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

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Baker et al. Guidelines on the intraoperative transfusion of red blood cells: a protocol for systematic review

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

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3 57 • The Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument, an
4
5 58 internationally validated tool, will be utilized to assess the quality of guidelines by four
6
7 59 independent reviewers
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10 60

11 **INTRODUCTION**
12

13 62 Red blood cell (RBC) transfusions although potentially lifesaving, are a costly and limited
14
15 63 resource, associated with possible harm. Potential adverse outcomes range in severity, from minor
16
17 64 to life-threatening. Relatively mild reactions include febrile non-hemolytic transfusion reactions,
18
19 65 minor allergic reactions, or development of RBC alloantibodies. RBC alloantibodies can usually be
20
21 66 managed with the provision of antigen negative products (1)(2). However, in the case of rare
22
23 67 antibodies, development of alloantibodies can complicate administration of future blood products
24
25 68 (1). Life-threatening transfusion reactions include anaphylaxis, transfusion related acute lung injury,
26
27 69 bacterial contamination of blood products resulting in sepsis, acute hemolytic transfusion reactions,
28
29 70 and transfusion associated circulatory overload (1)(2). While the risk of transfusion transmitted viral
30
31 71 infections has dropped drastically in recent years and the risk of this occurring is extremely low, it
32
33 72 remains a concern when deciding to transfuse patients (2). RBC transfusions may also cause
34
35 73 immunosuppression in the recipient, a process called “transfusion-related immunomodulation
36
37 74 (TRIM) (3). TRIM provides rationale for the negative association observed between RBC transfusion
38
39 75 and post-operative adverse events as well as cancer recurrence in patients undergoing oncology
40
41 76 surgery (4) (5) (6) (7) (8) (9) (10). At an estimated price tag of \$US761 per unit, RBC transfusions
42
43 77 are costly (11) (12). They are also in short supply, relying on altruistic blood donors to ensure
44
45 78 inventory stability (13) (14). Given their associated risk, expense and scarcity, it is critical they are
46
47 79 administered wisely.
48
49
50

51 80 There has been significant evolution in our understanding of humans’ ability to tolerate
52
53 81 anemia; resulting in a shift in approach to RBC transfusion prescribing practices from the “10/30”
54
55 82 rule (i.e. transfusion indicated below a hemoglobin of 10g/L or hematocrit <30%) to the widely
56
57 83 accepted transfusion trigger of 70g/L in the asymptomatic patient without significant cardiac
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84 comorbidity. This change came into effect following reporting of the TRICC trial and others that have
85 shown the safety of a restrictive transfusion threshold (15, 16) (17) (18). Importantly, the findings of
86 these studies, which have impacted transfusion practices across a broad spectrum of clinical
87 scenarios, are not necessarily applicable in the operative setting.

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

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

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111 over-transfusion of surgical patients (26) (27) (28) (29) (30). A recent survey of Canadian liver
112 surgeons and anesthesiologists highlights the lack of consensus between practitioners regarding
113 indications for transfusion. In response to the question “what is the most important information you
114 use to decide on intraoperative transfusion,” the majority of anesthesiologist selected hemoglobin
115 value (47.2% vs 19% of surgeons; $p < 0.05$), whereas surgeons selected hemodynamics (33.4% vs
116 14% of anesthesiologist; $p > 0.05$) (31). A prospective observational study of intraoperative
117 transfusion practices in Europe reported “physiologic trigger irrespective of hemoglobin” as the most
118 common indication for transfusion in a cohort of 5803 patients (32). Despite a global shift to a more
119 restrictive transfusion strategy, wide variability in practice patterns in the intraoperative setting exists,
120 and therefore warrants a review of the recommendations.

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

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

136

137 **OBJECTIVE**

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

142

143 **METHODS**

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

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

151 ***Eligibility criteria:***

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

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

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

166 Information sources and search strategy

167 MEDLINE (OVID interface, including In-Process and Epub Ahead of Print) and EMBASE
168 (OVID interface) and CINHAL will be systematically searched from inception to January 2019,
169 through application of a search strategy developed by a health science librarian with expertise in
170 systematic reviews. Search terms will include 'allogenic red blood cell transfusion', 'guideline' and
171 'operative'. The search will not be restricted by date, language or patient population (ie. adult versus
172 pediatric). A Peer Review of Electronic Search Strategies (PRESS) will be performed by a second
173 information specialist who is not associated with the project. A draft search strategy for Medline
174 can be found in Appendix 1. The following guideline-specific databases will also be searched:
175 National Institute for Health and Care Excellence (NICE) (UK), the Canadian Medical Association
176 Infobase (Canada), the G-I-N International Guideline Library, the New Zealand Guidelines (NZG)
177 Group, The World Health Organization and the Scottish Intercollegiate Guidelines Network (SIGN)
178 (43-48). Google Scholar will be searched with '(intraoperative OR perioperative) AND (guideline
179 OR consensus OR recommendation OR statement)' and the first 200 records will be screened.
180 References of identified articles will be reviewed for relevant guidelines.

181 Study Records

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

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

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191 **Data Items**

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

199 **Outcomes & Prioritization**

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

203 **Characterization of identified guidelines**

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

206 **Guideline quality assessment: AGREE II**

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

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2
3 217 It is recommended that four assessors complete the AGREE II to achieve an intra-class
4
5 218 correlation coefficient ≥ 0.7 . Four appraisers will therefore be selected to complete the online training
6
7 219 and independently evaluate the included guidelines. Once complete, the evaluators will meet and
8
9 220 discuss any scores differing by more than 1 point. At that point, evaluators can amend or keep their
10
11 221 original score. Inter-rater reliability will be calculated using the intraclass correlation coefficient (ICC)
12
13 222 using SAS.

