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# Guidelines on the intraoperative transfusion of red blood cells: a protocol for systematic review

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## ABSTRACT

**Introduction** A significant proportion of red blood cell transfusions are administered intraoperatively; yet there is limited evidence to guide transfusion decisions in this setting. The objective of this systematic review is to explore the availability, quality and content of clinical practice guidelines (CPG) reporting on the indication for allogenic RBC transfusion in the intraoperative setting.

**Methods** Major electronic databases (MEDLINE, EMBASE and CINAHL), guideline clearinghouses and Google Scholar, will be systematically searched from inception to January 2019 for CPGs pertaining to indications for intraoperative allogenic RBC transfusion. Characteristics of eligible guidelines will be reported in a summary table. The AGREE II instrument will be used to appraise the quality of identified guidelines. Recommendations advising on indications for intraoperative RBC transfusion will be manually extracted and presented to allow for comparison of similarities and/or discrepancies in the literature. .

**Ethics and dissemination** The results of this systematic review will be disseminated through relevant conferences and peer-reviewed journals.

**Protocol registration number** PROSPERO CRD42018111487

**Strengths and limitations of this study:**

- The proposed study is the first systematic review to identify the availability of practice guidelines advising on intraoperative red blood cell transfusion
- A multidisciplinary group of methodologic and content experts are involved in this review
- The search strategy will be PRESS reviewed
- Guidelines in all languages will be considered for inclusion

- The Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument, an internationally validated tool, will be utilized to assess the quality of guidelines by four independent reviewers

## INTRODUCTION

Red blood cell (RBC) transfusions although potentially lifesaving, are a costly and limited resource, associated with possible harm. Potential adverse outcomes range in severity, from minor to life-threatening. Relatively mild reactions include febrile non-hemolytic transfusion reactions, minor allergic reactions, or development of RBC alloantibodies. RBC alloantibodies can usually be managed with the provision of antigen negative products (1)(2). However, in the case of rare antibodies, development of alloantibodies can complicate administration of future blood products (1). Life-threatening transfusion reactions include anaphylaxis, transfusion related acute lung injury, bacterial contamination of blood products resulting in sepsis, acute hemolytic transfusion reactions, and transfusion associated circulatory overload (1)(2). While the risk of transfusion transmitted viral infections has dropped drastically in recent years and the risk of this occurring is extremely low, it remains a concern when deciding to transfuse patients (2). RBC transfusions may also cause immunosuppression in the recipient, a process called “transfusion-related immunomodulation (TRIM) (3). TRIM provides rationale for the negative association observed between RBC transfusion and post-operative adverse events as well as cancer recurrence in patients undergoing oncology surgery (4) (5) (6) (7) (8) (9) (10). At an estimated price tag of $US761 per unit, RBC transfusions are costly (11) (12). They are also in short supply, relying on altruistic blood donors to ensure inventory stability (13) (14). Given their associated risk, expense and scarcity, it is critical they are administered wisely.

There has been significant evolution in our understanding of humans’ ability to tolerate anemia; resulting in a shift in approach to RBC transfusion prescribing practices from the “10/30” rule (i.e. transfusion indicated below a hemoglobin of 10g/L or hematocrit <30%) to the widely accepted transfusion trigger of 70g/L in the asymptomatic patient without significant cardiac

comorbidity. This change came into effect following reporting of the TRICC trial and others that have shown the safety of a restrictive transfusion threshold (15, 16) (17) (18). Importantly, the findings of these studies, which have impacted transfusion practices across a broad spectrum of clinical scenarios, are not necessarily applicable in the operative setting.

The operative setting presents a unique situation in which the indications for transfusion commonly reported in the non-operative patient have limited transferability. As blood loss, and consequently hemoglobin concentration can be unpredictable during surgery, hemoglobin concentrations may drop suddenly, making previous measurements of hemoglobin concentration invalid. This limits the feasibility of utilizing specific hemoglobin levels to guide RBC transfusion administration in surgical patients (19). There is some literature to suggest estimated surgical blood loss can be utilized to guide transfusion decisions (20) (21). However, there is good evidence to support the inability of clinicians to accurately predict blood loss (22). It is also important to appreciate that not all intraoperative bleeding is the same, varying from a persistent, slow ooze, to massive, rapid blood loss from a major vessel. Additionally, reliance on hemodynamics is complex as in addition to blood loss, it is a reflection of multiple variables, including but not limited to: anesthetic agents, patient positioning, presence of pneumoperitoneum and neurologic stimulation (23). In the non-operative setting, acute blood loss of approximately 20% results in a compensatory tachycardia (24). However, because of the other variables at play in the anesthetized patient, tachycardia is not a reliable marker of blood loss. Another common recommendation is to monitor for the presence of inadequate perfusion and oxygenation of vital organs (21). The ability to monitor for symptoms of decreased end-organ perfusion such as decreased level of consciousness, chest pain, or abdominal pain, are not possible in the unconscious patient under general anesthesia. Incorporation of decision rules specific to surgical patient, such as monitoring for ST changes, are fundamental to guiding appropriate RBC transfusion for a patient under general anesthesia for surgery(25).

The uncertainty of transfusion indications in this patient population is demonstrated by the abundance of literature reporting on the wide variability in transfusion practices but largely reporting

over-transfusion of surgical patients (26) (27) (28) (29) (30). A recent survey of Canadian liver surgeons and anesthesiologists highlights the lack of consensus between practitioners regarding indications for transfusion. In response to the question "what is the most important information you use to decide on intraoperative transfusion," the majority of anesthesiologist selected hemoglobin value (47.2% vs 19% of surgeons; $p<0.05$), whereas surgeons selected hemodynamics (33.4% vs 14% of anesthesiologist; $p>0.05$) (31). A prospective observational study of intraoperative transfusion practices in Europe reported "physiologic trigger irrespective of hemoglobin" as the most common indication for transfusion in a cohort of 5803 patients (32). Despite a global shift to a more restrictive transfusion strategy, wide variability in practice patterns in the intraoperative setting exists, and therefore warrants a review of the recommendations.

A preliminary search reveals guidance pertaining to RBC transfusion in the intraoperative patient population is lacking. Recently published guidelines from AABB, a worldwide leader in producing clinical practice guidelines for utilization of blood components, neglected to provide recommendations on indications for RBC transfusion in the intraoperative setting likely due to a lack of evidence on which to base recommendations (33). Guidelines endorsed by surgical and anesthesia societies offer vague recommendations with limited directives for when to transfuse, for example, to monitor for blood loss, check hemoglobin or hematocrit prior to transfusion, adopt a restrictive transfusion strategy or assess for adequate perfusion and oxygenation (34) (35) (36) (37) (38). As eluded to previously, reliance on these variables is limited in the intraoperative period. A formal review of the literature to understand available guidance for intraoperative RBC decisions is necessary.

In summary, blood transfusions are associated with possible harm and over-transfusion in the intraoperative setting is common. Although there is an abundance of guidance pertaining to indications for RBC transfusion, a review of guidance dedicated to the intraoperative patient does not currently exist.

## OBJECTIVE

The objective of this systematic review is to explore the availability, quality and consistency of published guidelines reporting on the indication for allogenic red blood cell transfusion in the intraoperative setting. We also aim to summarize the existing recommendations and associated level of evidence.

## METHODS

The Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) checklist guidelines were referenced for development of this protocol (39) (40). A PRISMA-P checklist is available as a supplementary document. The protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews on October 16, 2018 (CRD42018111487).

Any amendments made to the current protocol will be published using a protocol addendum, accompanied by the date of and rationale for the reported amendment, with the final manuscript.

***Eligibility criteria:***

Guidelines reporting on indications for allogenic red blood cell transfusion in the intraoperative setting will be considered for inclusion. Our definition of clinical practice guidelines is adopted from the Institute of Medicine and National Guideline Clearinghouse which define them as recommendations, derived from systematic review of evidence, from collective opinions of an expert panel, aimed at health care providers intended to improve patient care (41, 42). An article will be included if it: (1) is presented as a clinical practice guideline; (2) is based on a systematic review of evidence; (3) is produced by a medical association, professional society, public or private organization or government agency and not by an individual(s) not sponsored or supported by the above groups; (4) includes recommendations for indications for allogenic red blood cell transfusion in the intraoperative setting; (5) in any language; (6) full-text available.

We plan on excluding: (1) documents that do not meet the definition of a guideline as stated above; (2) guidelines pertaining to the perioperative period that do not make specific

recommendations on the intraoperative setting (3) previous documents replaced by updated versions from the same organization.

***Information sources and search strategy***

MEDLINE (OVID interface, including In-Process and Epub Ahead of Print) and EMBASE (OVID interface) and CINHAL will be systematically searched from inception to January 2019, through application of a search strategy developed by a health science librarian with expertise in systematic reviews. Search terms will include 'allogenic red blood cell transfusion', 'guideline' and 'operative'. The search will not be restricted by date, language or patient population (ie. adult versus pediatric). A Peer Review of Electronic Search Strategies (PRESS) will be performed by a second information specialist who is not associated with the project. A draft search strategy for Medline can be found in Appendix 1. The following guideline-specific databases will also be searched: National Institute for Health and Care Excellence (NICE) (UK), the Canadian Medical Association Infobase (Canada), the G-I-N International Guideline Library, the New Zealand Guidelines (NZG) Group, The World Health Organization and the Scottish Intercollegiate Guidelines Network (SIGN) (43-48). Google Scholar will be searched with '(intraoperative OR perioperative) AND (guideline OR consensus OR recommendation OR statement)' and the first 200 records will be screened. References of identified articles will be reviewed for relevant guidelines.

