Supplementary File 2. Study Protocol

The Effectiveness of Behavioural Interventions Targeting Inappropriate Physician Transfusion Practices: A Systematic Review

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Abstract

Background: Recent evidence has demonstrated that a restrictive strategy for allogeneic red blood cell transfusion may be equally as effective or potentially superior to a liberal transfusion strategy. Despite this evidence, uptake of restrictive transfusion practices among ordering physicians has been variable. A number of interventions to modify physician transfusion practices, such as education, clinical practice guidelines, and audit and feedback mechanisms have been described in the literature. The relative efficacy or effectiveness of these interventions, with regards to changing physician behaviours and/or improving appropriateness of transfusions, is not well understood.

Objective: This protocol outlines the procedures of a de novo systematic review of the literature examining the impact of behavioural interventions on physician transfusion practices, appropriateness of transfusions, and costs.

Methods: A systematic review will be completed. Seven multidisciplinary electronic databases will be searched from inception. Abstracts and full-text papers will be screened for inclusion, in duplicate, based on established criteria. Studies will be included if they: report original data from a primary study; report outcomes on a behavioral intervention targeting physician transfusion practices. Each included study will be assessed in duplicate for quality, using the Cochrane Risk of Bias Checklist for Randomized Controlled Trials and the Downs and Blacks Checklist for non-randomized studies.

Results: Contingent on the number of final studies identified, as well as the potential heterogeneity in the characteristics of the articles and their reported outcomes, a meta-analysis may be conducted. Should meta-analysis of pooled results be permitted, the analysis will be also be stratified by study design type. If meta-analysis is not possible, a narrative approach to synthesizing results will be used. Anticipated outcomes include: proportion of physicians using restrictive transfusion strategies, rate of appropriateness of transfusions, change in healthcare system costs, patient hospital length-of-stay, risk of adverse events, and physician attitudes and acceptability towards the interventions.

Conclusions: The findings of this study will provide insight into which interventions most effectively change physician behaviour concerning allogeneic blood transfusions. The results of this research will help guide decision-makers and health care practitioners in their adoption of updated allogeneic red blood cell transfusion strategies.

Background
Blood and blood products, such as red blood cells (RBC), are scarce health resources that must be managed carefully to ensure judicious use, patient safety, and availability for those most in need of transfusions.[1] Attempts to improve blood product utilization across a variety of clinical settings have promoted the use of more restrictive transfusion strategies.[2-5] For example, evidence-based guidelines in the Intensive Care Unit (ICU) recommend RBC transfusions for certain patients (e.g. non-hemorrhagic) with a Hgb level below 7 grams per deciliter; above this, transfusions may be clinically inappropriate and increase risk of adverse events and prolong hospital stay.[6,7] Despite these recommendations, a number of observational studies have demonstrated variable uptake of restrictive transfusion practices among ordering physicians.[8]

In various clinical settings, physicians' transfusion practices are likely influenced by a myriad of social, cultural, and environmental factors. A number of interventions to modify physician transfusion practices, such as education, clinical practice guidelines, and audit and feedback mechanisms have been described in the literature.[9,10] The relative efficacy or effectiveness of these interventions, with regards to changing physician behaviours and/or improving appropriateness of transfusions, is not well understood.

Previous systematic reviews that have examined the impact of behavioural interventions on physician transfusion practices reported substantial variability in the reduction in inappropriate transfusion post-intervention.[9,10] Moreover, there were marked limitations in the quality of evidence included in these previous reviews, and none of the evidence examined the cost-effectiveness of the behavioural interventions.

This protocol outlines the procedures of a *de novo* systematic review of the literature examining the impact of behavioural interventions on physician transfusion practices, appropriateness of transfusions, and costs.

Primary Research Question:
What is the efficacy or effectiveness of behavioural interventions on physicians' transfusion practices, in comparison to standard care?

Secondary Research Question:
What is the impact of the behavioural interventions on the rate of RBC transfusions, appropriateness of RBC transfusions, and healthcare system costs?

