transfusion are clinically relevant and prognostically important events in perioperative care.⁶ 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

Version Date: 6 March 2017

1
2
3 example, the Bleeding Academic Research Consortium (BARC) was established in 2010 to
4
5 standardise endpoint reporting in cardiovascular clinical trials.¹²
6
7

8 The 'Standardised Endpoints for Perioperative Medicine' (StEP) initiative is an
9
10 international multidisciplinary programme with an overarching goal of developing
11
12 comprehensive and standardised endpoint definitions for straightforward, clinically sensible and
13
14 valid application to clinical trials in perioperative medicine.¹³ The initiative will use
15
16 methodology adapted from existing guideline taskforces.¹⁴⁻¹⁶ It is comprised of a
17
18 multidisciplinary range of experts, who are themselves organised into several endpoint-specific
19
20 subgroups. Each subgroup will use a consensus-building process (e.g., Delphi or nominal group
21
22 methods) to define standardised definitions for endpoints within specific domains, such as
23
24 cardiovascular or respiratory complications. The Blood Loss and Transfusion subgroup of StEP
25
26 is composed of a range of content and methodology experts, including senior researchers with
27
28 expertise in anaesthesiology, surgery, transfusion medicine, haematology, multicentre clinical
29
30 trials, and clinical epidemiology. The subgroup is tasked with developing standardised
31
32 definitions for clinically significant blood loss or transfusion in the perioperative period. These
33
34 definitions will linked to recommendations regarding data collection in RCTs, such as how
35
36 perioperative blood loss and blood product transfusion should be measured.
37
38
39
40
41
42

43 To establish a baseline and inform the consensus-based development of these
44
45 standardised endpoint definitions, a systematic and thorough evaluation of the existing literature
46
47 is critical. A scoping review is an ideal approach for achieving this objective. Specifically,
48
49 scoping reviews are suited for mapping broad areas of the literature to gain an understanding of
50
51 the extent, range, and nature of research activity within a field.¹⁷⁻²³ As a prelude to developing
52
53
54
55
56
57
58
59
60

Version Date: 6 March 2017

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.
2. 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?

Version Date: 6 March 2017

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.¹⁴ 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.²¹⁻²³

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

Version Date: 6 March 2017

Stage 1: Identifying the Research Questions

Our aims are to (i) provide an understanding of the current extent of the published literature in perioperative medicine where blood loss and transfusion were reported as endpoints, (ii) map the types of definitions used, and (iii) 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 (e.g., platelets, plasma). The details of the three questions are presented in Table 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 sub-domains, 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 (i.e., 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 focussed on the association of blood loss or transfusion with intermediate- or long-term outcomes (i.e., more than 30-days after surgery). Notably, perioperative blood loss and transfusion can plausibly have important intermediate- and long-term effects on patients’ health;

Version Date: 6 March 2017

1
2
3 however, most perioperative randomised trials focus on measuring the effects of interventions on
4
5 shorter-term outcomes, typically within 30-days after surgery. Hence, the demonstration of a
6
7 dose-response association between different magnitudes of blood loss and transfusion with short-
8
9 term postoperative outcomes will help support the criterion validity of any endpoint definition
10
11 recommended by the StEP Blood Loss and Transfusion subgroup.
12
13

Stage 2: Search Strategy

14
15
16 Given the volume and extent of the literature addressing blood loss and transfusion in
17
18 perioperative medicine, we will exclude the grey literature since it is highly likely that almost all
19
20 relevant information is already captured by the indexed published literature. In addition, the
21
22 literature search will be restricted to English-language articles published in a contemporary
23
24 period, which is defined as 2005 onwards.
25
26
27
28

Eligibility Criteria for Studies

29
30
31 The pre-specified inclusion and exclusion criteria are presented in Table 2. These criteria were
32
33 used to guide development of the electronic database search, and help establish an initial abstract
34
35 screening form.
36
37
38

Databases

39
40
41 The electronic databases to be searched are Medline, Medline In-Process, Embase, and PubMed-
42
43 NOT-Medline.
44
45

Search Strategy

46
47
48 The electronic search strategy was developed iteratively by a team of three authors (JB, ME,
49
50 DNW) that included a research librarian. The primary search terms were focused on variations of
51
52 blood loss and transfusion, with secondary search terms including various terms related to
53
54 significant or clinically important bleeding. These terms were combined using Boolean operators
55
56
57
58
59
60

Version Date: 6 March 2017

1
2
3 with other terms to capture relevant fields (perioperative medicine and related fields), consensus-
4
5 based endpoint definitions, or postoperative outcomes. These search results were filtered to
6
7 include English-language studies in adult humans from 2005 onwards. In iterative steps, we
8
9 evaluated 200 to 400 abstracts identified by successive versions of this search strategy to
10
11 determine if further refinement of the strategy was required. The final version of the search
12
13 strategy is presented in the Appendix. Once the final search strategy is implemented, the results
14
15 (after elimination of any duplicates) will be uploaded into DistillerSR (2016, Evidence Partners,
16
17 Ottawa, Ontario, Canada) to facilitate further article screening and selection. This list of
18
19 potentially relevant studies will be supplemented as needed by consulting content experts in the
20
21 Blood Loss and Transfusion subgroup of StEP.
22
23
24
25
26

27 **Stage 3: Study Selection**

28
29 Study screening and selection will involve a multi-stage process with at least two reviewers. For
30
31 Questions 2 and 3, two reviewers (JB, LV) will conduct screening of titles or abstracts, and full-
32
33 text review of selected articles. All disagreements will be resolved by discussion, and where
34
35 necessary, involvement of a third reviewer (DNW). Due to the large volume of potentially
36
37 relevant articles identified for Question 1, a modified study selection process will take place. In
38
39 the first step, a single reviewer (JB) will screen abstracts to identify any potentially relevant
40
41 studies. To maximise sensitivity in this additional first step, any study with uncertain relevance
42
43 will be retained for consideration in the next screening stage. The remaining steps in the
44
45 screening and selection process will be identical to those employed for Questions 2 and 3. The
46
47 full inclusion and exclusion criteria applied for each stage of study screening and evaluation are
48
49 presented in Table 3. A PRISMA flow diagram will be used to report the conduct of this search
50
51 strategy.²⁴
52
53
54
55
56
57
58
59
60

Version Date: 6 March 2017

Stage 4: Charting the Data

An initial set of data categories to be abstracted are presented in Table 3. These initial data categories were identified based on their relevance to the goals of the StEP initiative.¹⁴ 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, LV). Their data extraction results will be compared, and any disagreements 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 (e.g., presence of transfusion, changes in haemoglobin values, 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

Version Date: 6 March 2017

1
2
3 structure used to classify the literature. Additionally, these content experts will help identify any
4
5 relevant studies that were not initially identified in the electronic database search. Importantly,
6
7 they will add insight into the relevance of the findings and which context the findings should be
8
9 interpreted.²¹⁻²⁴ The final results will be reported using a framework similar to that used in prior
10
11 scoping reviews applied to questions in critical care, anaesthesiology, and health policy.¹⁷⁻²⁴
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Version Date: 6 March 2017

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.