14
15 223 Domain scores will be reported separately using both the median and scaled domain scores,
16
17 224 as is recommended by the AGREE II consortium. The scaled domain score will be calculated as
18
19 225 follows: (obtained score-minimal possible score)/(maximal possible score-minimal possible
20
21 226 score)=__%. The minimum possible score is calculated as: (number of questions) x (number of
22
23 227 reviewers) x 1. The maximum possible score is calculated as: (number of questions) x (number of
24
25 228 reviewers) x 7.

26
27
28 229 **Recommendation synthesis**

29
30 230 A descriptive table of included studies will be presented displaying all recommendations
31
32 231 pertaining to indications for RBC transfusion in the intraoperative period. Recommendations will be
33
34 232 compared for consistency and/or repetition.

35
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37 233 **Analysis of subgroups or subsets**

38
39 234 Guidelines pertaining to indications for blood transfusion in cardiac versus non-cardiac
40
41 235 surgery patients will be grouped and considered separately .

42
43 236 **Dissemination**

44
45 237 The results of this review will be submitted for presentation at national and international
46
47 238 meetings and publication in a peer-reviewed journal.

48
49 239 **Reporting of review**

50
51 240 The findings of this systematic review will be reported according to the Preferred Reporting
52
53 241 Items for Systematic Reviews and Meta-analyses (PRISMA) statement. The completed checklist
54
55 242 will be provided as supplementary material.

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58 243 **Confidence in cumulative evidence**

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

248 ***Patient and public involvement***

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

257 **DISCUSSION**

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

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

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

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

289
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291 reviewing the search strategy, as well as retrieving articles.

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293 Academic Health Science Center Alternative Funding Plan Innovation Fund.

294 **Competing interests:** None to declare.

295 **Sponsor:** None to declare.

296 **Authors' Contribution**

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

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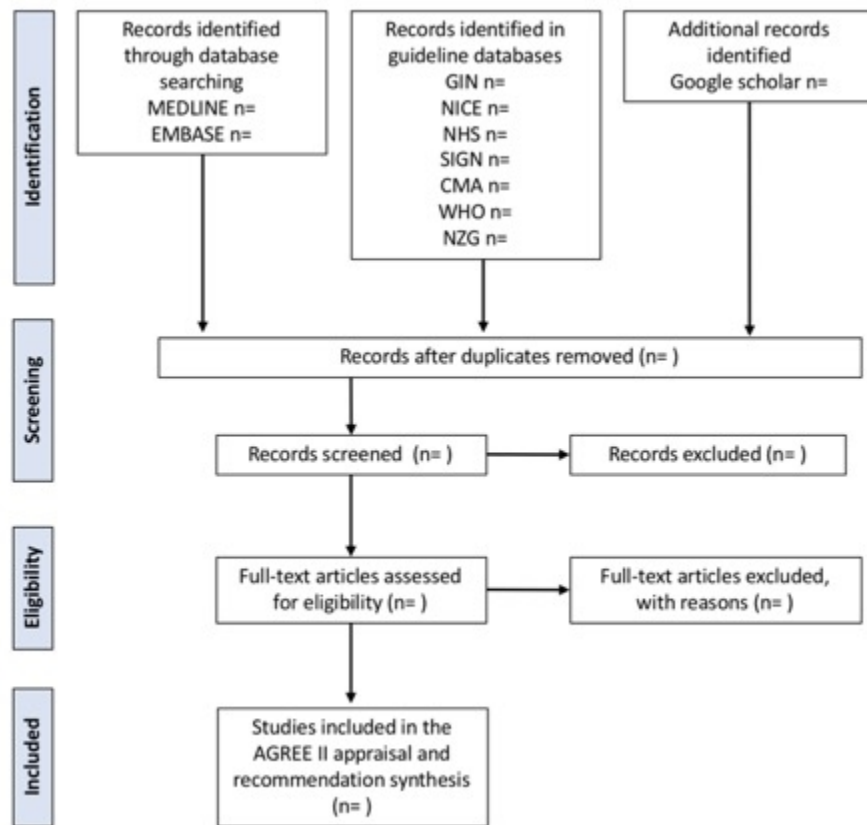