Using the PICOD methodology, the following details were used to derive the research question for the systematic review and meta-analysis:

Population	Physicians
Intervention	Any behavioural intervention
Comparator	Standard of care
Outcome	Any (e.g. physician transfusion practices; utilization of RBC transfusions; rate of appropriate RBC transfusions; healthcare system costs)

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Design	Randomized controlled trial (RCT), controlled clinical trial, comparative cohort studies

Search Strategy
MEDLINE, PubMed, EMBASE, the Cochrane Central Registry of Controlled Trials, the Cumulative Index to Nursing and Allied Health (CINAHL), the Cochrane Database of Systematic Reviews and the Health Technology Assessment (HTA) database will be used for this systematic review.

The search will include literature of all languages and published up until May 2015. The first Boolean search will be done by using the term "or" to explode (search by subject heading) and map (search by keyword) the following MeSH headings "*Blood Transfusion" or "transfusion*" or "overtransfusion*" or "blood or blood product* or plasma". This first set or terms will then be combined using the Boolean operator "and" with the MeSH headings and keyword terms such as "audit*" or "educat*" or "feedback" or "guideline*" or "intervention*" or "train or training". The search will not include "standard care" as the comparator in the search strategy in order to ensure that all relevant studies are included for the systematic review. The search will exclude animal studies, case reports, comments, editorials and letters. No other limitations will be applied. The details of the MEDLINE search are provided in Appendix 1.

The latter two databases will be specifically searched to identify previously published publications or systematic reviews of relevance. The reference lists of identified systematic reviews will then be hand-searched in duplicate to identify additional relevant articles. The clinical trial registry "clinical trials.gov" will also be consulted to identify ongoing trials and study protocols.

Identification of Articles Eligible for Systematic Review:
An initial screen of resulting abstracts will be screened in duplicate. Based on the above PICOD, abstracts will be included for the subsequent full-text review if they report:
1. Original data from a primary study
2. A behavioural intervention targeting physician transfusion practices as the intervention

Abstracts will be excluded if they do not meet the above criteria. No fixed definition of a behavioural intervention will be applied; thus any definition used within the included studies will be accepted. Abstracts selected for inclusion by either reviewer will proceed to the full-text review.

Abstracts included after the first screen will proceed to full-text review which will be completed by two reviewers. Full-text articles will be included if they meet the inclusion criteria based on the above PICOD criteria (presented in Table 1). Any disagreement between reviewers will be resolved through discussion and consensus. A kappa statistic for reviewer agreement will also be calculated.

Table 1: Inclusion and Exclusion Criteria for Review of Full-text Articles

Inclusion Criteria	Exclusion Criteria
Full-text articles	Articles not available in full-text

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Original data	Non-original data (e.g. reviews)
Peer-reviewed articles	Grey literature
Physicians (any healthcare setting)	Other healthcare professionals
RCT, controlled clinical trial, comparative cohort studies (including pre-post)	Case studies, commentaries, editorials, letters, opinions
Primary objective: clinical efficacy/effectiveness of interventions on physician transfusion practices	Animal studies
Interventions: behavioural interventions (e.g. education, audit and feedback)	Non-behavioural interventions
Comparator: standard of care	Not focused on primary objective
Any outcomes (e.g. number of transfusions, physician attitudes, etc)	

The final included articles will be divided into two categories based on their study design:
1. Group 1: RCTs and controlled clinical trials
2. Group 2: Comparative Cohort Studies

Data Extraction:
Relevant data from all included full-text articles will be extracted in duplicate using a standardized data extractions form. This data extraction form will be used to compile the detailed data by study type for Group 1 and Group 2. Any discrepancy in data extraction will be resolved through consensus and discussion. Authors will be contacted if relevant information is not reported or for clarification of results. Data extraction was designed to meet the PRISMA checklist standards for reporting of systematic reviews and meta-analyses.[11]

Quality Assessment
During data extraction, the quality of each included study will also be assessed. Quality assessment will be done in duplicate and will consist of a narrative assessment of quality coupled with scores from relevant quality assessment scales. Specifically, the Cochrane Risk of Bias Checklist will be used to evaluate the quality of the included RCTs in Group 1, and the Downs and Black Checklist[12] will be used to evaluate the quality of the included observational studies.[13]

Data Analysis and Synthesis
We will summarize the number of articles included and excluded in each step of the review process (abstract review and full-text review). This information will be presented in a flow-chart format, following PRISMA Guidelines.[11] If an article is excluded after undergoing full-text review, justification will be provided for its exclusion.