***Study Records***

Articles identified through the electronic databases (MEDLINE and EMBASE) will be imported into Covidence, an online citation manager (49). All titles and abstracts identified will be independently screened by two reviewers for relevance and categorized as relevant, possibly relevant, or irrelevant. Articles categorized as relevant or possibly relevant will be retrieved for further evaluation. Full texts will also reviewed in duplicate for eligibility. Google translate will be used to translate non-English, non-French articles, with the exception of those written in Chinese (50). Any disagreement regarding relevancy will be resolved by a senior author. Reason for study exclusion will be documented and presented in the PRISMA flow diagram for study screening (Figure 1).

Guidelines identified from the guideline repositories will be recorded in an Excel spread sheet.

***Data Items***

Data pertaining to the publication details (authors, year of publication, journal, etc), population(s) in which the intraoperative transfusion guidelines pertain to (type of surgery), patient variables taken into consideration in determining appropriateness for transfusion (example: hemodynamics, blood loss, evidence of cardiac ischemia, etc.), and grading of recommendation if assigned will be extracted. Data extraction forms (DEF) will be developed and piloted independently by two reviewers on a set of 5 randomly selected guidelines. Modifications will be made to the DEF as necessary. Data will be extracted independently by two reviewers, in duplicate.

***Outcomes & Prioritization***

The objectives are to (1) characterize the clinical practice guidelines advising on intraoperative RBC utilization (2) appraise their quality and (3) provide a descriptive summary of the included guidelines.

***Characterization of identified guidelines***

A descriptive table of identified guidelines will be presented. This table will include information publication information as well as the target patient population of the guideline.

***Guideline quality assessment: AGREE II***

The Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument will be used to assess the quality of included guidelines (51). The AGREE II instrument is a validated questionnaire aimed at assessing the methodologic quality of clinical practice guidelines and has been widely adopted in the scientific literature (51) (52) (53). It is comprised of 23 questions scored on a seven-point Likert scale (whereby 7 indicates the highest quality), covering 6 domains, inclusive of scope and purpose of the guidelines, stakeholder involvement, rigour of development, clarity of presentation and editorial independent. There are two additional questions. The first assesses the overall quality of the guideline, rated on a seven-point Likert scale. The final question asks the evaluator whether they would recommend using this guideline, to which the assessor responds "yes," "yes, with modifications," or "no."

It is recommended that four assessors complete the AGREE II to achieve an intra-class correlation coefficient ≥0.7. Four appraisers will therefore be selected to complete the online training and independently evaluate the included guidelines. Once complete, the evaluators will meet and discuss any scores differing by more than 1 point. At that point, evaluators can amend or keep their original score. Inter-rater reliability will be calculated using the intraclass correlation coefficient (ICC) using SAS.

Domain scores will be reported separately using both the median and scaled domain scores, as is recommended by the AGREE II consortium. The scaled domain score will be calculated as follows: (obtained score-minimal possible score)/(maximal possible score-minimal possible score)=__%. The minimum possible score is calculated as: (number of questions) x (number of reviewers) x 1. The maximum possible score is calculated as: (number of questions) x (number of reviewers) x 7.

***Recommendation synthesis***

A descriptive table of included studies will be presented displaying all recommendations pertaining to indications for RBC transfusion in the intraoperative period. Recommendations will be compared for consistency and/or repetition.

***Analysis of subgroups or subsets***

Guidelines pertaining to indications for blood transfusion in cardiac versus non-cardiac surgery patients will be grouped and considered separately .

***Dissemination***

The results of this review will be submitted for presentation at national and international meetings and publication in a peer-reviewed journal.

***Reporting of review***

The findings of this systematic review will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. The completed checklist will be provided as supplementary material.

***Confidence in cumulative evidence***

The quality of recommendations will be evaluated by using the systematic and comprehensive approach known as Grading of Recommendations, Assessment, Development and Evaluations (GRADE) (54). The quality of evidence will be assessed across the domains of risk of bias, consistency, directness, precision and publication bias.

***Patient and public involvement***

This investigation is aligned with research priorities established by The Canadian Blood Services (CBS), a not-for-profit charitable organization, responsible for managing the Canadian blood supply (with the exception of Quebec) (55). Specifically, they have identified: (1) promoting appropriate blood product utilization and (2) ensuring an adequate blood product supply, as two of five research priorities. CBS invites public participation in their bi-annual board meetings, where a number of issues are addressed, inclusive of priority research agendas. Patients or the public were not involved in the development of our specific research question or outcome measures of interests.

## DISCUSSION

A significant number of patients receive intra-operative transfusion. However, there is substantial variation in transfusion practice and a paucity of guidance available. Despite the fact that a plea for intraoperative blood transfusion guidelines was made over 20 years ago, widely adopted recommendations have yet to be developed. (56) A systematic review of transfusion guidelines in the intraoperative setting has not previously been performed. Although a quality appraisal of RBC and plasma guidelines was published in 2018, it did not identify intraoperative recommendations (34). Additionally, their search strategy did not include guideline clearinghouses or the grey literature.

There are several methodologic strengths of our review, these include multidisciplinary input, a PRESS reviewed search strategy, review of the grey literature and application of the AGREE II tool to assess the quality of identified guidelines by four independent reviewers.

This systematic review will allow for identification, appraisal and summary of literature devoted to the guidance of intraoperative allogenic RBC transfusion. The Perioperative Anesthesia Clinical Trials Group (PACT) identified transfusion as 1 of 7 themes that has a significant impact on mortality, reinforcing the importance of this review (57). The results of this review will provide rationale and justification for development of guidance, or the need for prospective evaluation of various intra-operative transfusion strategies. If evidence-informed recommendations for the use of intra-operative transfusion can be developed and disseminated the incidence of over-transfusion may be reduced, ensuring responsible use of this limited resource, and minimizing patient exposure to the risks of transfusion.

To achieve this goal will require collaboration between surgeons, anesthetists, and transfusion specialists. Given the paucity of high quality data on which to base guidelines, this collaboration must first identifies areas where only expert opinion exists and propose methods for further examination. The input of patients who have had intra-operative transfusion should be sought to determine where patient preference may supersede rigorous adherence to guidelines. Following well planned knowledge translation phase, auditing to monitor compliance with the guidelines will need to be done. Additionally, following guideline implementation quality assurance initiatives with patient centred outcomes will also be necessary to ensure that the safety and tolerability of developed guidelines. Thus, it is unlikely that final guideline recommendations regarding intra-operative transfusion will be forthcoming in the near future. However, this review reinforces the urgent need to begin the undertaking.

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**Competing interests:** None to declare.

**Sponsor:** None to declare.

## Authors' Contribution

All authors were involved in the study conception and design. The protocol was drafted and registered with PROSPERO by LB, a Master's student in epidemiology at The University of Ottawa and General Surgery Resident at The Ottawa Hospital. LP is a medical student at The University of Ottawa. AD is a medical librarian at The Ottawa Hospital. DF, a senior scientist in clinical epidemiology at The Ottawa Hospital Research Institute, Director of the Clinical Epidemiology Program, Full Professor in the Department of Medicine, Surgery & School of Epidemiology and Public Health, provided methodology expertise. GM, a an associate scientist in clinical epidemiology at The Ottawa Hospital Research Institute, assistant professor in the department of surgery and attending surgeon in the Liver and Pancreas Unit at The Ottawa Hospital, provided content and methodologic expertise. All authors reviewed and approved the final manuscript. GM is the guarantor of the protocol.

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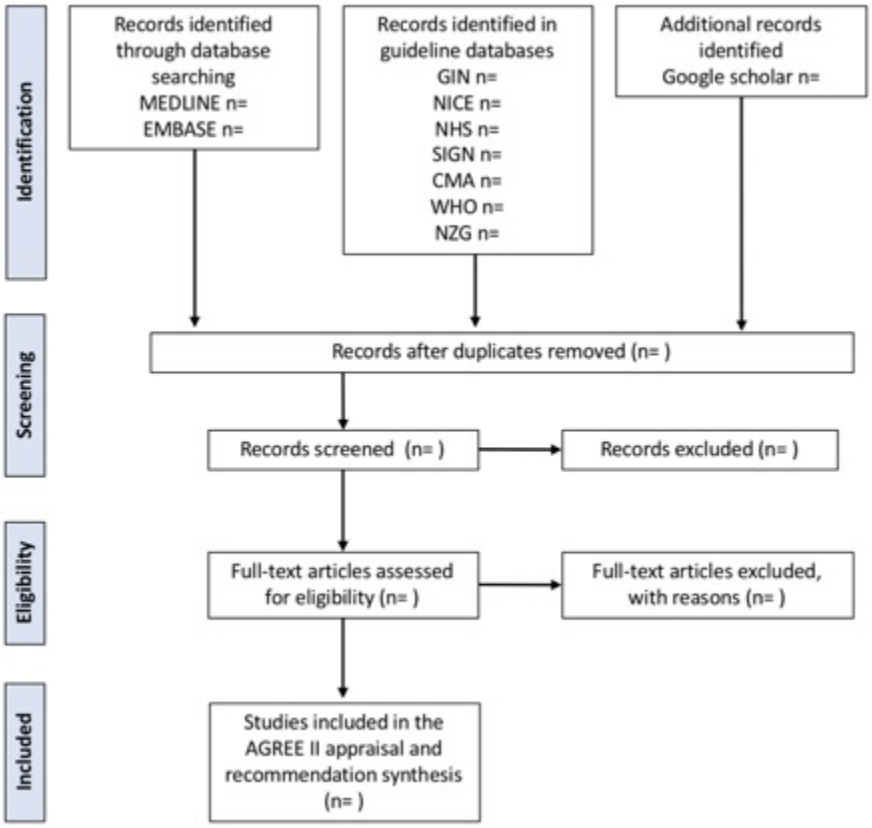