Figure 1: PRISMA Flow Diagram

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/
 9 or Perioperative Care/ (69769)
 10 (intraoperat* or intra-operat* or perioperat* or peri-operat*).tw,kw. (205937)
 11 (surg* or operat*).ti. (708792) - added this line
 12 (transfus* adj5 (operat* or surg*)).tw. (8642)
 13 ((undergoing or during) adj4 (surg* or operat*)).tw. (180983) - expanded this line by taking out
 14 'transfus*
 15 or/8-12 (968870)
 16 7 and 13 (18339)
 17 exp clinical pathway/ (6046)
 18 clinical protocol/ (25911)
 19 exp consensus/ (9313)
 20 exp consensus development conference/ (11078)
 21 exp consensus development conferences as topic/ (2618)
 22 guidelines as topic/ (37008)
 23 exp practice guideline/ (24266)
 24 practice guidelines as topic/ (105996)
 25 health planning guidelines/ (4007)
 26 (guideline or practice guideline or consensus development conference or consensus development
 27 conference, NIH).pt. (39641)
 28 (standards or guideline or guidelines).ti,kf,kw. (96689)
 29 ((practice or treatment* or clinical) adj guideline*).ab. (33765)
 30 (CPG or CPGs).ti. (5320)
 31 consensus*.ti,kf,kw. (22038)
 32 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw.
 33 (17432)
 34 recommendat*.ti,kf,kw. (35650)
 35 or/15-30 (334141)
 36 14 and 31 (550)
 37 (rbc transfusion* or red blood cell* transfusion*).ti. (1054)
 38 (transfus* and (intraoperat* or intra-operat* or perioperat* or peri-operat*)).ti. (1014)
 39 33 or 34 (1999)
 40 (guideline or practice guideline or consensus development conference or consensus development
 41 conference, NIH).pt. (39641)
 42 (standards or guideline or guidelines).ti,kf,kw. (96689)
 43 36 or 37 (122196)
 44 35 and 38 (61)
 45 32 or 39 (578)
 46 animals/ not humans/ (4465996)
 47 40 not 41 (577)
 48 (exp infants/ or child/) not adult/ (1517431)
 49 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	<input type="checkbox"/>	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	x	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	x	<input type="checkbox"/>	49
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	x	<input type="checkbox"/>	4-33
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	x	<input type="checkbox"/>	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	<input type="checkbox"/>	149-150
Support					
Sources	5a	Indicate sources of financial or other support for the review	x	<input type="checkbox"/>	292-293
Sponsor	5b	Provide name for the review funder and/or sponsor	x	<input type="checkbox"/>	295
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	x	N/A
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	x	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	Appendix 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	x	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	206-228
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	x	<input type="checkbox"/>	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)	<input type="checkbox"/>	x	N/A
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	x	<input type="checkbox"/>	233-235
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	x	<input type="checkbox"/>	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)	<input type="checkbox"/>	x	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input type="checkbox"/>	x	N/A

For peer review only

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-029684.R1
Article Type:	Protocol
Date Submitted by the Author:	08-Mar-2019
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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

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Manuscripts

Baker et al. Guidelines on the intraoperative transfusion of red blood cells: a protocol for systematic review

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

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3 57 • The Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument, an
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5 58 internationally validated tool, will be utilized to assess the quality of guidelines by four
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7 59 independent reviewers
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11 **INTRODUCTION**
12

13 62 Red blood cell (RBC) transfusions although potentially lifesaving, are a costly and limited
14 63 resource, associated with possible harm. Potential adverse outcomes range in severity, from minor
15 64 to life-threatening. Relatively mild reactions include febrile non-hemolytic transfusion reactions,
16 65 minor allergic reactions, or development of RBC alloantibodies. RBC alloantibodies can usually be
17 66 managed with the provision of antigen negative products (1)(2). However, in the case of rare
18 67 antibodies, development of alloantibodies can complicate administration of future blood products
19 68 (1). Life-threatening transfusion reactions include anaphylaxis, transfusion related acute lung injury,
20 69 bacterial contamination of blood products resulting in sepsis, acute hemolytic transfusion reactions,
21 70 and transfusion associated circulatory overload (1)(2). While the risk of transfusion transmitted viral
22 71 infections has dropped drastically in recent years and the risk of this occurring is extremely low, it
23 72 remains a concern when deciding to transfuse patients (2). RBC transfusions may also cause
24 73 immunosuppression in the recipient, a process called “transfusion-related immunomodulation
25 74 (TRIM) (3). TRIM provides rationale for the negative association observed between RBC transfusion
26 75 and post-operative adverse events as well as cancer recurrence in patients undergoing oncology
27 76 surgery (4) (5) (6) (7) (8) (9) (10). At an estimated price tag of 102-761 USD per unit, RBC
28 77 transfusions are costly (11) (12) (13) (14). They are also in short supply, relying on altruistic blood
29 78 donors to ensure inventory stability (15) (16). Given their associated risk, expense and scarcity, it is
30 79 critical they are administered wisely.
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51 80 There has been significant evolution in our understanding of humans’ ability to tolerate
52 81 anemia; resulting in a shift in approach to RBC transfusion prescribing practices from the “10/30”
53 82 rule (i.e. transfusion indicated below a hemoglobin of 10g/L or hematocrit <30%) to the widely
54 83 accepted transfusion trigger of 70g/L in the asymptomatic patient without significant cardiac
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84 comorbidity. This change came into effect following reporting of the TRICC trial and others that have
85 shown the safety of a restrictive transfusion threshold (17, 18) (19) (20). Importantly, the findings of
86 these studies, which have impacted transfusion practices across a broad spectrum of clinical
87 scenarios, are not necessarily applicable in the operative setting.

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

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111 hypothesize that transfusion reactions in the intra-operative setting are underreported. This, in
112 combination with the evidence that patients who receive intraoperative transfusions suffer increased
113 short and long term morbidity, advocates for careful consideration of transfusion administration (28)
114 (7).

115 The uncertainty of transfusion indications in this patient population is demonstrated by the
116 abundance of literature reporting on the wide variability in transfusion practices but largely reporting
117 over-transfusion of surgical patients (29) (30) (31) (32) (33). A recent survey of Canadian liver
118 surgeons and anesthesiologists highlights the lack of consensus between practitioners regarding
119 indications for transfusion. In response to the question “what is the most important information you
120 use to decide on intraoperative transfusion,” the majority of anesthesiologist selected hemoglobin
121 value (47.2% vs 19% of surgeons; $p < 0.05$), whereas surgeons selected hemodynamics (33.4% vs
122 14% of anesthesiologist; $p > 0.05$) (34). A prospective observational study of intraoperative
123 transfusion practices in Europe reported “physiologic trigger irrespective of hemoglobin” as the most
124 common indication for transfusion in a cohort of 5803 patients (35). Despite a global shift to a more
125 restrictive transfusion strategy, wide variability in practice patterns in the intraoperative setting exists,
126 and therefore warrants a review of the recommendations.