Version Date: 6 March 2017

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.

Version Date: 6 March 2017

REFERENCES

1. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
2. Plint AC, Moher D, Morrison A, *et al.* Does the CONSORT Checklist improve the quality of reports of randomized controlled trials? A systematic review. *Med J Aust* 2006;185:263-7.
3. Koreshetz W. A core set of trial outcomes for every medical discipline? *BMJ* 2015;350:h85.
4. Williamson PR, Altman DG, Blazeby JM, *et al.* Developing core outcome sets for clinical trials: issues to consider. *Trials* 2012;13:132.
5. Gorst SL, Altman DG, Blazeby JM, *et al.* COMET V Meeting Summary. *Trials* 2015;16(Suppl 3):A1.
6. Wu WC, Smith TS, Henderson WG, *et al.* Operative blood loss, blood transfusion, and 30-day mortality in older patients after noncardiac surgery. *Ann Surg* 2010;252:11-7.
7. Martin RCG, Brennan MF, Jaques DP. Quality of complication reporting in the surgical literature. *Ann Surg* 2002; 235: 803-13.
8. Rahbari NN, Garden OJ, Padbury R, *et al.* Post-hepatectomy hemorrhage: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *HPB (Oxford)* 2011;13:528-35.

Version Date: 6 March 2017

- 1
2
3 9. Wente MN, Veit JA, Bassi C, *et al.* Postpancreatectomy hemorrhage (PPH): an
4 International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery*
5
6 2007;142:20-5.
7
8
- 9
10 10. Opondo D, Gravas S, Joyce A, *et al.* Standardization of outcomes reporting in
11
12 percutaneous nephrolithotomy. *J Endourol* 2014;28:767-74.
13
14
- 15 11. Dyke C, Aronson S, Dietrich W, *et al.* Universal definition of perioperative bleeding in
16
17 adult cardiac surgery. *J Thorac Cardiovasc Surg* 2014; 147: 1458-63.
18
19
- 20 12. Mehran R, Rao S, Bhatt DL, for the Bleeding Academic Research Consortium.
21
22 Standardized bleeding definitions for cardiovascular clinical trials. *Circulation*
23
24 2011;123:2736-47.
25
26
- 27 13. Boney O, Moonesinghe SR, Myles PS, Grocott MPW. Standardizing endpoints in
28
29 perioperative research. *Can J Anaesth* 2016;63:159-68.
30
31
- 32 14. Myles PS, Grocott MP, Boney O, Moonesinghe SR, on behalf of the COMPAC-StEP
33
34 Group. Standardizing end points in perioperative trials: towards a core and extended
35
36 outcome set. *Br J Anaesth* 2016;116:586-9.
37
38
- 39 15. Prinsen CA, Vohra S, Rose MR, *et al.* Core Outcome Measures in Effectiveness Trials
40
41 (COMET) initiative: protocol for an international Delphi study to achieve consensus on
42
43 how to select outcome measurement instruments for outcomes included in a 'core
44
45 outcome set'. *Trials* 2014;15:247
46
47
- 48 16. Bellera CA, Pulido M, Gourgou S, *et al.* Protocol of the Definition for the Assessment of
49
50 Time-to-Event Endpoints in CANcer Trials (DATECAN) project: formal consensus
51
52 method for the development of guidelines for the standardized time-to-event endpoints'
53
54 definitions in cancer clinical trials. *Eur J Cancer* 2013;49:769-81.
55
56
57
58
59
60

Version Date: 6 March 2017

17. Brien SE, Lorenzetti DL, Lewis S, Kennedy J, Ghali WA. Overview of a formal scoping review on health system report cards. *Implement Sci* 2010;5:2.
18. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *Int J Evid Based Healthc* 2015; 13:141-6.
19. Duffett M, Choong K, Hartling L, *et al.* Randomized controlled trials in pediatric critical care: a scoping review. *Crit Care* 2013;17:R256.
20. Halas G, Schultz ASH, Rothney J, Goertzen L, Wener P, Katz A. A scoping review protocol to map the research foci trends in tobacco control over the last decade. *BMJ Open* 2015;5:e006643.
21. Arksey H, O'Malley L. Scoping Studies: Towards a methodological framework. *Int J Soc Res Methodol* 2005;8:19-32.
22. Levac D, Colquhoun H, O'Brein K. Scoping studies: advancing the methodology. *Implement Sci* 2010;5:69.
23. Daudt HML, van Mossel C, Scott SJ. Enhancing the scoping review methodology: a large, inter-professional team's experience with Arksey and O'Malley's framework. *BMC Med Res Methodol* 2013;13:48.
24. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic Reviews and meta analyses: the PRISMA Statement. *PLoS Med* 2009;6:e1000097.

Version Date: 6 March 2017

ACKNOWLEDGEMENTS

DNW and KK are supported in part by Merit Awards from the Department of Anesthesia at the University of Toronto. PSM is supported by an Australian National Health and Medical Research Council (NHMRC) Practitioner Fellowship. DNW is supported in part by a New Investigator Award from the Canadian Institutes of Health Research (CIHR).