Figure 1: PRISMA Flow Diagram

159x149mm (72 x 72 DPI)

Appendix I: Search Strategy

Database: Ovid MEDLINE(R) ALL <1946 to January 21, 2019>
Search Strategy:
---

1 *blood transfusion/ or blood component transfusion/ or erythrocyte transfusion/ (36153)
2 ((red blood cell$ or rbc or erythrocyte$ or red cell$) adj3 (transfus$ or infus* or retransfus*)).tw. (10506)
3 (blood adj4 transfus*).tw. (54555) - I expanded this
4 RBCT.tw,kw. (95)
5 (RBC transfusion or red blood cell transfusion).kw. (110)
6 (hemotransfus$ or haemotransfus$).tw,kw. (234)
7 or/1-6 (78107)
8 INTRAOPERATIVE COMPLICATIONS/ or INTRAOPERATIVE CARE/ or INTRAOPERATIVE PERIOD/ or Perioperative Care/ (69769)
9 (intraoperat* or intra-operat* or perioperat* or peri-operat*).tw,kw. (205937)
10 (surg* or operat*).ti. (708792) - added this line
11 (transfus* adj5 (operat* or surg*)).tw. (8642)
12 ((undergoing or during) adj4 (surg* or operat*)).tw. (180983) - expanded this line by taking out 'transfus*'
13 or/8-12 (968870)
14 7 and 13 (18339)
15 exp clinical pathway/ (6046)
16 clinical protocol/ (25911)
17 exp consensus/ (9313)
18 exp consensus development conference/ (11078)
19 exp consensus development conferences as topic/ (2618)
20 guidelines as topic/ (37008)
21 exp practice guideline/ (24266)
22 practice guidelines as topic/ (105996)
23 health planning guidelines/ (4007)
24 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. (39641)
25 (standards or guideline or guidelines).ti,kf,kw. (96689)
26 ((practice or treatment* or clinical) adj guideline*).ab. (33765)
27 (CPG or CPGs).ti. (5320)
28 consensus*.ti,kf,kw. (22038)
29 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw. (17432)
30 recommendat*.ti,kf,kw. (35650)
31 or/15-30 (334141)
32 14 and 31 (550)
33 (rbc transfusion* or red blood cell* transfusion*).ti. (1054)
34 (transfus* and (intraoperat* or intra-operat* or perioperat* or peri-operat*)).ti. (1014)
35 33 or 34 (1999)
36 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. (39641)
37 (standards or guideline or guidelines).ti,kf,kw. (96689)
38 36 or 37 (122196)
39 35 and 38 (61)
40 32 or 39 (578)
41 animals/ not humans/ (4465996)
42 40 not 41 (577)
43 (exp infants/ or child/) not adult/ (1517431)
44 42 not 43 (546)

# PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **ADMINISTRATIVE INFORMATION** | | | | | |
| **Title** | | | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | x | ☐ | 1-2 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | ☐ | x | N/A |
| **Registration** | 2 | If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract | x | ☐ | 49 |
| **Authors** | | | | | |
| Contact | 3a | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author | x | ☐ | 4-33 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | x | ☐ | 296-307 |
| **Amendments** | 4 | 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 | x | ☐ | 149-150 |
| **Support** | | | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | x | ☐ | 292-293 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | x | ☐ | 295 |
| Role of sponsor/funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | ☐ | x | N/A |
| **INTRODUCTION** | | | | | |
| **Rationale** | 6 | Describe the rationale for the review in the context of what is already known | x | ☐ | 62-135 |
| **Objectives** | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | x | ☐ | 138-141 |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **METHODS** | | | | | |
| **Eligibility criteria** | 8 | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review | x | ☐ | 151-165 |
| **Information sources** | 9 | Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage | x | ☐ | 166-180 |
| **Search strategy** | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | x | ☐ | Appendix 1 |
| ***STUDY RECORDS*** | | | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | x | ☐ | 181-190 |
| Selection process | 11b | State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis) | x | ☐ | 183-189 |
| Data collection process | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | x | ☐ | 196-198 |
| **Data items** | 12 | List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications | x | ☐ | 191-196 |
| **Outcomes and prioritization** | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | x | ☐ | 199-202 |
| **Risk of bias in individual studies** | 14 | 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 | x | ☐ | 206-228 |
| ***DATA*** | | | | | |
| **Synthesis** | 15a | Describe criteria under which study data will be quantitatively synthesized | x | ☐ | 229-232 |
| | 15b | 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 (e.g., $I^2$, Kendall's tau) | ☐ | x | N/A |
| | 15c | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression) | x | ☐ | 233-235 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | x | ☐ | 229-232 |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **Meta-bias(es)** | 16 | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies) | ☐ | x | N/A |
| **Confidence in cumulative evidence** | 17 | Describe how the strength of the body of evidence will be assessed (e.g., GRADE) | ☐ | x | N/A |

BMJ Open

# Guidelines on the intraoperative transfusion of red blood cells: a protocol for systematic review



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2019-029684.R1 |
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| Primary Subject Heading: | Surgery |
| Secondary Subject Heading: | Anaesthesia, Evidence based practice |
| Keywords: | Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, SURGERY, Blood bank & transfusion medicine < HAEMATOLOGY, Adult anaesthesia < ANAESTHETICS, Paediatric anaesthesia < ANAESTHETICS |
| | |

# Guidelines on the intraoperative transfusion of red blood cells: a protocol for systematic review

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## ABSTRACT

**Introduction** A significant proportion of red blood cell transfusions are administered intraoperatively; yet there is limited evidence to guide transfusion decisions in this setting. The objective of this systematic review is to explore the availability, quality and content of clinical practice guidelines (CPG) reporting on the indication for allogenic RBC transfusion in the intraoperative setting.

**Methods** Major electronic databases (MEDLINE, EMBASE and CINAHL), guideline clearinghouses and Google Scholar, will be systematically searched from inception to January 2019 for CPGs pertaining to indications for intraoperative allogenic RBC transfusion. Characteristics of eligible guidelines will be reported in a summary table. The AGREE II instrument will be used to appraise the quality of identified guidelines. Recommendations advising on indications for intraoperative RBC transfusion will be manually extracted and presented to allow for comparison of similarities and/or discrepancies in the literature. .

**Ethics and dissemination** The results of this systematic review will be disseminated through relevant conferences and peer-reviewed journals.

**Protocol registration number** PROSPERO CRD42018111487

**Strengths and limitations of this study:**

- The proposed study is the first systematic review to identify the availability of practice guidelines advising on intraoperative red blood cell transfusion
- A multidisciplinary group of methodologic and content experts are involved in this review
- The search strategy will be PRESS reviewed
- Guidelines in all languages will be considered for inclusion

- The Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument, an internationally validated tool, will be utilized to assess the quality of guidelines by four independent reviewers

## INTRODUCTION

Red blood cell (RBC) transfusions although potentially lifesaving, are a costly and limited resource, associated with possible harm. Potential adverse outcomes range in severity, from minor to life-threatening. Relatively mild reactions include febrile non-hemolytic transfusion reactions, minor allergic reactions, or development of RBC alloantibodies. RBC alloantibodies can usually be managed with the provision of antigen negative products (1)(2). However, in the case of rare antibodies, development of alloantibodies can complicate administration of future blood products (1). Life-threatening transfusion reactions include anaphylaxis, transfusion related acute lung injury, bacterial contamination of blood products resulting in sepsis, acute hemolytic transfusion reactions, and transfusion associated circulatory overload (1)(2). While the risk of transfusion transmitted viral infections has dropped drastically in recent years and the risk of this occurring is extremely low, it remains a concern when deciding to transfuse patients (2). RBC transfusions may also cause immunosuppression in the recipient, a process called “transfusion-related immunomodulation (TRIM) (3). TRIM provides rationale for the negative association observed between RBC transfusion and post-operative adverse events as well as cancer recurrence in patients undergoing oncology surgery (4) (5) (6) (7) (8) (9) (10). At an estimated price tag of 102-761 USD per unit, RBC transfusions are costly (11) (12) (13) (14). They are also in short supply, relying on altruistic blood donors to ensure inventory stability (15) (16). Given their associated risk, expense and scarcity, it is critical they are administered wisely.

There has been significant evolution in our understanding of humans’ ability to tolerate anemia; resulting in a shift in approach to RBC transfusion prescribing practices from the “10/30” rule (i.e. transfusion indicated below a hemoglobin of 10g/L or hematocrit <30%) to the widely accepted transfusion trigger of 70g/L in the asymptomatic patient without significant cardiac

comorbidity. This change came into effect following reporting of the TRICC trial and others that have shown the safety of a restrictive transfusion threshold (17, 18) (19) (20). Importantly, the findings of these studies, which have impacted transfusion practices across a broad spectrum of clinical scenarios, are not necessarily applicable in the operative setting.