We will present data on the number and characteristics of included studies from the systematic review, as well as the number and characteristics of included studies identified for meta-analysis. All clinical outcomes reported by included studies will be reported narratively and summarized in tables. Anticipated outcomes include: proportion of physicians using restrictive transfusion strategies, rate of appropriateness of transfusions, change in healthcare system costs, patient hospital length-of-stay, risk of adverse events, and physician attitudes and acceptability towards

the interventions. The way in which the outcomes were recorded or identified in each study (i.e. patient-reported, validated instruments, physician assessment, , etc.) will also be collected and described in this review, as the potential for heterogeneity in these methods may lead to heterogeneity in the reported data.

Depending on the number of final studies identified, and heterogeneity of included studies, as, meta-analysis may be conducted. Should meta-analysis of pooled results be permitted, the analysis will be also be stratified by study design type (i.e. in Group 1 and Group 2).

Significance
The findings of this study will provide insight into which interventions most effectively change physician behaviour concerning allogeneic blood transfusions. The results of this research will help guide decision-makers and health care practitioners in their adoption of updated allogeneic red blood cell transfusion strategies.

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Reference List

1.   Shander A, Hofmann A, Gombotz H, Theusinger OM, Spahn DR. Estimating the cost of blood: past, present, and future directions. *Best Practice & Research Clinical Anaesthesiology.* 2007;21(2):271-289.

2.   Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *New England Journal of Medicine.* 1999;340(6):409-417.

3.   Lacroix J, Hébert PC, Hutchison JS, et al. Transfusion strategies for patients in pediatric intensive care units. *New England Journal of Medicine.* 2007;356(16):1609-1619.

4.   Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. *New England Journal of Medicine.* 2011;365(26):2453-2462.

5.   Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. *New England Journal of Medicine.* 2014;371(15):1381-1391.

6.   Napolitano LM, Kurek S, Luchette FA, et al. Clinical practice guideline: Red blood cell transfusion in adult trauma and critical care*. *Critical care medicine.* 2009;37(12):3124-3157.

7.   Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev.* 2012;4.

8.   Francis JJ, Stockton C, Eccles MP, et al. Evidence‐based selection of theories for designing behaviour change interventions: Using methods based on theoretical construct domains to understand clinicians' blood transfusion behaviour. *British Journal of Health Psychology.* 2009;14(4):625-646.

9.   Tinmouth A, MacDougall L, Fergusson D, et al. Reducing the amount of blood transfused: a systematic review of behavioral interventions to change physicians' transfusion practices. *Archives of internal medicine.* 2005;165(8):845-852.

10.   Wilson K, MacDougall L, Fergusson D, Graham I, Tinmouth A, Hébert PC. The effectiveness of interventions to reduce physician's levels of inappropriate transfusion: what can be learned from a systematic review of the literature. *Transfusion.* 2002;42(9):1224-1229.

11.   Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1.

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Appendix 1

MEDLINE Search Strategy

1. exp *Blood Transfusion/
2. (transfusion* or overtransfusion*).tw.
3. ((blood or blood product* or plasma) adj5 (usage or utilization)).tw.
4. 1 or 2 or 3
5. limit 4 to animals
6. limit 4 to (animals and humans)
7. 5 not 6
8. 4 not 7
9. limit 8 to (case reports or comment or editorial or letter or "review")
10. 8 not 9
11. ((systematic or critical or scoping) and (review or synthesis)).ti.
12. 8 and 11
13. limit 8 to systematic reviews
14. 10 or 12 or 13
15. Physician's Practice Patterns/
16. physicians/ or hospitalists/ or surgeons/
17. "Internship and Residency"/
18. exp Medical Staff/
19. (clinical staff or doctors or hospitalist* or house officer* or house staff or housestaff or intern or interns* or medical officer* or medical staff or physician* or residents or surgeon*).tw,kw.
20. 15 or 16 or 17 or 18 or 19
21. exp Medical Staff/ed [Education]
22. exp "Internship and Residency"/ed [Education]
23. education, medical/ or exp education, medical, continuing/
24. exp Medical Audit/
25. exp Guideline Adherence/ or exp Practice Guidelines as Topic/
26. exp Quality Assurance, Health Care/
27. Quality Control/
28. (audit* or educat* or feedback or guideline* or intervention* or program* or train or training).tw.
29. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 14 and 20 and 29