For peer review only

Version Date: 6 March 2017

CONTRIBUTORS

1
2
3
4
5
6
7
8
9
10 JB, LV, ME, PSM and DNW contributed to the conception and design of the study. JB wrote the
11 first draft of the protocol. JB, LV, MJ, KK, AAK, AL, CDM, MFM, TR, ME, PSM, and DNW
12 revised the protocol critically for important intellectual content. DNW is the guarantor. All
13 authors have read and approved the final version of the manuscript to be published.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Version Date: 6 March 2017

FUNDING STATEMENT

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

For peer review only

Version Date: 6 March 2017

COMPETING INTERESTS STATEMENT

AAK has received support for research and/or honoraria from Pharmacosmos, Vifor Pharma, CSL Behring, Brightwake Ltd and Fisher Paykel. TR has received support for research and/or honoraria from Pharmacosmos, Vifor Pharma, Acelity, and Libresse/Bodyform. TR is a director of the Iron Clinic Ltd (London, UK), director of Veincare London Ltd (London, UK), and Vascular Surgery lead for 18-Week Support Ltd (London, UK). The remaining authors have no competing interests or conflicts to declare.

Version Date: 6 March 2017

Table 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 focussed 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 consensus-based 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 (i.e., within 30 days or less after surgery) outcome including complications (e.g., myocardial infarction, stroke, acute kidney injury), death, and hospital length of stay

Version Date: 6 March 2017

Table 2. Inclusion and exclusion criteria used to identify potentially relevant studies

Inclusion Criteria	Exclusion Criteria
<ol style="list-style-type: none"> 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) 6.) Research targeting patients undergoing surgery, anaesthetic procedures, and minimally invasive interventions, as well as patients who have been admitted to a post-surgical critical care unit 	<ol style="list-style-type: none"> 1.) Journal articles that were not original research or systematic reviews (e.g., case reports, case series, opinion pieces, commentaries, or editorials)

Version Date: 6 March 2017

Table 3. Inclusion criteria and data extraction fields by stage of article processing

Article Processing Stage	Inclusion Criteria and Domains to be Extracted		
	Question 1	Question 2	Question 3
Initial Title and Abstract Screen	<ul style="list-style-type: none"> • Randomised controlled trials • Systematic reviews or meta-analyses will be excluded 	<ul style="list-style-type: none"> • Research including adults • Consensus-based criteria or systematic review of clinical trials that included a pre-specified definitions of major blood loss or transfusion as a study endpoint 	<ul style="list-style-type: none"> • Evaluates dose-response association between transfusion or blood loss with patient outcomes • Surgical, anaesthesiology or perioperative disciplines only (obstetrics or trauma literature excluded)
Second Abstract Screen and Full Text Evaluation	<ul style="list-style-type: none"> • Study design confirmed as randomised controlled trial • Major blood loss or transfusion reported as an endpoint • ≥ 500 participants • Within fields of perioperative medicine, anaesthesiology or surgery 	<ul style="list-style-type: none"> • Consensus-based statement, guideline, or recommendation for defining significant blood loss or transfusion endpoints • Systematic review or evidence synthesis that refers to a consensus-based definition of major blood loss or transfusion 	<ul style="list-style-type: none"> • Study pertains to surgery, anaesthesiology, or perioperative medicine • Reports dose-response association between transfusion or blood loss with patient outcomes
Data Extraction	<ul style="list-style-type: none"> • Sample size • Intervention and control being compared • Endpoint definition for major blood loss or transfusion 	<ul style="list-style-type: none"> • Name of organisations and/or panels involved • Definition of significant blood loss or transfusion • Patient 	<ul style="list-style-type: none"> • Patient sample in which the outcome was measured • Type of study (e.g., retrospective cohort study) • Number of patients included • Exposure

Version Date: 6 March 2017

		population to which definition applies <ul style="list-style-type: none">• Interventions to which definition applies	definition and how it was measured (e.g., >500 mL blood loss identified from anaesthetic record) <ul style="list-style-type: none">• Definition of outcome and how it was measured (e.g., 30-day all-cause mortality)
--	--	--	---

For peer review only

Appendix

APPENDIX

A. Literature Search (Question 1)

The databases to be searched are:

- a. Medline
- b. Medline In-Process
- c. Embase
- d. Pubmed-NOT-Medline

(a) Medline Search Strategy

#	Search Terms
1	Blood Loss, Surgical/
2	Endotamponade/ [new MeSH as of 2011]
3	(blood loss* adj3 significan*).mp,kw.
4	(blood loss* adj3 substantial*).mp.
5	(blood loss* adj3 acute*).mp.
6	(blood loss* adj3 considerabl*).mp.
7	(blood loss* adj3 excess*).mp.
8	(blood loss* adj3 major).mp.
9	(blood loss* adj3 massive).mp.
10	(blood loss* adj5 serious*).mp.
11	(blood loss* adj3 (severe or severely)).mp.
12	(blood loss* adj3 appreciab*).mp.
13	(blood loss* adj3 greater than).mp.
14	(blood loss* adj3 ml).mp.
15	(blood lost adj3 significan*).mp.
16	(blood lost adj3 substantial*).mp.
17	(blood lost adj3 considerabl*).mp.
18	(blood lost adj3 excess*).mp.
19	(blood lost adj3 major).mp.
20	(blood lost adj3 massive).mp.
21	(blood lost adj3 serious*).mp.
22	(blood lost adj3 (severe or severely)).mp.
23	(blood lost adj3 greater than).mp.
24	(blood lost adj3 ml).mp.

Appendix

25	(bleed* adj3 significan*).mp.
26	(bleed* adj3 substantial*).mp.
27	(bleed* adj3 considerabl*).mp.
28	(bleed* adj3 acute*).mp.
29	(bleed* adj3 excess*).mp.
30	(bleed* adj3 major).mp.
31	(bleed* adj3 massive).mp.
32	(bleed* adj3 serious*).mp.
33	(bleed* adj3 (severe or severely)).mp.
34	(bleed* adj3 greater than).mp.
35	(bleed* adj3 ml).mp.
36	Hemorrhage/ and (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*).mp.
37	(h?emorrhag* adj3 (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*)).mp.
38	(massive adj3 transfusion?).mp,kw.
39	(massively adj3 transfuse?).mp,kw.
40	or/1-39 [Massive / Acute Blood Loss]
41	exp surgical procedures, operative/
42	su.fs.
43	exp perioperative care/
44	exp perioperative period/
45	intraop*.mp,kw.
46	intra-op*.mp,kw.
47	periop*.mp,kw.
48	operative*.mp,kw.
49	operation?.mp,kw.
50	(surgery or surgeries or surgical*).mp,kw.
51	Surgeon/
52	exp Specialties, Surgical/
53	Anesthesiology/
54	exp "Anesthesia and Analgesia"/
55	an?esth*.mp,kw.
56	or/41-55 [Surgery OR Perioperative OR Anesthesia]