The operative setting presents a unique situation in which the indications for transfusion commonly reported in the non-operative patient have limited transferability. As blood loss, and consequently hemoglobin concentration can be unpredictable during surgery, hemoglobin concentrations may drop suddenly, making previous measurements of hemoglobin concentration invalid. This limits the feasibility of utilizing specific hemoglobin levels to guide RBC transfusion administration in surgical patients (21). There is some literature to suggest estimated surgical blood loss can be utilized to guide transfusion decisions (22) (23). However, there is good evidence to support the inability of clinicians to accurately predict blood loss (24). It is also important to appreciate that not all intraoperative bleeding is the same, varying from a persistent, slow ooze, to massive, rapid blood loss from a major vessel. Additionally, reliance on hemodynamics is complex as in addition to blood loss, it is a reflection of multiple variables, including but not limited to: anesthetic agents, patient positioning, presence of pneumoperitoneum and neurologic stimulation (25). In the non-operative setting, acute blood loss of approximately 20% results in a compensatory tachycardia (26). However, because of the other variables at play in the anesthetized patient, tachycardia is not a reliable marker of blood loss. Another common recommendation is to monitor for the presence of inadequate perfusion and oxygenation of vital organs (23). The ability to monitor for symptoms of decreased end-organ perfusion such as decreased level of consciousness, chest pain, or abdominal pain, are not possible in the unconscious patient under general anesthesia. Incorporation of decision rules specific to surgical patient, such as monitoring for ST changes, are fundamental to guiding appropriate RBC transfusion for a patient under general anesthesia for surgery(27). Another aspect unique to the unconscious patient under general anesthesia, subject to dynamic changes in hemodynamics for a number of reasons, is our limited ability to identify transfusion reactions. Although literature in this area is lacking, it would be reasonable to

hypothesize that transfusion reactions in the intra-operative setting are underreported. This, in combination with the evidence that patients who receive intraoperative transfusions suffer increased short and long term morbidity, advocates for careful consideration of transfusion administration (28) (7).

The uncertainty of transfusion indications in this patient population is demonstrated by the abundance of literature reporting on the wide variability in transfusion practices but largely reporting over-transfusion of surgical patients (29) (30) (31) (32) (33). A recent survey of Canadian liver surgeons and anesthesiologists highlights the lack of consensus between practitioners regarding indications for transfusion. In response to the question "what is the most important information you use to decide on intraoperative transfusion," the majority of anesthesiologist selected hemoglobin value (47.2% vs 19% of surgeons; $p<0.05$), whereas surgeons selected hemodynamics (33.4% vs 14% of anesthesiologist; $p>0.05$) (34). A prospective observational study of intraoperative transfusion practices in Europe reported "physiologic trigger irrespective of hemoglobin" as the most common indication for transfusion in a cohort of 5803 patients (35). Despite a global shift to a more restrictive transfusion strategy, wide variability in practice patterns in the intraoperative setting exists, and therefore warrants a review of the recommendations.

A preliminary search reveals guidance pertaining to RBC transfusion in the intraoperative patient population is lacking. Recently published guidelines from AABB, a worldwide leader in producing clinical practice guidelines for utilization of blood components, neglected to provide recommendations on indications for RBC transfusion in the intraoperative setting likely due to a lack of evidence on which to base recommendations (36). Guidelines endorsed by surgical and anesthesia societies offer vague recommendations with limited directives for when to transfuse, for example, to monitor for blood loss, check hemoglobin or hematocrit prior to transfusion, adopt a restrictive transfusion strategy or assess for adequate perfusion and oxygenation (37) (38) (39) (40) (41). As alluded to previously, reliance on these variables is limited in the intraoperative period. A formal review of the literature to understand available guidance for intraoperative RBC decisions is necessary.

In summary, blood transfusions are associated with possible harm and over-transfusion in the intraoperative setting is common. Although there is an abundance of guidance pertaining to indications for RBC transfusion, a review of guidance dedicated to the intraoperative patient does not currently exist.

## OBJECTIVE

The objective of this systematic review is to explore the availability, quality and consistency of published guidelines reporting on the indication for allogenic red blood cell transfusion in the intraoperative setting. We also aim to summarize the existing recommendations and associated level of evidence.

## METHODS

The Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) checklist guidelines were referenced for development of this protocol (42) (43). A PRISMA-P checklist is available as a supplementary document. The protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews on October 16, 2018 (CRD42018111487).

Any amendments made to the current protocol will be published using a protocol addendum, accompanied by the date of and rationale for the reported amendment, with the final manuscript.

***Eligibility criteria:***

Guidelines reporting on indications for allogenic red blood cell transfusion in the intraoperative setting will be considered for inclusion. Our definition of clinical practice guidelines is adopted from the Institute of Medicine and National Guideline Clearinghouse which define them as recommendations, derived from systematic review of evidence, from collective opinions of an expert panel, aimed at health care providers intended to improve patient care (44, 45). An article will be included if it: (1) is presented as a clinical practice guideline; (2) is based on a systematic review of evidence; (3) is produced by a medical association, professional society, public or private

organization or government agency and not by an individual(s) not sponsored or supported by the above groups; (4) includes recommendations for indications for allogenic red blood cell transfusion in patients undergoing general anesthesia in an operating room; (5) in any language; (6) full-text available.

We plan on excluding: (1) documents that do not meet the definition of a guideline as stated above; (2) guidelines pertaining to the perioperative period that do not make specific recommendations on the intraoperative setting (3) previous documents replaced by updated versions from the same organization.

***Information sources and search strategy***

MEDLINE (OVID interface, including In-Process and Epub Ahead of Print) and EMBASE (OVID interface) and CINHAL will be systematically searched from inception to January 2019, through application of a search strategy developed by a health science librarian with expertise in systematic reviews. Search terms will include 'allogenic red blood cell transfusion', 'guideline' and 'operative'. The search will not be restricted by date, language or patient population (ie. adult versus pediatric). A Peer Review of Electronic Search Strategies (PRESS) will be performed by a second information specialist who is not associated with the project. A draft search strategy for Medline can be found in Appendix 1. The following guideline-specific databases will also be searched: National Institute for Health and Care Excellence (NICE) (UK), the Canadian Medical Association Infobase (Canada), the G-I-N International Guideline Library, the New Zealand Guidelines (NZG) Group, The World Health Organization and the Scottish Intercollegiate Guidelines Network (SIGN) (46-51). Google Scholar will be searched with '(intraoperative OR perioperative) AND (guideline OR consensus OR recommendation OR statement)' and the first 200 records will be screened. References of identified articles will be reviewed for relevant guidelines.

***Study Records***

Articles identified through the electronic databases (MEDLINE and EMBASE) will be imported into Covidence, an online citation manager (52). All titles and abstracts identified will be independently screened by two reviewers for relevance and categorized as relevant, possibly

relevant, or irrelevant. Articles categorized as relevant or possibly relevant will be retrieved for further evaluation. Full texts will also reviewed in duplicate for eligibility. Google translate will be used to translate non-English, non-French articles, with the exception of those written in Chinese (53). Any disagreement regarding relevancy will be resolved by a senior author, independent from the reviewers. Reason for study exclusion will be documented and presented in the PRISMA flow diagram for study screening (Figure 1).

Guidelines identified from the guideline repositories will be recorded in an Excel spread sheet.

***Data Items***

Data pertaining to the publication details (authors, year of publication, journal, etc) will be identified. All relevant recommendations will be extracted from the guidelines to aid in the determination of population(s) in which the intraoperative transfusion guidelines pertain to (type of surgery), patient variables taken into consideration in determining appropriateness for transfusion, and grading of recommendation if assigned will be extracted. We will identify whether or not the following variables are accounted for in identified decision rules or recommendations: patient comorbidities-specifically a history of coronary artery disease, hemodynamics (hypotension, tachycardia, or presence of vasopressor support), estimated blood loss, evidence of cardiac ischemia, and evidence of end organ ischemia in addition to cardiac. Data extraction forms (DEF) will be developed and piloted independently by two reviewers on a set of 5 randomly selected guidelines. Modifications will be made to the DEF as necessary. Data will be extracted independently by two reviewers, in duplicate.

***Outcomes & Prioritization***

The objectives are to (1) characterize the clinical practice guidelines advising on intraoperative RBC utilization (2) appraise their quality and (3) provide a descriptive summary of the included guidelines.

***Characterization of identified guidelines***

A descriptive table of identified guidelines will be presented. This table will include information publication information as well as the target patient population of the guideline.

***Guideline quality assessment: AGREE II***

The Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument will be used to assess the quality of included guidelines (54). The AGREE II instrument is a validated questionnaire aimed at assessing the methodologic quality of clinical practice guidelines and has been widely adopted in the scientific literature (54) (55) (56). It is comprised of 23 questions scored on a seven-point Likert scale (whereby 7 indicates the highest quality), covering 6 domains, inclusive of scope and purpose of the guidelines, stakeholder involvement, rigour of development, clarity of presentation and editorial independent. There are two additional questions. The first assesses the overall quality of the guideline, rated on a seven-point Likert scale. The final question asks the evaluator whether they would recommend using this guideline, to which the assessor responds "yes," "yes, with modifications," or "no."

It is recommended that four assessors complete the AGREE II to achieve an intra-class correlation coefficient ≥0.7. Four appraisers will therefore be selected to complete the online training and independently evaluate the included guidelines. Once complete, the evaluators will meet and discuss any scores differing by more than 1 point. At that point, evaluators can amend or keep their original score. Inter-rater reliability will be calculated using the intraclass correlation coefficient (ICC) using SAS.

Domain scores will be reported separately using both the median and scaled domain scores, as is recommended by the AGREE II consortium. The scaled domain score will be calculated as follows: (obtained score-minimal possible score)/(maximal possible score-minimal possible score)=__%. The minimum possible score is calculated as: (number of questions) x (number of reviewers) x 1. The maximum possible score is calculated as: (number of questions) x (number of reviewers) x 7.