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

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

142

143 **OBJECTIVE**

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

148

149 **METHODS**

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

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

157 ***Eligibility criteria:***

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

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

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

173 Information sources and search strategy

174 MEDLINE (OVID interface, including In-Process and Epub Ahead of Print) and EMBASE
175 (OVID interface) and CINHALL will be systematically searched from inception to January 2019,
176 through application of a search strategy developed by a health science librarian with expertise in
177 systematic reviews. Search terms will include 'allogenic red blood cell transfusion', 'guideline' and
178 'operative'. The search will not be restricted by date, language or patient population (ie. adult versus
179 pediatric). A Peer Review of Electronic Search Strategies (PRESS) will be performed by a second
180 information specialist who is not associated with the project. A draft search strategy for Medline
181 can be found in Appendix 1. The following guideline-specific databases will also be searched:
182 National Institute for Health and Care Excellence (NICE) (UK), the Canadian Medical Association
183 Infobase (Canada), the G-I-N International Guideline Library, the New Zealand Guidelines (NZG)
184 Group, The World Health Organization and the Scottish Intercollegiate Guidelines Network (SIGN)
185 (46-51). Google Scholar will be searched with '(intraoperative OR perioperative) AND (guideline
186 OR consensus OR recommendation OR statement)' and the first 200 records will be screened.
187 References of identified articles will be reviewed for relevant guidelines.

188 Study Records

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

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

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

199 **Data Items**

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

212 **Outcomes & Prioritization**

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

216 **Characterization of identified guidelines**

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

219 Guideline quality assessment: AGREE II

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

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

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

242 Recommendation synthesis

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

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3 246 **Analysis of subgroups or subsets**

4
5 247 Guidelines pertaining to indications for blood transfusion in cardiac versus non-cardiac
6
7 248 surgery patients will be grouped and considered separately. In addition, guidelines published
8
9 249 following publication of the TRICC trial in May 1997 will be considered separately in our descriptive
10
11 250 analysis (18). The rationale for this being that the prevailing theme of current practice is a result of
12
13 251 this trial.

14
15 252 **Dissemination**

16
17
18 253 The results of this review will be submitted for presentation at national and international
19
20 254 meetings and publication in a peer-reviewed journal.

21
22 255 **Reporting of review**

23
24 256 The findings of this systematic review will be reported according to the Preferred Reporting
25
26 257 Items for Systematic Reviews and Meta-analyses (PRISMA) statement. The completed checklist
27
28 258 will be provided as supplementary material.

29
30 259 **Confidence in cumulative evidence**

31
32
33 260 The quality of recommendations will be evaluated by using the systematic and
34
35 261 comprehensive approach known as Grading of Recommendations, Assessment, Development and
36
37 262 Evaluations (GRADE) (57). The quality of evidence will be assessed across the domains of risk of
38
39 263 bias, consistency, directness, precision and publication bias.

40
41 264 **Patient and public involvement**

42
43
44 265 This investigation is aligned with research priorities established by The Canadian Blood
45
46 266 Services (CBS), a not-for-profit charitable organization, responsible for managing the Canadian
47
48 267 blood supply (with the exception of Quebec) (58). Specifically, they have identified: (1) promoting
49
50 268 appropriate blood product utilization and (2) ensuring an adequate blood product supply, as two of
51
52 269 five research priorities. CBS invites public participation in their bi-annual board meetings, where a
53
54 270 number of issues are addressed, inclusive of priority research agendas. Patients or the public

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

273 **DISCUSSION**

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

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

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

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

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3 297 further examination. The input of patients who have had intra-operative transfusion should be
4
5 298 sought to determine where patient preference may supersede rigorous adherence to guidelines.
6
7 299 Following well planned knowledge translation phase, auditing to monitor compliance with the
8
9 300 guidelines will need to be done. Additionally, following guideline implementation quality assurance
10
11 301 initiatives with patient centred outcomes will also be necessary to ensure that the safety and
12
13 302 tolerability of developed guidelines. Thus, it is unlikely that final guideline recommendations
14
15 303 regarding intra-operative transfusion will be forthcoming in the near future. However, this review
16
17 304 reinforces the urgent need to begin the undertaking.
18
19
20 305

21
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23
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25

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27
28 309 Academic Health Science Center Alternative Funding Plan Innovation Fund.
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30 310 **Competing interests:** None to declare.
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32 311 **Sponsor:** None to declare.
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312 Authors' Contribution