Appendix

57	40 and 56
58	40 and 56 [** Massive Blood Loss + Sx/Periop/Anesth **]
59	limit 58 to english language
60	limit 59 to humans
61	limit 60 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")
62	limit 61 to yr="2005 -Current"
63	exp Randomized Controlled Trial/
64	exp Randomized Controlled Trials as Topic/
65	(pragmatic adj6 (trial or trials or study or studies)).mp,kw.
66	(randomi#ed adj6 (trial or trials or study or studies)).mp,kw.
67	or/63-66
68	62 and 67 [** Massive Blood Loss + Sx/Periop/Anesth + RCTs (w Limits) **]
69	remove duplicates from 68

(b) Medline In-Process Search Strategy

#	Search Terms
1	Blood Loss, Surgical/
2	Endotamponade/ [new MeSH as of 2011]
3	(blood loss* adj3 significan*).mp,kw.
4	(blood loss* adj3 substantial*).mp.
5	(blood loss* adj3 acute*).mp.
6	(blood loss* adj3 considerabl*).mp.
7	(blood loss* adj3 excess*).mp.
8	(blood loss* adj3 major).mp.
9	(blood loss* adj3 massive).mp.
10	(blood loss* adj5 serious*).mp.
11	(blood loss* adj3 (severe or severely)).mp.
12	(blood loss* adj3 appreciab*).mp.
13	(blood loss* adj3 greater than).mp.
14	(blood loss* adj3 ml).mp.
15	(blood lost adj3 significan*).mp.

Appendix

16	(blood lost adj3 substantial*).mp.
17	(blood lost adj3 considerabl*).mp.
18	(blood lost adj3 excess*).mp.
19	(blood lost adj3 major).mp.
20	(blood lost adj3 massive).mp.
21	(blood lost adj3 serious*).mp.
22	(blood lost adj3 (severe or severely)).mp.
23	(blood lost adj3 greater than).mp.
24	(blood lost adj3 ml).mp.
25	(bleed* adj3 significan*).mp.
26	(bleed* adj3 substantial*).mp.
27	(bleed* adj3 considerabl*).mp.
28	(bleed* adj3 acute*).mp.
29	(bleed* adj3 excess*).mp.
30	(bleed* adj3 major).mp.
31	(bleed* adj3 massive).mp.
32	(bleed* adj3 serious*).mp.
33	(bleed* adj3 (severe or severely)).mp.
34	(bleed* adj3 greater than).mp.
35	(bleed* adj3 ml).mp.
36	Hemorrhage/ and (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*).mp.
37	(h ² emorrhag* adj3 (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*)).mp.
38	(massive adj3 transfusion?).mp,kw.
39	(massively adj3 transfuse?).mp,kw.
40	or/1-39 [Massive / Acute Blood Loss]
41	exp surgical procedures, operative/
42	su.fs.
43	exp perioperative care/
44	exp perioperative period/
45	intraop*.mp,kw.
46	intra-op*.mp,kw.
47	perio ² p*.mp,kw.

Appendix

48	operative*.mp,kw.
49	operation?.mp,kw.
50	(surgery or surgeries or surgical*).mp,kw.
51	Surgeon/
52	exp Specialties, Surgical/
53	Anesthesiology/
54	exp "Anesthesia and Analgesia"/
55	an?esth*.mp,kw.
56	or/41-55 [Surgery OR Perioperative OR Anesthesia]
57	40 and 56 [** Massive Blood Loss + Sx/Periop/Anesth **]
58	exp Randomized Controlled Trial/
59	exp Randomized Controlled Trials as Topic/
60	(pragmatic adj6 (trial or trials or study or studies)).mp,kw.
61	(randomi#ed adj6 (trial or trials or study or studies)).mp,kw.
62	or/58-61
63	57 and 62
64	remove duplicates from 63
65	limit 64 to yr="2005 -Current"

(c) Embase Search Strategy

#	Search Terms
1	operative blood loss/
2	endotamponad*.mp,kw.
3	(blood loss* adj3 significan*).mp,kw.
4	(blood loss* adj3 substantial*).mp.
5	(blood loss* adj3 acute*).mp.
6	(blood loss* adj3 considerabl*).mp.
7	(blood loss* adj3 excess*).mp.
8	(blood loss* adj3 major).mp.
9	(blood loss* adj3 massive).mp.
10	(blood loss* adj5 serious*).mp.
11	(blood loss* adj3 (severe or severely)).mp.
12	(blood loss* adj3 appreciab*).mp.

Appendix

13	(blood loss* adj3 greater than).mp.
14	(blood loss* adj3 ml).mp.
15	(blood lost adj3 significan*).mp.
16	(blood lost adj3 substantial*).mp.
17	(blood lost adj3 considerabl*).mp.
18	(blood lost adj3 excess*).mp.
19	(blood lost adj3 major).mp.
20	(blood lost adj3 massive).mp.
21	(blood lost adj3 serious*).mp.
22	(blood lost adj3 (severe or severely)).mp.
23	(blood lost adj3 greater than).mp.
24	(blood lost adj3 ml).mp.
25	(bleed* adj3 significan*).mp.
26	(bleed* adj3 substantial*).mp.
27	(bleed* adj3 considerabl*).mp.
28	(bleed* adj3 acute*).mp.
29	(bleed* adj3 excess*).mp.
30	(bleed* adj3 major).mp.
31	(bleed* adj3 massive).mp.
32	(bleed* adj3 serious*).mp.
33	(bleed* adj3 (severe or severely)).mp.
34	(bleed* adj3 greater than).mp.
35	(bleed* adj3 ml).mp.
36	bleeding/ and (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*).mp.
37	(h?emorrhag* adj3 (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*)).mp.
38	(massive adj3 transfusion?).mp,kw.
39	(massively adj3 transfuse?).mp,kw.
40	or/1-39 [Massive / Acute Blood Loss]
41	exp surgery/
42	su.fs.
43	exp perioperative care/
44	exp perioperative period/