***Recommendation synthesis***

A descriptive table of included studies will be presented displaying all recommendations pertaining to indications for RBC transfusion in the intraoperative period. Recommendations will be compared for consistency and/or repetition.

***Analysis of subgroups or subsets***

Guidelines pertaining to indications for blood transfusion in cardiac versus non-cardiac surgery patients will be grouped and considered separately. In addition, guidelines published following publication of the TRICC trial in May 1997 will be considered separately in our descriptive analysis (18). The rationale for this being that the prevailing theme of current practice is a result of this trial.

***Dissemination***

The results of this review will be submitted for presentation at national and international meetings and publication in a peer-reviewed journal.

***Reporting of review***

The findings of this systematic review will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. The completed checklist will be provided as supplementary material.

***Confidence in cumulative evidence***

The quality of recommendations will be evaluated by using the systematic and comprehensive approach known as Grading of Recommendations, Assessment, Development and Evaluations (GRADE) (57). The quality of evidence will be assessed across the domains of risk of bias, consistency, directness, precision and publication bias.

***Patient and public involvement***

This investigation is aligned with research priorities established by The Canadian Blood Services (CBS), a not-for-profit charitable organization, responsible for managing the Canadian blood supply (with the exception of Quebec) (58). Specifically, they have identified: (1) promoting appropriate blood product utilization and (2) ensuring an adequate blood product supply, as two of five research priorities. CBS invites public participation in their bi-annual board meetings, where a number of issues are addressed, inclusive of priority research agendas. Patients or the public

were not involved in the development of our specific research question or outcome measures of interests.

## DISCUSSION

A significant number of patients receive intra-operative transfusion. However, there is substantial variation in transfusion practice and a paucity of guidance available. Despite the fact that a plea for intraoperative blood transfusion guidelines was made over 20 years ago, widely adopted recommendations have yet to be developed. (59) A systematic review of transfusion guidelines in the intraoperative setting has not previously been performed. Although a quality appraisal of RBC and plasma guidelines was published in 2018, it did not identify intraoperative recommendations (37). Additionally, their search strategy did not include guideline clearinghouses or the grey literature.

There are several methodologic strengths of our review, these include multidisciplinary input, a PRESS reviewed search strategy, review of the grey literature and application of the AGREE II tool to assess the quality of identified guidelines by four independent reviewers.

This systematic review will allow for identification, appraisal and summary of literature devoted to the guidance of intraoperative allogenic RBC transfusion. The Perioperative Anesthesia Clinical Trials Group (PACT) identified transfusion as 1 of 7 themes that has a significant impact on mortality, reinforcing the importance of this review (60). The results of this review will provide rationale and justification for development of guidance, or the need for prospective evaluation of various intra-operative transfusion strategies. If evidence-informed recommendations for the use of intra-operative transfusion can be developed and disseminated the incidence of over-transfusion may be reduced, ensuring responsible use of this limited resource, and minimizing patient exposure to the risks of transfusion.

To achieve this goal will require collaboration between surgeons, anesthetists, and transfusion specialists. Given the paucity of high quality data on which to base guidelines, this collaboration must first identifies areas where only expert opinion exists and propose methods for

further examination. The input of patients who have had intra-operative transfusion should be sought to determine where patient preference may supersede rigorous adherence to guidelines. Following well planned knowledge translation phase, auditing to monitor compliance with the guidelines will need to be done. Additionally, following guideline implementation quality assurance initiatives with patient centred outcomes will also be necessary to ensure that the safety and tolerability of developed guidelines. Thus, it is unlikely that final guideline recommendations regarding intra-operative transfusion will be forthcoming in the near future. However, this review reinforces the urgent need to begin the undertaking.

**Acknowledgements:** The authors thank Josee Skuce for her help with developing and PRESS reviewing the search strategy, as well as retrieving articles.

**Funding:** Canadian Blood Services Blood Efficiency and Accelerator Award Program and The Academic Health Science Center Alternative Funding Plan Innovation Fund.

**Competing interests:** None to declare.

**Sponsor:** None to declare.

## Authors' Contribution

Laura Baker is responsible for aiding in the conception of the work, drafting and revising the manuscript, approves the submitted version and is accountable for all aspects of the work.

Lily Park, Richard Gilbert, Andre Martel, Hilalion Ahn, Alexandra Davies, Daniel McIsaac, Elianna Saidenberg and Alan Tinmouth are responsible for aiding in the conception of the work, revising the manuscript, approving the final version and are in agreement to being accountable for all aspects of the work.

Dean Fergusson and Guillaume Martel are responsible for aiding in the conception of the work, revising it for important intellectual content, give their approval of the content for publication and agree to accountability for all aspects of the work. GM is the guarantor of the protocol.

1. Hendrickson JE, Roubinian NH, Chowdhury D, Brambilla D, Murphy EL, Wu Y, et al. Incidence of transfusion reactions: a multicenter study utilizing systematic active surveillance and expert adjudication. Transfusion. 2016;56(10):2587-96.
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49. Canadian Medical Association Infobase.
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Figure 1: Flow diagram of study selection process.

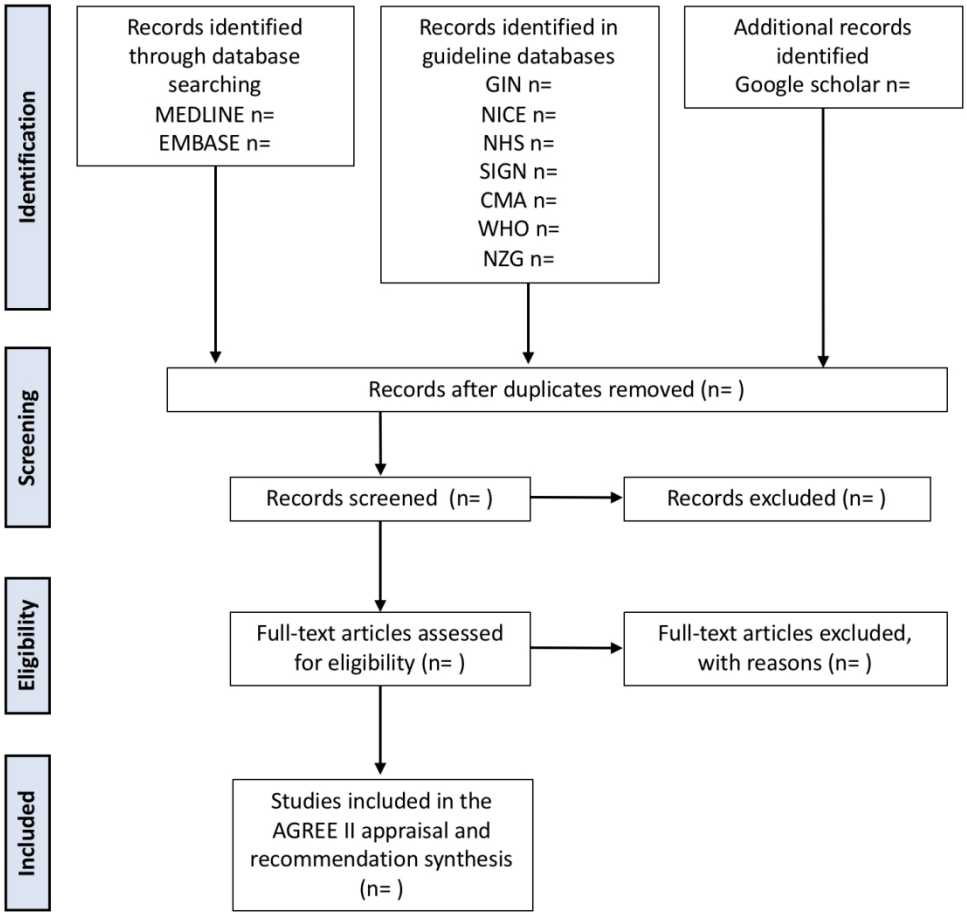


Figure 1: Flow diagram of study selection process.

Appendix I: Search Strategy

Database: Ovid MEDLINE(R) ALL <1946 to January 21, 2019>
Search Strategy:
---

1 *blood transfusion/ or blood component transfusion/ or erythrocyte transfusion/ (36153)
2 ((red blood cell$ or rbc or erythrocyte$ or red cell$) adj3 (transfus$ or infus* or retransfus*)).tw. (10506)
3 (blood adj4 transfus*).tw. (54555) - I expanded this
4 RBCT.tw,kw. (95)
5 (RBC transfusion or red blood cell transfusion).kw. (110)
6 (hemotransfus$ or haemotransfus$).tw,kw. (234)
7 or/1-6 (78107)
8 INTRAOPERATIVE COMPLICATIONS/ or INTRAOPERATIVE CARE/ or INTRAOPERATIVE PERIOD/ or Perioperative Care/ (69769)
9 (intraoperat* or intra-operat* or perioperat* or peri-operat*).tw,kw. (205937)
10 (surg* or operat*).ti. (708792) - added this line
11 (transfus* adj5 (operat* or surg*)).tw. (8642)
12 ((undergoing or during) adj4 (surg* or operat*)).tw. (180983) - expanded this line by taking out 'transfus*'
13 or/8-12 (968870)
14 7 and 13 (18339)
15 exp clinical pathway/ (6046)
16 clinical protocol/ (25911)
17 exp consensus/ (9313)
18 exp consensus development conference/ (11078)
19 exp consensus development conferences as topic/ (2618)
20 guidelines as topic/ (37008)
21 exp practice guideline/ (24266)
22 practice guidelines as topic/ (105996)
23 health planning guidelines/ (4007)
24 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. (39641)
25 (standards or guideline or guidelines).ti,kf,kw. (96689)
26 ((practice or treatment* or clinical) adj guideline*).ab. (33765)
27 (CPG or CPGs).ti. (5320)
28 consensus*.ti,kf,kw. (22038)
29 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw. (17432)
30 recommendat*.ti,kf,kw. (35650)
31 or/15-30 (334141)
32 14 and 31 (550)
33 (rbc transfusion* or red blood cell* transfusion*).ti. (1054)
34 (transfus* and (intraoperat* or intra-operat* or perioperat* or peri-operat*)).ti. (1014)
35 33 or 34 (1999)
36 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. (39641)
37 (standards or guideline or guidelines).ti,kf,kw. (96689)
38 36 or 37 (122196)
39 35 and 38 (61)
40 32 or 39 (578)
41 animals/ not humans/ (4465996)
42 40 not 41 (577)
43 (exp infants/ or child/) not adult/ (1517431)
44 42 not 43 (546)

# PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **ADMINISTRATIVE INFORMATION** | | | | | |
| **Title** | | | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | x | ☐ | 1-2 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | ☐ | x | N/A |
| **Registration** | 2 | If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract | x | ☐ | 49 |
| **Authors** | | | | | |
| Contact | 3a | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author | x | ☐ | 4-33 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | x | ☐ | 312-323 |
| **Amendments** | 4 | 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 | x | ☐ | 155-156 |
| **Support** | | | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | x | ☐ | 308-309 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | x | ☐ | 311 |
| Role of sponsor/funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | ☐ | x | N/A |
| **INTRODUCTION** | | | | | |
| **Rationale** | 6 | Describe the rationale for the review in the context of what is already known | x | ☐ | 61-141 |
| **Objectives** | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | x | ☐ | 143-147 |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **METHODS** | | | | | |
| **Eligibility criteria** | 8 | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review | x | ☐ | 157-172 |
| **Information sources** | 9 | Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage | x | ☐ | 173-187 |
| **Search strategy** | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | x | ☐ | Appendix 1 |
| ***STUDY RECORDS*** | | | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | x | ☐ | 189-190 |
| Selection process | 11b | State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis) | x | ☐ | 190-193 |
| Data collection process | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | x | ☐ | 199-211 |
| **Data items** | 12 | List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications | x | ☐ | 199-211 |
| **Outcomes and prioritization** | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | x | ☐ | 212-215 |
| **Risk of bias in individual studies** | 14 | 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 | x | ☐ | 219-241 |
| ***DATA*** | | | | | |
| **Synthesis** | 15a | Describe criteria under which study data will be quantitatively synthesized | x | ☐ | 219 |
| | 15b | 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 (e.g., $I^2$, Kendall's tau) | ☐ | x | N/A |
| | 15c | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression) | x | ☐ | 246-251 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | x | ☐ | 242-245 |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **Meta-bias(es)** | 16 | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies) | ☐ | x | N/A |
| **Confidence in cumulative evidence** | 17 | Describe how the strength of the body of evidence will be assessed (e.g., GRADE) | ☐ | x | N/A |

BMJ Open

# Guidelines on the intraoperative transfusion of red blood cells: a protocol for systematic review

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|---|---|
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| | |

# Guidelines on the intraoperative transfusion of red blood cells: a protocol for systematic review

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## ABSTRACT

**Introduction** A significant proportion of red blood cell transfusions are administered intraoperatively; yet there is limited evidence to guide transfusion decisions in this setting. The objective of this systematic review is to explore the availability, quality and content of clinical practice guidelines (CPG) reporting on the indication for allogenic RBC transfusion during surgery.

**Methods** Major electronic databases (MEDLINE, EMBASE and CINAHL), guideline clearinghouses and Google Scholar, will be systematically searched from inception to January 2019 for CPGs pertaining to indications for intraoperative allogenic RBC transfusion. Characteristics of eligible guidelines will be reported in a summary table. The AGREE II instrument will be used to appraise the quality of identified guidelines. Recommendations advising on indications for intraoperative RBC transfusion will be manually extracted and presented to allow for comparison of similarities and/or discrepancies in the literature. .

**Ethics and dissemination** The results of this systematic review will be disseminated through relevant conferences and peer-reviewed journals.

**Protocol registration number** PROSPERO CRD42018111487

**Strengths and limitations of this study:**

- The proposed study is the first systematic review to identify the availability of practice guidelines advising on intraoperative red blood cell transfusion
- A multidisciplinary group of methodologic and content experts are involved in this review
- The search strategy will be PRESS reviewed
- Guidelines in all languages will be considered for inclusion

- The Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument, an internationally validated tool, will be utilized to assess the quality of guidelines by four independent reviewers

## INTRODUCTION

Red blood cell (RBC) transfusions although potentially lifesaving, are a costly and limited resource, associated with possible harm. Potential adverse outcomes range in severity, from minor to life-threatening. Relatively mild reactions include febrile non-hemolytic transfusion reactions, minor allergic reactions, or development of RBC alloantibodies. RBC alloantibodies can usually be managed with the provision of antigen negative products (1)(2). However, in the case of rare antibodies, development of alloantibodies can complicate administration of future blood products (1). Life-threatening transfusion reactions include anaphylaxis, transfusion related acute lung injury, bacterial contamination of blood products resulting in sepsis, acute hemolytic transfusion reactions, and transfusion associated circulatory overload (1)(2). While the risk of transfusion transmitted viral infections has dropped drastically in recent years and the risk of this occurring is extremely low, it remains a concern when deciding to transfuse patients (2). RBC transfusions may also cause immunosuppression in the recipient, a process called “transfusion-related immunomodulation (TRIM) (3). TRIM provides rationale for the negative association observed between RBC transfusion and post-operative adverse events as well as cancer recurrence in patients undergoing oncology surgery (4) (5) (6) (7) (8) (9) (10). At an estimated price tag of 102-761 USD per unit, RBC transfusions are costly (11) (12) (13) (14). They are also in short supply, relying on altruistic blood donors to ensure inventory stability (15) (16). Given their associated risk, expense and scarcity, it is critical they are administered wisely.

There has been significant evolution in our understanding of humans’ ability to tolerate anemia; resulting in a shift in approach to RBC transfusion prescribing practices from the “10/30” rule (i.e. transfusion indicated below a hemoglobin of 10g/L or hematocrit <30%) to the widely accepted transfusion trigger of 70g/L in the asymptomatic patient without significant cardiac

comorbidity. This change came into effect following reporting of the TRICC trial and others that have shown the safety of a restrictive transfusion threshold (17, 18) (19) (20). Importantly, the findings of these studies, which have impacted transfusion practices across a broad spectrum of clinical scenarios, are not necessarily applicable in the operative setting.

The operative setting presents a unique situation in which the indications for transfusion commonly reported in the non-operative patient have limited transferability. As blood loss, and consequently hemoglobin concentration can be unpredictable during surgery, hemoglobin concentrations may drop suddenly, making previous measurements of hemoglobin concentration invalid. This limits the feasibility of utilizing specific hemoglobin levels to guide RBC transfusion administration in surgical patients (21). There is some literature to suggest estimated surgical blood loss can be utilized to guide transfusion decisions (22) (23). However, there is good evidence to support the inability of clinicians to accurately predict blood loss (24). It is also important to appreciate that not all intraoperative bleeding is the same, varying from a persistent, slow ooze, to massive, rapid blood loss from a major vessel. Additionally, reliance on hemodynamics is complex as in addition to blood loss, it is a reflection of multiple variables, including but not limited to: anesthetic agents, patient positioning, presence of pneumoperitoneum and neurologic stimulation (25). In the non-operative setting, acute blood loss of approximately 20% results in a compensatory tachycardia (26). However, because of the other variables at play in the anesthetized patient, tachycardia is not a reliable marker of blood loss. Another common recommendation is to monitor for the presence of inadequate perfusion and oxygenation of vital organs (23). The ability to monitor for symptoms of decreased end-organ perfusion such as decreased level of consciousness, chest pain, or abdominal pain, are not possible in the unconscious patient under general anesthesia. Incorporation of decision rules specific to surgical patient, such as monitoring for ST changes, are fundamental to guiding appropriate RBC transfusion for a patient under general anesthesia for surgery(27). Another aspect unique to the unconscious patient under general anesthesia, subject to dynamic changes in hemodynamics for a number of reasons, is our limited ability to identify transfusion reactions. Although literature in this area is lacking, it would be reasonable to

hypothesize that transfusion reactions in the intra-operative setting are underreported. This, in combination with the evidence that patients who receive intraoperative transfusions suffer increased short and long term morbidity, advocates for careful consideration of transfusion administration (28) (7).

The uncertainty of transfusion indications in this patient population is demonstrated by the abundance of literature reporting on the wide variability in transfusion practices but largely reporting over-transfusion of surgical patients (29) (30) (31) (32) (33). A recent survey of Canadian liver surgeons and anesthesiologists highlights the lack of consensus between practitioners regarding indications for transfusion. In response to the question "what is the most important information you use to decide on intraoperative transfusion," the majority of anesthesiologist selected hemoglobin value (47.2% vs 19% of surgeons; $p<0.05$), whereas surgeons selected hemodynamics (33.4% vs 14% of anesthesiologist; $p>0.05$) (34). A prospective observational study of intraoperative transfusion practices in Europe reported "physiologic trigger irrespective of hemoglobin" as the most common indication for transfusion in a cohort of 5803 patients (35). Despite a global shift to a more restrictive transfusion strategy, wide variability in practice patterns in the intraoperative setting exists, and therefore warrants a review of the recommendations.