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

315

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

320

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

325

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30 473 Figure 1: Flow diagram of study selection process.
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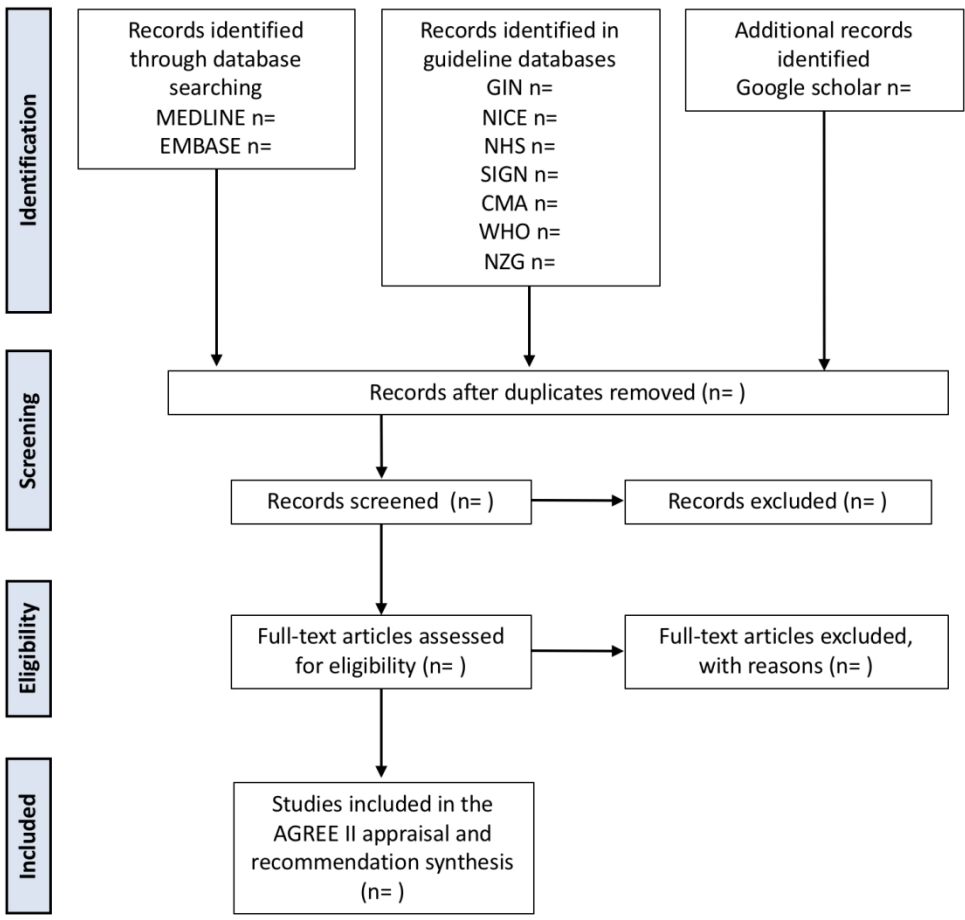


Figure 1: Flow diagram of study selection process.

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/
 9 or Perioperative Care/ (69769)
 10 (intraoperat* or intra-operat* or perioperat* or peri-operat*).tw,kw. (205937)
 11 (surg* or operat*).ti. (708792) - added this line
 12 (transfus* adj5 (operat* or surg*)).tw. (8642)
 13 ((undergoing or during) adj4 (surg* or operat*)).tw. (180983) - expanded this line by taking out
 14 'transfus*
 15 or/8-12 (968870)
 16 7 and 13 (18339)
 17 exp clinical pathway/ (6046)
 18 clinical protocol/ (25911)
 19 exp consensus/ (9313)
 20 exp consensus development conference/ (11078)
 21 exp consensus development conferences as topic/ (2618)
 22 guidelines as topic/ (37008)
 23 exp practice guideline/ (24266)
 24 practice guidelines as topic/ (105996)
 25 health planning guidelines/ (4007)
 26 (guideline or practice guideline or consensus development conference or consensus development
 27 conference, NIH).pt. (39641)
 28 (standards or guideline or guidelines).ti,kf,kw. (96689)
 29 ((practice or treatment* or clinical) adj guideline*).ab. (33765)
 30 (CPG or CPGs).ti. (5320)
 31 consensus*.ti,kf,kw. (22038)
 32 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw.
 33 (17432)
 34 recommendat*.ti,kf,kw. (35650)
 35 or/15-30 (334141)
 36 14 and 31 (550)
 37 (rbc transfusion* or red blood cell* transfusion*).ti. (1054)
 38 (transfus* and (intraoperat* or intra-operat* or perioperat* or peri-operat*)).ti. (1014)
 39 33 or 34 (1999)
 40 (guideline or practice guideline or consensus development conference or consensus development
 41 conference, NIH).pt. (39641)
 42 (standards or guideline or guidelines).ti,kf,kw. (96689)
 43 36 or 37 (122196)
 44 35 and 38 (61)
 45 32 or 39 (578)
 46 animals/ not humans/ (4465996)
 47 40 not 41 (577)
 48 (exp infants/ or child/) not adult/ (1517431)
 49 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	<input type="checkbox"/>	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	x	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	x	<input type="checkbox"/>	49
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	x	<input type="checkbox"/>	4-33
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	x	<input type="checkbox"/>	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	<input type="checkbox"/>	155-156
Support					
Sources	5a	Indicate sources of financial or other support for the review	x	<input type="checkbox"/>	308-309
Sponsor	5b	Provide name for the review funder and/or sponsor	x	<input type="checkbox"/>	311
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	x	N/A
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	x	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	Appendix 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	x	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	219-241
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	x	<input type="checkbox"/>	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)	<input type="checkbox"/>	x	N/A
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	x	<input type="checkbox"/>	246-251
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	x	<input type="checkbox"/>	242-245

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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)	<input type="checkbox"/>	x	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input type="checkbox"/>	x	N/A

For peer review only

BMJ Open

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

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Baker et al. Guidelines on the intraoperative transfusion of red blood cells: a protocol for systematic review