Appendix

45	intraop*.mp,kw.
46	intra-op*.mp,kw.
47	periop*.mp,kw.
48	operative*.mp,kw.
49	operation?.mp,kw.
50	(surgery or surgeries or surgical*).mp,kw.
51	Surgeon/
52	anesthesiological procedure/
53	Anesthesiology/
54	exp anesthesia/
55	exp analgesia/
56	an?esth*.mp,kw.
57	or/41-56 [Surgery OR Perioperative OR Anesthesia]
58	40 and 57 [** Massive Blood Loss + Sx/Periop/Anesth **]
59	randomized controlled trial/
60	"randomized controlled trial (topic)"/
61	ct.fs. [Clinical Trial subheading]
62	(pragmatic adj6 (trial or trials or study or studies)).mp,kw.
63	(randomi#ed adj6 (trial or trials or study or studies)).mp,kw.
64	or/59-63
65	58 and 64 [** Massive Blood Loss + Sx/Periop/Anesth + RCTs**]
66	limit 65 to yr="2005 -Current"
67	limit 66 to human
68	limit 67 to english language
69	limit 68 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
70	68 not 69
71	limit 68 to (adult <18 to 64 years> or aged <65+ years>)
72	70 or 71
73	limit 72 to (book or book series or conference abstract or conference proceeding or "conference review")
74	72 not 73
75	from 74 keep 1-4999

Appendix

76	remove duplicates from 75
77	from 74 keep 5000-9331
78	remove duplicates from 77
79	76 or 78

(d) PubMed-NOT-Medline Search Strategy

Search	Query
#5	Search (((((((blood loss OR hemorrhage OR blood transfusion)) AND (hemoglobin OR hemoglobins OR haemoglobin OR haemoglobins))) AND (surgery OR surgeries OR surgical OR surgeon OR surgeons OR operation OR operations OR operative OR perioperative OR peroperative OR intraoperative OR anesthesia OR anaesthesia OR anesthesiology OR anaesthesiology OR anesthetic OR anesthetics))) AND (random OR randomly OR randomized OR randomised OR randomization OR randomisation OR pragmatic OR placebo OR placebos OR double-blind OR double-blinds OR double-blinded OR double-blinding))) NOT medline [sb] Sort by: PublicationDate
#4	Search medline [sb] Sort by: PublicationDate
#3	Search (((((((blood loss OR hemorrhage OR blood transfusion)) AND (hemoglobin OR hemoglobins OR haemoglobin OR haemoglobins))) AND (surgery OR surgeries OR surgical OR surgeon OR surgeons OR operation OR operations OR operative OR perioperative OR peroperative OR intraoperative OR anesthesia OR anaesthesia OR anesthesiology OR anaesthesiology OR anesthetic OR anesthetics))) AND (random OR randomly OR randomized OR randomised OR randomization OR randomisation OR pragmatic OR placebo OR placebos OR double-blind OR double-blinds OR double-blinded OR double-blinding)) Sort by: PublicationDate
#2	Search random OR randomly OR randomized OR randomised OR randomization OR randomisation OR pragmatic OR placebo OR placebos OR double-blind OR double-blinds OR double-blinded OR double-blinding Sort by: PublicationDate
#1	Search (((((blood loss OR hemorrhage OR blood transfusion)) AND (hemoglobin OR hemoglobins OR haemoglobin OR haemoglobins))) AND (surgery OR surgeries OR surgical OR surgeon OR surgeons OR operation OR operations OR operative OR perioperative OR peroperative OR intraoperative OR anesthesia OR anaesthesia OR anesthesiology OR anaesthesiology OR anesthetic OR anesthetics)) Sort by: PublicationDate

Appendix

B. Literature Search (Question 2)**The databases to be searched are:**

- a. Medline

(a) Medline Search Strategy

#	Search Terms
1	Blood Loss, Surgical/
2	Endotamponade/ [new MeSH as of 2011]
3	(blood loss* adj3 significan*).mp,kw.
4	(blood loss* adj3 substantial*).mp.
5	(blood loss* adj3 acute*).mp.
6	(blood loss* adj3 considerabl*).mp.
7	(blood loss* adj3 excess*).mp.
8	(blood loss* adj3 major).mp.
9	(blood loss* adj3 massive).mp.
10	(blood loss* adj5 serious*).mp.
11	(blood loss* adj3 (severe or severely)).mp.
12	(blood loss* adj3 appreciab*).mp.
13	(blood loss* adj3 greater than).mp.
14	(blood loss* adj3 ml).mp.
15	(blood lost adj3 significan*).mp.
16	(blood lost adj3 substantial*).mp.
17	(blood lost adj3 considerabl*).mp.
18	(blood lost adj3 excess*).mp.
19	(blood lost adj3 major).mp.
20	(blood lost adj3 massive).mp.
21	(blood lost adj3 serious*).mp.
22	(blood lost adj3 (severe or severely)).mp.
23	(blood lost adj3 greater than).mp.
24	(blood lost adj3 ml).mp.
25	(bleed* adj3 significan*).mp.
26	(bleed* adj3 substantial*).mp.
27	(bleed* adj3 considerabl*).mp.
28	(bleed* adj3 acute*).mp.

Appendix

29	(bleed* adj3 excess*).mp.
30	(bleed* adj3 major).mp.
31	(bleed* adj3 massive).mp.
32	(bleed* adj3 serious*).mp.
33	(bleed* adj3 (severe or severly)).mp.
34	(bleed* adj3 greater than).mp.
35	(bleed* adj3 ml).mp.
36	Hemorrhage/ and (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*).mp.
37	(h?emorrhag* adj3 (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*)).mp.
38	(massive adj3 transfusion?).mp,kw.
39	(massively adj3 transfuse?).mp,kw.
40	bleed???.mp. and (definition or definitions or defined or define or defines).ab. /freq=2
41	(bleed???.mp. and (definition or definitions or defined or define)).ti.
42	(bleed* adj6 (criteria or criterion)).mp,kw.
43	(bleed???.mp. adj3 classifi*).mp,kw.
44	or/1-43 [Massive / Acute Blood Loss]
45	exp Consensus Development Conference/ or exp Consensus/
46	consensus.mp,kw.
47	exp Guideline/
48	exp Guidelines as Topic/
49	guideline?.mp,kw.
50	Clinical Protocols/
51	Critical Pathways/
52	protocol*.mp,kw.
53	((critical or clinical) adj2 pathway?).mp,kw.
54	Taskforce??.af.
55	Task force??.af.
56	(systematic adj3 (review or reviews or overview?)).mp,kw.
57	Meta-Analysis/
58	Meta-Analysis as Topic/
59	meta-anal*.mp,kw.
60	metaanal*.mp,kw.