A preliminary search reveals guidance pertaining to RBC transfusion in the intraoperative patient population is lacking. Recently published guidelines from AABB, a worldwide leader in producing clinical practice guidelines for utilization of blood components, neglected to provide recommendations on indications for RBC transfusion in the intraoperative setting likely due to a lack of evidence on which to base recommendations (36). Guidelines endorsed by surgical and anesthesia societies offer vague recommendations with limited directives for when to transfuse, for example, to monitor for blood loss, check hemoglobin or hematocrit prior to transfusion, adopt a restrictive transfusion strategy or assess for adequate perfusion and oxygenation (37) (38) (39) (40) (41). As alluded to previously, reliance on these variables is limited in the intraoperative period. A formal review of the literature to understand available guidance for intraoperative RBC decisions is necessary.

In summary, blood transfusions are associated with possible harm and over-transfusion in the intraoperative setting is common. Although there is an abundance of guidance pertaining to indications for RBC transfusion, a review of guidance dedicated to the intraoperative patient does not currently exist.

## OBJECTIVE

The objective of this systematic review is to explore the availability, quality and consistency of published guidelines reporting on the indication for allogenic red blood cell transfusion in the intraoperative setting. We also aim to summarize the existing recommendations and associated level of evidence.

## METHODS

The Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) checklist guidelines were referenced for development of this protocol (42) (43). A PRISMA-P checklist is available as a supplementary document. The protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews on October 16, 2018 (CRD42018111487).

Any amendments made to the current protocol will be published using a protocol addendum, accompanied by the date of and rationale for the reported amendment, with the final manuscript.

***Eligibility criteria:***

Guidelines reporting on indications for allogenic red blood cell transfusion in the intraoperative setting will be considered for inclusion. Our definition of clinical practice guidelines is adopted from the Institute of Medicine and National Guideline Clearinghouse which define them as recommendations, derived from systematic review of evidence, from collective opinions of an expert panel, aimed at health care providers intended to improve patient care (44, 45). An article will be included if it: (1) is presented as a clinical practice guideline; (2) is based on a systematic review of evidence; (3) is produced by a medical association, professional society, public or private

organization or government agency and not by an individual(s) not sponsored or supported by the above groups; (4) includes recommendations for indications for allogenic red blood cell transfusion in patients undergoing general anesthesia in an operating room; (5) in any language; (6) full-text available.

We plan on excluding: (1) documents that do not meet the definition of a guideline as stated above; (2) guidelines pertaining to the perioperative period that do not make specific recommendations on the intraoperative setting (3) previous documents replaced by updated versions from the same organization.

***Information sources and search strategy***

MEDLINE (OVID interface, including In-Process and Epub Ahead of Print) and EMBASE (OVID interface) and CINHAL will be systematically searched from inception to January 2019, through application of a search strategy developed by a health science librarian with expertise in systematic reviews. Search terms will include 'allogenic red blood cell transfusion', 'guideline' and 'operative'. The search will not be restricted by date, language or patient population (ie. adult versus pediatric). A Peer Review of Electronic Search Strategies (PRESS) will be performed by a second information specialist who is not associated with the project. A draft search strategy for Medline can be found in Appendix 1. The following guideline-specific databases will also be searched: National Institute for Health and Care Excellence (NICE) (UK), the Canadian Medical Association Infobase (Canada), the G-I-N International Guideline Library, the New Zealand Guidelines (NZG) Group, The World Health Organization and the Scottish Intercollegiate Guidelines Network (SIGN) (46-51). Google Scholar will be searched with '(intraoperative OR perioperative) AND (guideline OR consensus OR recommendation OR statement)' and the first 200 records will be screened. References of identified articles will be reviewed for relevant guidelines.

***Study Records***

Articles identified through the electronic databases (MEDLINE and EMBASE) will be imported into Covidence, an online citation manager (52). All titles and abstracts identified will be independently screened by two reviewers for relevance and categorized as relevant, possibly

relevant, or irrelevant. Articles categorized as relevant or possibly relevant will be retrieved for further evaluation. Full texts will also reviewed in duplicate for eligibility. Google translate will be used to translate non-English, non-French articles, with the exception of those written in Chinese (53). Any disagreement regarding relevancy will be resolved by a senior author, independent from the reviewers. Reason for study exclusion will be documented and presented in the PRISMA flow diagram for study screening (Figure 1).

Guidelines identified from the guideline repositories will be recorded in an Excel spread sheet.

***Data Items***

Data pertaining to the publication details (authors, year of publication, journal, etc) will be identified. All relevant recommendations will be extracted from the guidelines to aid in the determination of population(s) in which the intraoperative transfusion guidelines pertain to (type of surgery), patient variables taken into consideration in determining appropriateness for transfusion, and grading of recommendation if assigned will be extracted. We will identify whether or not the following variables are accounted for in identified decision rules or recommendations: patient comorbidities-specifically a history of coronary artery disease, hemodynamics (hypotension, tachycardia, or presence of vasopressor support), estimated blood loss, evidence of cardiac ischemia, and evidence of end organ ischemia in addition to cardiac. Data extraction forms (DEF) will be developed and piloted independently by two reviewers on a set of 5 randomly selected guidelines. Modifications will be made to the DEF as necessary. Data will be extracted independently by two reviewers, in duplicate.

***Outcomes & Prioritization***

The objectives are to (1) characterize the clinical practice guidelines advising on intraoperative RBC utilization (2) appraise their quality and (3) provide a descriptive summary of the included guidelines.

***Characterization of identified guidelines***

A descriptive table of identified guidelines will be presented. This table will include information publication information as well as the target patient population of the guideline.

***Guideline quality assessment: AGREE II***

The Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument will be used to assess the quality of included guidelines (54). The AGREE II instrument is a validated questionnaire aimed at assessing the methodologic quality of clinical practice guidelines and has been widely adopted in the scientific literature (54) (55) (56). It is comprised of 23 questions scored on a seven-point Likert scale (whereby 7 indicates the highest quality), covering 6 domains, inclusive of scope and purpose of the guidelines, stakeholder involvement, rigour of development, clarity of presentation and editorial independent. There are two additional questions. The first assesses the overall quality of the guideline, rated on a seven-point Likert scale. The final question asks the evaluator whether they would recommend using this guideline, to which the assessor responds "yes," "yes, with modifications," or "no."

It is recommended that four assessors complete the AGREE II to achieve an intra-class correlation coefficient ≥0.7. Four appraisers will therefore be selected to complete the online training and independently evaluate the included guidelines. Once complete, the evaluators will meet and discuss any scores differing by more than 1 point. At that point, evaluators can amend or keep their original score. Inter-rater reliability will be calculated using the intraclass correlation coefficient (ICC) using SAS.

Domain scores will be reported separately using both the median and scaled domain scores, as is recommended by the AGREE II consortium. The scaled domain score will be calculated as follows: (obtained score-minimal possible score)/(maximal possible score-minimal possible score)=__%. The minimum possible score is calculated as: (number of questions) x (number of reviewers) x 1. The maximum possible score is calculated as: (number of questions) x (number of reviewers) x 7.

***Recommendation synthesis***

A descriptive table of included studies will be presented displaying all recommendations pertaining to indications for RBC transfusion in the intraoperative period. Recommendations will be compared for consistency and/or repetition.

***Analysis of subgroups or subsets***

Guidelines pertaining to indications for blood transfusion in cardiac versus non-cardiac surgery patients will be grouped and considered separately. In addition, guidelines published following publication of the TRICC trial in May 1997 will be considered separately in our descriptive analysis (18). The rationale for this being that the prevailing theme of current practice is a result of this trial.

***Dissemination***

The results of this review will be submitted for presentation at national and international meetings and publication in a peer-reviewed journal.

***Reporting of review***

The findings of this systematic review will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. The completed checklist will be provided as supplementary material.

***Confidence in cumulative evidence***

The quality of recommendations will be evaluated by using the systematic and comprehensive approach known as Grading of Recommendations, Assessment, Development and Evaluations (GRADE) (57). The quality of evidence will be assessed across the domains of risk of bias, consistency, directness, precision and publication bias.

***Patient and public involvement***

This investigation is aligned with research priorities established by The Canadian Blood Services (CBS), a not-for-profit charitable organization, responsible for managing the Canadian blood supply (with the exception of Quebec) (58). Specifically, they have identified: (1) promoting appropriate blood product utilization and (2) ensuring an adequate blood product supply, as two of five research priorities. CBS invites public participation in their bi-annual board meetings, where a number of issues are addressed, inclusive of priority research agendas. Patients or the public

were not involved in the development of our specific research question or outcome measures of interests.

## DISCUSSION

A significant number of patients receive intra-operative transfusion. However, there is substantial variation in transfusion practice and a paucity of guidance available. Despite the fact that a plea for intraoperative blood transfusion guidelines was made over 20 years ago, widely adopted recommendations have yet to be developed. (59) A systematic review of transfusion guidelines in the intraoperative setting has not previously been performed. Although a quality appraisal of RBC and plasma guidelines was published in 2018, it did not identify intraoperative recommendations (37). Additionally, their search strategy did not include guideline clearinghouses or the grey literature.

There are several methodologic strengths of our review, these include multidisciplinary input, a PRESS reviewed search strategy, review of the grey literature and application of the AGREE II tool to assess the quality of identified guidelines by four independent reviewers.