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

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3 57 • The Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument, an
4
5 58 internationally validated tool, will be utilized to assess the quality of guidelines by four
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7 59 independent reviewers
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11 **INTRODUCTION**
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13 62 Red blood cell (RBC) transfusions although potentially lifesaving, are a costly and limited
14 63 resource, associated with possible harm. Potential adverse outcomes range in severity, from minor
15 64 to life-threatening. Relatively mild reactions include febrile non-hemolytic transfusion reactions,
16 65 minor allergic reactions, or development of RBC alloantibodies. RBC alloantibodies can usually be
17 66 managed with the provision of antigen negative products (1)(2). However, in the case of rare
18 67 antibodies, development of alloantibodies can complicate administration of future blood products
19 68 (1). Life-threatening transfusion reactions include anaphylaxis, transfusion related acute lung injury,
20 69 bacterial contamination of blood products resulting in sepsis, acute hemolytic transfusion reactions,
21 70 and transfusion associated circulatory overload (1)(2). While the risk of transfusion transmitted viral
22 71 infections has dropped drastically in recent years and the risk of this occurring is extremely low, it
23 72 remains a concern when deciding to transfuse patients (2). RBC transfusions may also cause
24 73 immunosuppression in the recipient, a process called “transfusion-related immunomodulation
25 74 (TRIM) (3). TRIM provides rationale for the negative association observed between RBC transfusion
26 75 and post-operative adverse events as well as cancer recurrence in patients undergoing oncology
27 76 surgery (4) (5) (6) (7) (8) (9) (10). At an estimated price tag of 102-761 USD per unit, RBC
28 77 transfusions are costly (11) (12) (13) (14). They are also in short supply, relying on altruistic blood
29 78 donors to ensure inventory stability (15) (16). Given their associated risk, expense and scarcity, it is
30 79 critical they are administered wisely.
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51 80 There has been significant evolution in our understanding of humans’ ability to tolerate
52 81 anemia; resulting in a shift in approach to RBC transfusion prescribing practices from the “10/30”
53 82 rule (i.e. transfusion indicated below a hemoglobin of 10g/L or hematocrit <30%) to the widely
54 83 accepted transfusion trigger of 70g/L in the asymptomatic patient without significant cardiac
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84 comorbidity. This change came into effect following reporting of the TRICC trial and others that have
85 shown the safety of a restrictive transfusion threshold (17, 18) (19) (20). Importantly, the findings of
86 these studies, which have impacted transfusion practices across a broad spectrum of clinical
87 scenarios, are not necessarily applicable in the operative setting.

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

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111 hypothesize that transfusion reactions in the intra-operative setting are underreported. This, in
112 combination with the evidence that patients who receive intraoperative transfusions suffer increased
113 short and long term morbidity, advocates for careful consideration of transfusion administration (28)
114 (7).

115 The uncertainty of transfusion indications in this patient population is demonstrated by the
116 abundance of literature reporting on the wide variability in transfusion practices but largely reporting
117 over-transfusion of surgical patients (29) (30) (31) (32) (33). A recent survey of Canadian liver
118 surgeons and anesthesiologists highlights the lack of consensus between practitioners regarding
119 indications for transfusion. In response to the question “what is the most important information you
120 use to decide on intraoperative transfusion,” the majority of anesthesiologist selected hemoglobin
121 value (47.2% vs 19% of surgeons; $p < 0.05$), whereas surgeons selected hemodynamics (33.4% vs
122 14% of anesthesiologist; $p > 0.05$) (34). A prospective observational study of intraoperative
123 transfusion practices in Europe reported “physiologic trigger irrespective of hemoglobin” as the most
124 common indication for transfusion in a cohort of 5803 patients (35). Despite a global shift to a more
125 restrictive transfusion strategy, wide variability in practice patterns in the intraoperative setting exists,
126 and therefore warrants a review of the recommendations.

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

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3 138 In summary, blood transfusions are associated with possible harm and over-transfusion in
4
5 139 the intraoperative setting is common. Although there is an abundance of guidance pertaining to
6
7 140 indications for RBC transfusion, a review of guidance dedicated to the intraoperative patient does
8
9 141 not currently exist.

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13 143 **OBJECTIVE**

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15 144 The objective of this systematic review is to explore the availability, quality and consistency
16
17 145 of published guidelines reporting on the indication for allogenic red blood cell transfusion in the
18
19 146 intraoperative setting. We also aim to summarize the existing recommendations and associated
20
21 147 level of evidence.

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25 149 **METHODS**

26
27 150 The Preferred Reporting Items for Systematic Review and Meta-analysis Protocols
28
29 151 (PRISMA-P) checklist guidelines were referenced for development of this protocol (42) (43). A
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31 152 PRISMA-P checklist is available as a supplementary document. The protocol was registered with
32
33 153 the PROSPERO International Prospective Register of Systematic Reviews on October 16, 2018
34
35 154 (CRD42018111487).

36
37 155 Any amendments made to the current protocol will be published using a protocol addendum,
38
39 156 accompanied by the date of and rationale for the reported amendment, with the final manuscript.