Appendix

61	metanal*.mp,kw.
62	(practi#e adj1 parameter).mp,kw.
63	statement?.ti.
64	or/45-63 [Consensus or Guideline or Protocol or Taskforce or Systematic Review]
65	44 and 64 [Massive / Acute Blood Loss + Consensus or Guideline or Protocol or Taskforce or Systematic Review]
	<i>Limits applied:</i>
66	limit 65 to english language
67	limit 66 to humans
68	limit 67 to yr="2005 -Current"
69	remove duplicates from 68

Appendix

C. Literature Search (Question 3)**The databases to be searched are:**

- a. Medline
- b. Medline In-Process
- c. Embase
- d. Pubmed-NOT-Medline

(a) Medline Search Strategy

#	Search Terms
1	Blood Loss, Surgical/
2	Endotamponade/ [new MeSH as of 2011]
3	(blood loss* adj3 significan*).mp,kw.
4	(blood loss* adj3 substantial*).mp.
5	(blood loss* adj3 acute*).mp.
6	(blood loss* adj3 considerabl*).mp.
7	(blood loss* adj3 excess*).mp.
8	(blood loss* adj3 major).mp.
9	(blood loss* adj3 massive).mp.
10	(blood loss* adj5 serious*).mp.
11	(blood loss* adj3 (severe or severely)).mp.
12	(blood loss* adj3 appreciab*).mp.
13	(blood loss* adj3 greater than).mp.
14	(blood loss* adj3 ml).mp.
15	(blood lost adj3 significan*).mp.
16	(blood lost adj3 substantial*).mp.
17	(blood lost adj3 considerabl*).mp.
18	(blood lost adj3 excess*).mp.
19	(blood lost adj3 major).mp.
20	(blood lost adj3 massive).mp.
21	(blood lost adj3 serious*).mp.
22	(blood lost adj3 (severe or severely)).mp.
23	(blood lost adj3 greater than).mp.
24	(blood lost adj3 ml).mp.
25	(bleed* adj3 significan*).mp.

Appendix

26	(bleed* adj3 substantial*).mp.
27	(bleed* adj3 considerabl*).mp.
28	(bleed* adj3 acute*).mp.
29	(bleed* adj3 excess*).mp.
30	(bleed* adj3 major).mp.
31	(bleed* adj3 massive).mp.
32	(bleed* adj3 serious*).mp.
33	(bleed* adj3 (severe or severly)).mp.
34	(bleed* adj3 greater than).mp.
35	(bleed* adj3 ml).mp.
36	Hemorrhage/ and (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*).mp.
37	(h?emorrhag* adj3 (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*)).mp.
38	(massive adj3 transfusion?).mp,kw.
39	(massively adj3 transfuse?).mp,kw.
40	or/1-39 [Massive / Acute Blood Loss]
41	exp HEMOGLOBINS/
42	hemoglobin*.mp,kw.
43	haemoglobin*.mp,kw.
44	or/41-43 [Hemoglobins]
45	40 and 44 [Massive / Acute Blood Loss + Hemoglobins]
46	exp surgical procedures, operative/
47	su.fs.
48	exp perioperative care/
49	exp perioperative period/
50	intraop*.mp,kw.
51	intra-op*.mp,kw.
52	perio*.mp,kw.
53	operative*.mp,kw.
54	operation?.mp,kw.
55	(surgery or surgeries or surgical* or surgeon?).mp,kw.
56	Surgeon/
57	exp Specialties, Surgical/

Appendix

1	
2	
3	
4	58 Anesthesiology/
5	59 exp "Anesthesia and Analgesia"/
6	60 an?esth*.mp,kw.
7	61 or/46-60 [Surgery OR Perioperative OR Anesthesia]
8	62 45 and 61 [** Massive Blood Loss + Hemoglobins + Sx/Periop/Anesth **]
9	63 exp cohort studies/
10	64 exp prognosis/
11	65 exp morbidity/
12	66 exp mortality/
13	67 exp survival analysis/
14	68 exp models, statistical/
15	69 prognos*.tw.
16	70 predict*.tw.
17	71 course*.tw.
18	72 diagnosed.tw.
19	73 cohort*.tw.
20	74 death.tw.
21	75 or/63-74
22	76 62 and 75 [** Massive Blood Loss + Hemoglobins + Sx/Periop/Anesth + M/M/Prognosis **]
23	77 limit 76 to english language
24	78 limit 77 to humans
25	79 limit 78 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")
26	80 limit 79 to yr="2005 -Current"
27	81 remove duplicates from 80
28	82 blood transfusion/ or blood component transfusion/ or erythrocyte transfusion/
29	83 (blood adj3 transfus*).mp,kw.
30	84 prbc.mp,kw.
31	85 packed red blood cell?.mp,kw.
32	86 (erythrocyte? adj2 transfus*).mp,kw.
33	87 (red blood cell? adj2 transfus*).mp,kw.
34	88 (rbc adj2 transfus*).mp,kw.
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	
60	

Appendix

89	or/82-88 [Blood Transfusion & related terms]
90	61 and 75 and 89
91	44 and 90
92	limit 91 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")
93	limit 92 to (english language and humans)
94	limit 93 to yr="2005 -Current"
95	remove duplicates from 94
96	81 or 95
97	96 not 81 [Blood Transfusion related citations]

(b) Medline In-Process Search Strategy

#	Search Terms
1	Blood Loss, Surgical/
2	Endotamponade/ [new MeSH as of 2011]
3	(blood loss* adj3 significan*).mp,kw.
4	(blood loss* adj3 substantial*).mp.
5	(blood loss* adj3 acute*).mp.
6	(blood loss* adj3 considerabl*).mp.
7	(blood loss* adj3 excess*).mp.
8	(blood loss* adj3 major).mp.
9	(blood loss* adj3 massive).mp.
10	(blood loss* adj5 serious*).mp.
11	(blood loss* adj3 (severe or severely)).mp.
12	(blood loss* adj3 appreciab*).mp.
13	(blood loss* adj3 greater than).mp.
14	(blood loss* adj3 ml).mp.
15	(blood lost adj3 significan*).mp.
16	(blood lost adj3 substantial*).mp.
17	(blood lost adj3 considerabl*).mp.
18	(blood lost adj3 excess*).mp.