This systematic review will allow for identification, appraisal and summary of literature devoted to the guidance of intraoperative allogenic RBC transfusion. The Perioperative Anesthesia Clinical Trials Group (PACT) identified transfusion as 1 of 7 themes that has a significant impact on mortality, reinforcing the importance of this review (60). The results of this review will provide rationale and justification for development of guidance, or the need for prospective evaluation of various intra-operative transfusion strategies. If evidence-informed recommendations for the use of intra-operative transfusion can be developed and disseminated the incidence of over-transfusion may be reduced, ensuring responsible use of this limited resource, and minimizing patient exposure to the risks of transfusion.

To achieve this goal will require collaboration between surgeons, anesthetists, and transfusion specialists. Given the paucity of high quality data on which to base guidelines, this collaboration must first identifies areas where only expert opinion exists and propose methods for

further examination. The input of patients who have had intra-operative transfusion should be sought to determine where patient preference may supersede rigorous adherence to guidelines. Following well planned knowledge translation phase, auditing to monitor compliance with the guidelines will need to be done. Additionally, following guideline implementation quality assurance initiatives with patient centred outcomes will also be necessary to ensure that the safety and tolerability of developed guidelines. Thus, it is unlikely that final guideline recommendations regarding intra-operative transfusion will be forthcoming in the near future. However, this review reinforces the urgent need to begin the undertaking.

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**Competing interests:** None to declare.

**Sponsor:** None to declare.

## Authors' Contribution

Laura Baker is responsible for aiding in the conception of the work, drafting and revising the manuscript, approves the submitted version and is accountable for all aspects of the work.

Lily Park, Richard Gilbert, Andre Martel, Hilalion Ahn, Alexandra Davies, Daniel McIsaac, Elianna Saidenberg and Alan Tinmouth are responsible for aiding in the conception of the work, revising the manuscript, approving the final version and are in agreement to being accountable for all aspects of the work.

Dean Fergusson and Guillaume Martel are responsible for aiding in the conception of the work, revising it for important intellectual content, give their approval of the content for publication and agree to accountability for all aspects of the work. GM is the guarantor of the protocol.

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Figure 1: Flow diagram of study selection process.

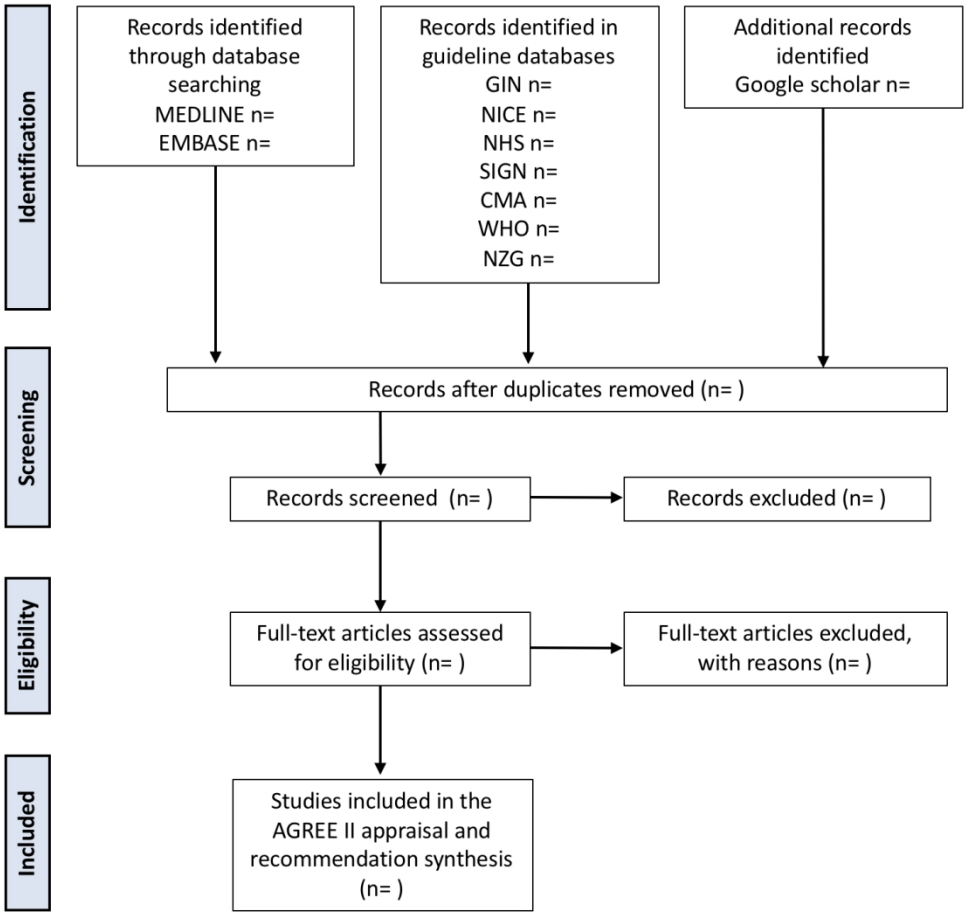


Figure 1: Flow diagram of study selection process.

Appendix I: Search Strategy

Database: Ovid MEDLINE(R) ALL <1946 to January 21, 2019>
Search Strategy:
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1 *blood transfusion/ or blood component transfusion/ or erythrocyte transfusion/ (36153)
2 ((red blood cell$ or rbc or erythrocyte$ or red cell$) adj3 (transfus$ or infus* or retransfus*)).tw. (10506)
3 (blood adj4 transfus*).tw. (54555) - I expanded this
4 RBCT.tw,kw. (95)
5 (RBC transfusion or red blood cell transfusion).kw. (110)
6 (hemotransfus$ or haemotransfus$).tw,kw. (234)
7 or/1-6 (78107)
8 INTRAOPERATIVE COMPLICATIONS/ or INTRAOPERATIVE CARE/ or INTRAOPERATIVE PERIOD/ or Perioperative Care/ (69769)
9 (intraoperat* or intra-operat* or perioperat* or peri-operat*).tw,kw. (205937)
10 (surg* or operat*).ti. (708792) - added this line
11 (transfus* adj5 (operat* or surg*)).tw. (8642)
12 ((undergoing or during) adj4 (surg* or operat*)).tw. (180983) - expanded this line by taking out 'transfus*'
13 or/8-12 (968870)
14 7 and 13 (18339)
15 exp clinical pathway/ (6046)
16 clinical protocol/ (25911)
17 exp consensus/ (9313)
18 exp consensus development conference/ (11078)
19 exp consensus development conferences as topic/ (2618)
20 guidelines as topic/ (37008)
21 exp practice guideline/ (24266)
22 practice guidelines as topic/ (105996)
23 health planning guidelines/ (4007)
24 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. (39641)
25 (standards or guideline or guidelines).ti,kf,kw. (96689)
26 ((practice or treatment* or clinical) adj guideline*).ab. (33765)
27 (CPG or CPGs).ti. (5320)
28 consensus*.ti,kf,kw. (22038)
29 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw. (17432)
30 recommendat*.ti,kf,kw. (35650)
31 or/15-30 (334141)
32 14 and 31 (550)
33 (rbc transfusion* or red blood cell* transfusion*).ti. (1054)
34 (transfus* and (intraoperat* or intra-operat* or perioperat* or peri-operat*)).ti. (1014)
35 33 or 34 (1999)
36 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. (39641)
37 (standards or guideline or guidelines).ti,kf,kw. (96689)
38 36 or 37 (122196)
39 35 and 38 (61)
40 32 or 39 (578)
41 animals/ not humans/ (4465996)
42 40 not 41 (577)
43 (exp infants/ or child/) not adult/ (1517431)
44 42 not 43 (546)

# PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **ADMINISTRATIVE INFORMATION** | | | | | |
| **Title** | | | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | x | ☐ | 1-2 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | ☐ | x | N/A |
| **Registration** | 2 | If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract | x | ☐ | 49 |
| **Authors** | | | | | |
| Contact | 3a | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author | x | ☐ | 4-33 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | x | ☐ | 312-323 |
| **Amendments** | 4 | 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 | x | ☐ | 155-156 |
| **Support** | | | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | x | ☐ | 308-309 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | x | ☐ | 311 |
| Role of sponsor/funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | ☐ | x | N/A |
| **INTRODUCTION** | | | | | |
| **Rationale** | 6 | Describe the rationale for the review in the context of what is already known | x | ☐ | 61-141 |
| **Objectives** | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | x | ☐ | 143-147 |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **METHODS** | | | | | |
| **Eligibility criteria** | 8 | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review | x | ☐ | 157-172 |
| **Information sources** | 9 | Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage | x | ☐ | 173-187 |
| **Search strategy** | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | x | ☐ | Appendix 1 |
| ***STUDY RECORDS*** | | | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | x | ☐ | 189-190 |
| Selection process | 11b | State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis) | x | ☐ | 190-193 |
| Data collection process | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | x | ☐ | 199-211 |
| **Data items** | 12 | List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications | x | ☐ | 199-211 |
| **Outcomes and prioritization** | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | x | ☐ | 212-215 |
| **Risk of bias in individual studies** | 14 | 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 | x | ☐ | 219-241 |
| ***DATA*** | | | | | |
| **Synthesis** | 15a | Describe criteria under which study data will be quantitatively synthesized | x | ☐ | 219 |
| | 15b | 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 (e.g., $I^2$, Kendall's tau) | ☐ | x | N/A |
| | 15c | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression) | x | ☐ | 246-251 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | x | ☐ | 242-245 |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **Meta-bias(es)** | 16 | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies) | ☐ | x | N/A |
| **Confidence in cumulative evidence** | 17 | Describe how the strength of the body of evidence will be assessed (e.g., GRADE) | ☐ | x | N/A |