40
41 157 ***Eligibility criteria:***

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43 158 Guidelines reporting on indications for allogenic red blood cell transfusion in the
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45 159 intraoperative setting will be considered for inclusion. Our definition of clinical practice guidelines is
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47 160 adopted from the Institute of Medicine and National Guideline Clearinghouse which define them as
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49 161 recommendations, derived from systematic review of evidence, from collective opinions of an expert
50
51 162 panel, aimed at health care providers intended to improve patient care (44, 45). An article will be
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53 163 included if it: (1) is presented as a clinical practice guideline; (2) is based on a systematic review of
54
55 164 evidence; (3) is produced by a medical association, professional society, public or private

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

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

173 Information sources and search strategy

174 MEDLINE (OVID interface, including In-Process and Epub Ahead of Print) and EMBASE
175 (OVID interface) and CINHAL will be systematically searched from inception to January 2019,
176 through application of a search strategy developed by a health science librarian with expertise in
177 systematic reviews. Search terms will include 'allogenic red blood cell transfusion', 'guideline' and
178 'operative'. The search will not be restricted by date, language or patient population (ie. adult versus
179 pediatric). A Peer Review of Electronic Search Strategies (PRESS) will be performed by a second
180 information specialist who is not associated with the project. A draft search strategy for Medline
181 can be found in Appendix 1. The following guideline-specific databases will also be searched:
182 National Institute for Health and Care Excellence (NICE) (UK), the Canadian Medical Association
183 Infobase (Canada), the G-I-N International Guideline Library, the New Zealand Guidelines (NZG)
184 Group, The World Health Organization and the Scottish Intercollegiate Guidelines Network (SIGN)
185 (46-51). Google Scholar will be searched with '(intraoperative OR perioperative) AND (guideline
186 OR consensus OR recommendation OR statement)' and the first 200 records will be screened.
187 References of identified articles will be reviewed for relevant guidelines.

188 Study Records

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

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

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

199 **Data Items**

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

212 **Outcomes & Prioritization**

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

216 **Characterization of identified guidelines**

217 A descriptive table of identified guidelines will be presented. This table will include
218 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: $(\text{obtained score} - \text{minimal possible score}) / (\text{maximal possible score} - \text{minimal possible score}) = _ \%$. The minimum possible score is calculated as: $(\text{number of questions}) \times (\text{number of reviewers}) \times 1$. The maximum possible score is calculated as: $(\text{number of questions}) \times (\text{number of reviewers}) \times 7$.

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.

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3 246 **Analysis of subgroups or subsets**

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5 247 Guidelines pertaining to indications for blood transfusion in cardiac versus non-cardiac
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7 248 surgery patients will be grouped and considered separately. In addition, guidelines published
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9 249 following publication of the TRICC trial in May 1997 will be considered separately in our descriptive
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11 250 analysis (18). The rationale for this being that the prevailing theme of current practice is a result of
12
13 251 this trial.

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15 252 **Dissemination**

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18 253 The results of this review will be submitted for presentation at national and international
19
20 254 meetings and publication in a peer-reviewed journal.

21
22 255 **Reporting of review**

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24 256 The findings of this systematic review will be reported according to the Preferred Reporting
25
26 257 Items for Systematic Reviews and Meta-analyses (PRISMA) statement. The completed checklist
27
28 258 will be provided as supplementary material.

29
30 259 **Confidence in cumulative evidence**

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33 260 The quality of recommendations will be evaluated by using the systematic and
34
35 261 comprehensive approach known as Grading of Recommendations, Assessment, Development and
36
37 262 Evaluations (GRADE) (57). The quality of evidence will be assessed across the domains of risk of
38
39 263 bias, consistency, directness, precision and publication bias.

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41 264 **Patient and public involvement**

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44 265 This investigation is aligned with research priorities established by The Canadian Blood
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46 266 Services (CBS), a not-for-profit charitable organization, responsible for managing the Canadian
47
48 267 blood supply (with the exception of Quebec) (58). Specifically, they have identified: (1) promoting
49
50 268 appropriate blood product utilization and (2) ensuring an adequate blood product supply, as two of
51
52 269 five research priorities. CBS invites public participation in their bi-annual board meetings, where a
53
54 270 number of issues are addressed, inclusive of priority research agendas. Patients or the public

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

273 **DISCUSSION**

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

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

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

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

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3 297 further examination. The input of patients who have had intra-operative transfusion should be
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5 298 sought to determine where patient preference may supersede rigorous adherence to guidelines.
6
7 299 Following well planned knowledge translation phase, auditing to monitor compliance with the
8
9 300 guidelines will need to be done. Additionally, following guideline implementation quality assurance
10
11 301 initiatives with patient centred outcomes will also be necessary to ensure that the safety and
12
13 302 tolerability of developed guidelines. Thus, it is unlikely that final guideline recommendations
14
15 303 regarding intra-operative transfusion will be forthcoming in the near future. However, this review
16
17 304 reinforces the urgent need to begin the undertaking.
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20 305

21
22 306 **Acknowledgements:** The authors thank Josee Skuce for her help with developing and PRESS
23
24 307 reviewing the search strategy, as well as retrieving articles.
25

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27
28 309 Academic Health Science Center Alternative Funding Plan Innovation Fund.
29

30 310 **Competing interests:** None to declare.
31

32 311 **Sponsor:** None to declare.
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312 **Authors' Contribution**