Appendix

19	(blood lost adj3 major).mp.
20	(blood lost adj3 massive).mp.
21	(blood lost adj3 serious*).mp.
22	(blood lost adj3 (severe or severely)).mp.
23	(blood lost adj3 greater than).mp.
24	(blood lost adj3 ml).mp.
25	(bleed* adj3 significan*).mp.
26	(bleed* adj3 substantial*).mp.
27	(bleed* adj3 considerabl*).mp.
28	(bleed* adj3 acute*).mp.
29	(bleed* adj3 excess*).mp.
30	(bleed* adj3 major).mp.
31	(bleed* adj3 massive).mp.
32	(bleed* adj3 serious*).mp.
33	(bleed* adj3 (severe or severly)).mp.
34	(bleed* adj3 greater than).mp.
35	(bleed* adj3 ml).mp.
36	Hemorrhage/ and (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*).mp.
37	(h?emorrhag* adj3 (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*)).mp.
38	(massive adj3 transfusion?).mp,kw.
39	(massively adj3 transfuse?).mp,kw.
40	blood transfusion/ or blood component transfusion/ or erythrocyte transfusion/
41	(blood adj3 transfus*).mp,kw.
42	prbc.mp,kw.
43	packed red blood cell?.mp,kw.
44	(erythrocyte? adj2 transfus*).mp,kw.
45	(red blood cell? adj2 transfus*).mp,kw.
46	(rbc adj2 transfus*).mp,kw.
47	or/1-46 [Massive / Acute Blood Loss / Blood Transfusion]
48	exp HEMOGLOBINS/
49	hemoglobin*.mp,kw.
50	haemoglobin*.mp,kw.

Appendix

51	or/48-50 [Hemoglobins]
52	47 and 51 [Massive / Acute Blood Loss + Hemoglobins]
53	exp surgical procedures, operative/
54	su.fs.
55	exp perioperative care/
56	exp perioperative period/
57	intraop*.mp,kw.
58	intra-op*.mp,kw.
59	periop*.mp,kw.
60	operative*.mp,kw.
61	operation?.mp,kw.
62	(surgery or surgeries or surgical* or surgeon?).mp,kw.
63	Surgeon/
64	exp Specialties, Surgical/
65	Anesthesiology/
66	exp "Anesthesia and Analgesia"/
67	an?esth*.mp,kw.
68	or/53-67 [Surgery OR Perioperative OR Anesthesia]
69	52 and 68 [** Massive Blood Loss + Hemoglobins + Sx/Periop/Anesth **]
70	exp cohort studies/
71	exp prognosis/
72	exp morbidity/
73	exp mortality/
74	exp survival analysis/
75	exp models, statistical/
76	prognos*.tw.
77	predict*.tw.
78	course*.tw.
79	diagnosed.tw.
80	cohort*.tw.
81	death.tw.
82	or/70-81

Appendix

83	69 and 82 [** Massive Blood Loss + Hemoglobins + Sx/Periop/Anesth + M/M/Prognosis **]
84	remove duplicates from 83

(c) Embase Search Strategy

#	Search Terms
1	operative blood loss/ [Embase]
2	[endotamponade - has a different meaning in Embase; do not use]
3	(blood loss* adj3 significan*).mp,kw.
4	(blood loss* adj3 substantial*).mp.
5	(blood loss* adj3 acute*).mp.
6	(blood loss* adj3 considerabl*).mp.
7	(blood loss* adj3 excess*).mp.
8	(blood loss* adj3 major).mp.
9	(blood loss* adj3 massive).mp.
10	(blood loss* adj5 serious*).mp.
11	(blood loss* adj3 (severe or severely)).mp.
12	(blood loss* adj3 appreciab*).mp.
13	(blood loss* adj3 greater than).mp.
14	(blood loss* adj3 ml).mp.
15	(blood lost adj3 significan*).mp.
16	(blood lost adj3 substantial*).mp.
17	(blood lost adj3 considerabl*).mp.
18	(blood lost adj3 excess*).mp.
19	(blood lost adj3 major).mp.
20	(blood lost adj3 massive).mp.
21	(blood lost adj3 serious*).mp.
22	(blood lost adj3 (severe or severely)).mp.
23	(blood lost adj3 greater than).mp.
24	(blood lost adj3 ml).mp.
25	(bleed* adj3 significan*).mp.
26	(bleed* adj3 substantial*).mp.
27	(bleed* adj3 considerabl*).mp.

Appendix

28	(bleed* adj3 acute*).mp.
29	(bleed* adj3 excess*).mp.
30	(bleed* adj3 major).mp.
31	(bleed* adj3 massive).mp.
32	(bleed* adj3 serious*).mp.
33	(bleed* adj3 (severe or severely)).mp.
34	(bleed* adj3 greater than).mp.
35	(bleed* adj3 ml).mp.
36	exp bleeding/ and (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*).mp.
37	(h?emorrhag* adj3 (acute* or significan* or substantial* or considerabl* or excess* or serious* or sever* or appreciabl*)).mp.
38	(massive adj3 transfusion?).mp,kw.
39	(massively adj3 transfuse?).mp,kw.
40	blood transfusion/ or blood component therapy/ or erythrocyte transfusion/
41	erythrocyte concentrate/
42	(blood adj3 transfus*).mp,kw.
43	prbc.mp,kw.
44	packed red blood cell?.mp,kw.
45	(erythrocyte? adj2 transfus*).mp,kw.
46	(red blood cell? adj2 transfus*).mp,kw.
47	(rbc adj2 transfus*).mp,kw.
48	or/1-47 [Massive / Acute Blood Loss / Blood Transfusion]
49	exp hemoglobin/
50	hemoglobin*.mp,kw.
51	haemoglobin*.mp,kw.
52	or/49-51 [Hemoglobins]
53	48 and 52 [Massive / Acute Blood Loss + Hemoglobins]
54	exp surgery/
55	su.fs.
56	exp peroperative care/
57	exp perioperative period/
58	intraop*.mp,kw.
59	intra-op*.mp,kw.

Appendix

1	
2	
3	
4	60 periop*.mp,kw.
5	61 operative*.mp,kw.
6	62 operation?.mp,kw.
7	63 (surgery or surgeries or surgical* or surgeon?).mp,kw.
8	64 Surgeon/
9	65 exp anesthetic agent/
10	66 Anesthesiology/
11	67 exp anesthesia/ or exp analgesia/
12	68 an?esth*.mp,kw.
13	69 or/54-68 [Surgery OR Perioperative OR Anesthesia]
14	70 53 and 69 [** Massive Blood Loss + Hemoglobins + Sx/Periop/Anesth **]
15	71 exp cohort analysis/
16	72 exp prognosis/ or prognostic assessment/
17	73 exp morbidity/
18	74 exp mortality/
19	75 exp survival/
20	76 statistical model/
21	77 prognos*.tw.
22	78 predict*.tw.
23	79 course*.tw.
24	80 diagnosed.tw.
25	81 cohort*.tw.
26	82 death.tw.
27	83 or/71-82
28	84 70 and 83 [** Massive Blood Loss + Hemoglobins + Sx/Periop/Anesth + M/M/Prognosis **]
29	85 limit 84 to english
30	86 (exp animals/ or exp animal experimentation/ or nonhuman/) not ((exp animals/ or exp animal experimentation/ or nonhuman/) and exp human/)
31	87 85 not 86
32	88 limit 85 to human
33	89 87 or 88
34	90 limit 89 to yr="2005 -Current"
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	
60	

Appendix

91	limit 90 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
92	90 not 91
93	limit 90 to (adult <18 to 64 years> or aged <65+ years>)
94	92 or 93
95	remove duplicates from 94
96	limit 95 to (book or book series or conference abstract or conference proceeding or "conference review")
97	95 not 96

(d) PubMed-NOT-Medline Search Strategy

Search	Query
#9	Search (((((((blood loss OR hemorrhage OR blood transfusion)) AND (hemoglobin OR hemoglobins OR haemoglobin OR haemoglobins))) AND (surgery OR surgeries OR surgical OR surgeon OR surgeons OR operation OR operations OR operative OR perioperative OR peroperative OR intraoperative OR anesthesia OR anaesthesia OR anesthesiology OR anaesthesiology OR anesthetic OR anesthetics))) AND (morbidity OR mortality OR prognosis OR survival OR cohort OR predict OR prediction OR course OR courses OR diagnosed OR death OR deaths))) AND (((publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR inprocess[sb] OR pubmednotmedline[sb] OR oldmedline[sb] OR ((pubstatusnihms OR pubstatuspmcsd) AND publisher[sb]))) Sort by: PublicationDate
#8	Search (((publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR inprocess[sb] OR pubmednotmedline[sb] OR oldmedline[sb] OR ((pubstatusnihms OR pubstatuspmcsd) AND publisher[sb]))) Sort by: PublicationDate
#7	Search (((((((blood loss OR hemorrhage OR blood transfusion)) AND (hemoglobin OR hemoglobins OR haemoglobin OR haemoglobins))) AND (surgery OR surgeries OR surgical OR surgeon OR surgeons OR operation OR operations OR operative OR perioperative OR peroperative OR intraoperative OR anesthesia OR anaesthesia OR anesthesiology OR anaesthesiology OR anesthetic OR anesthetics))) AND (morbidity OR mortality OR prognosis OR survival OR cohort OR predict OR prediction OR course OR courses OR diagnosed OR death OR deaths) Sort by: PublicationDate
#6	Search morbidity OR mortality OR prognosis OR survival OR cohort OR predict OR prediction OR course OR courses OR diagnosed OR death OR deaths Sort by: PublicationDate
#5	Search (((((((blood loss OR hemorrhage OR blood transfusion)) AND (hemoglobin OR hemoglobins OR haemoglobin OR haemoglobins))) AND (surgery OR surgeries OR surgical OR surgeon OR surgeons OR operation OR operations OR operative OR perioperative OR peroperative OR intraoperative OR anesthesia OR anaesthesia OR anesthesiology OR anaesthesiology OR anesthetic OR anesthetics) Sort by: PublicationDate

Appendix

#4	Search surgery OR surgeries OR surgical OR surgeon OR surgeons OR operation OR operations OR operative OR perioperative OR peroperative OR intraoperative OR anesthesia OR anaesthesia OR anesthesiology OR anaesthesiology OR anesthetic OR anesthetics Sort by: PublicationDate
#3	Search ((blood loss OR hemorrhage OR blood transfusion)) AND (hemoglobin OR hemoglobins OR haemoglobin OR haemoglobins) Sort by: PublicationDate
#2	Search hemoglobin OR hemoglobins OR haemoglobin OR haemoglobins Sort by: PublicationDate
#1	Search blood loss OR hemorrhage OR blood transfusion Sort by: PublicationDate

For peer review only

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Page	Checklist item
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	1	Identify the report as a protocol of a systematic review
Update	1b	NA	If the protocol is for an update of a previous systematic review, identify as such
Registration	2		If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:			
Contact	3a	1-2	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	21	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	NA	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:			
Sources	5a	20	Indicate sources of financial or other support for the review
Sponsor	5b	NA	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	NA	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION			
Rationale	6	6-7	Describe the rationale for the review in the context of what is already known
Objectives	7	8,24	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS			
Eligibility criteria	8	26-27	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	11	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Appendix	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:			

Data management	11a	12	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	12	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	13	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	13-14	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	26,27	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	NA	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	NA	Describe criteria under which study data will be quantitatively synthesised
	15b	NA	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)
	15c	NA	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	NA	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	NA	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	NA	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.