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

315

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

320

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

325

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327 of transfusion reactions: a multicenter study utilizing systematic active surveillance and expert
328 adjudication. *Transfusion*. 2016;56(10):2587-96.
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30 473 Figure 1: Flow diagram of study selection process.
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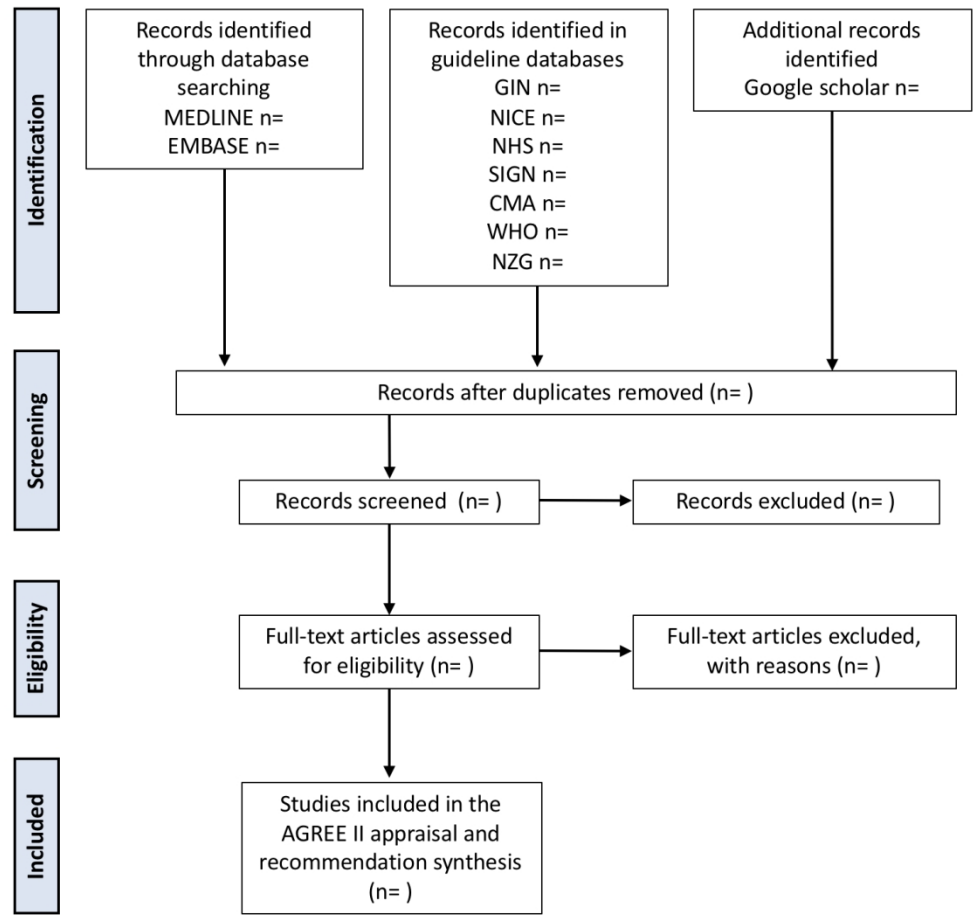


Figure 1: Flow diagram of study selection process.

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/
 9 or Perioperative Care/ (69769)
 10 (intraoperat* or intra-operat* or perioperat* or peri-operat*).tw,kw. (205937)
 11 (surg* or operat*).ti. (708792) - added this line
 12 (transfus* adj5 (operat* or surg*)).tw. (8642)
 13 ((undergoing or during) adj4 (surg* or operat*)).tw. (180983) - expanded this line by taking out
 14 'transfus*
 15 or/8-12 (968870)
 16 7 and 13 (18339)
 17 exp clinical pathway/ (6046)
 18 clinical protocol/ (25911)
 19 exp consensus/ (9313)
 20 exp consensus development conference/ (11078)
 21 exp consensus development conferences as topic/ (2618)
 22 guidelines as topic/ (37008)
 23 exp practice guideline/ (24266)
 24 practice guidelines as topic/ (105996)
 25 health planning guidelines/ (4007)
 26 (guideline or practice guideline or consensus development conference or consensus development
 27 conference, NIH).pt. (39641)
 28 (standards or guideline or guidelines).ti,kf,kw. (96689)
 29 ((practice or treatment* or clinical) adj guideline*).ab. (33765)
 30 (CPG or CPGs).ti. (5320)
 31 consensus*.ti,kf,kw. (22038)
 32 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw.
 33 (17432)
 34 recommendat*.ti,kf,kw. (35650)
 35 or/15-30 (334141)
 36 14 and 31 (550)
 37 (rbc transfusion* or red blood cell* transfusion*).ti. (1054)
 38 (transfus* and (intraoperat* or intra-operat* or perioperat* or peri-operat*)).ti. (1014)
 39 33 or 34 (1999)
 40 (guideline or practice guideline or consensus development conference or consensus development
 41 conference, NIH).pt. (39641)
 42 (standards or guideline or guidelines).ti,kf,kw. (96689)
 43 36 or 37 (122196)
 44 35 and 38 (61)
 45 32 or 39 (578)
 46 animals/ not humans/ (4465996)
 47 40 not 41 (577)
 48 (exp infants/ or child/) not adult/ (1517431)
 49 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	<input type="checkbox"/>	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	x	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	x	<input type="checkbox"/>	49
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	x	<input type="checkbox"/>	4-33
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	x	<input type="checkbox"/>	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	<input type="checkbox"/>	155-156
Support					
Sources	5a	Indicate sources of financial or other support for the review	x	<input type="checkbox"/>	308-309
Sponsor	5b	Provide name for the review funder and/or sponsor	x	<input type="checkbox"/>	311
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	x	N/A
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	x	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	Appendix 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	x	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	219-241
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	x	<input type="checkbox"/>	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)	<input type="checkbox"/>	x	N/A
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	x	<input type="checkbox"/>	246-251
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	x	<input type="checkbox"/>	242-245

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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)	<input type="checkbox"/>	x	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input type="checkbox"/>	x	N/A

For peer review only