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Behaviour modification interventions to optimize red blood cell transfusion practices: A systematic review and meta-analysis

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ABSTRACT

Objective: To assess the impact of behaviour modification interventions to promote restrictive red blood cell (RBC) transfusion practices.

Design: Systematic review and meta-analysis.

Setting, participants, interventions: MEDLINE, PubMed, EMBASE, Cochrane Central Registry of Controlled Trials, CINAHL, Cochrane Database of Systematic Reviews, and HTA database were searched to May 2016. Published randomized controlled trials or non-randomized studies examining an intervention to modify healthcare providers' RBC transfusion practice in any healthcare setting were included.

Primary and secondary outcomes: The primary outcome was the proportion of patients transfused. Secondary outcomes included the proportion of inappropriate transfusions, RBC units transfused per patient, in-hospital mortality, length of stay (LOS), pre-transfusion hemoglobin, and healthcare costs. Meta-analysis was conducted using a random-effects model and meta-regression was performed in cases of moderate to high heterogeneity. Publication bias was assessed by Begg's funnel plot.

Results: Seventy-five low to moderate quality studies were included: 31 evaluated a single intervention and 44 examined a multi-modal intervention. In all studies, an intervention was compared to standard of care or historical controls. Use of any intervention was associated with reductions in the odds of transfusion (OR: 0.63 [95% CI 0.56−0.71]), odds of inappropriate transfusion (OR: 0.46 [95% CI 0.36−0.59]), RBC units/patient (WMD: -0.50 units [95% CI -0.85−-0.16]), LOS (WMD: -1.14 days [95% CI -2.12−-0.16]), and pre-transfusion hemoglobin (-0.28 g/dL [95% CI -0.48−-0.08]). There was no difference in the pooled odds of mortality (OR: 0.90 [95% CI 0.80−1.02]). Protocol/algorithm and multi-modal interventions were associated

with the greatest decreases in the odds of transfusion. High heterogeneity was observed in all estimates and there was evidence for publication bias.

Conclusions: Most interventions to modify RBC transfusion practices were effective. However, the majority of studies were non-randomized, before and after studies. High-quality randomized trials are required to confirm effectiveness and cost-effectiveness of interventions.

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STRENGTHS AND LIMITATIONS OF STUDY

- In this systematic review and meta-analysis, 75 studies examining single and multi-modal interventions to modify red blood cell transfusion practices were identified.
- This is the most comprehensive systematic review and the first meta-analysis of these interventions to date.
- Included studies were of low to moderate quality and most were designed as non-randomized, before and after studies.
- No studies examined the comparative effectiveness between behaviour modification interventions, nor the cost-effectiveness of interventions.
- There was significant statistical heterogeneity and evidence for publication bias.

INTRODUCTION

Blood and blood products, such as red blood cells (RBC), are scarce and expensive health resources that must be managed carefully to ensure judicious use and availability for those most in need of transfusions.[1] Beyond blood conservation, transfusion safety and reducing the adverse events associated with transfusion must be considered. RBC transfusions have been associated with increased risk of infections, acute transfusion reactions, and, in certain cases, mortality.[2-4] High-quality evidence has accumulated over the past two decades in support of reducing patient exposure to RBC transfusions, through the adoption of more restrictive RBC transfusion thresholds.[5-9] A number of guidelines, such as those most recently released by the AABB (formerly the American Association of Blood Banks),[10] have also recommended against transfusion if hemoglobin levels are above 7 g/dL to 8 g/dL for most patients groups.

It is well documented that publication of such evidence alone is insufficient for affecting change.[11] Clinical practice is influenced by a myriad of social, cultural, and environmental factors that are not necessarily considered in guidelines.[12] Concerted change management efforts are, therefore, commonly undertaken to actively address these factors in order to implement recommended guidelines and achieve the desired practice change.

Interventions to specifically modify provider transfusion practices, such as education, audit and feedback, and computerized or paper order entry systems, have been described in prior studies.[13 14] Previous systematic reviews have examined the impact of these interventions on transfusion practices for various blood components (e.g. RBCs, fresh frozen plasma, platelets, cryoprecipitate). The findings of these syntheses report variability in outcomes—including a paucity of economic outcomes—and limitations in both the quality of evidence and breadth of interventions examined.[13-15] With the exception of one systematic review published in 2015 that

exclusively focused on the impacts of electronic decision support,[15] these previous reviews are dated (last published in 2005).[13 14]

Therefore, a *de novo* systematic review synthesizing the current literature in this area, concentrating on all behaviour modification interventions targeting RBC transfusion practices, is useful as healthcare organizations respond to meet recent RBC transfusion guideline recommendations. The objective of this study was to determine the effectiveness of behaviour modification interventions that change RBC transfusion practices, specifically, the effects of interventions on the proportion of patients transfused, as well as patient and healthcare system outcomes.

MATERIALS AND METHODS

A systematic review of the published literature was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Supplementary File 1).[16] The protocol for this systematic review is registered on the PROSPERO website (2015:CRD42015024757; Supplementary File 2).[17]

Search Strategy

The electronic search strategy was developed by an Information Specialist (DLL). MEDLINE, PubMed, EMBASE, the Cochrane Central Registry of Controlled Trials, the Cumulative Index to Nursing and Allied Health, the Cochrane Database of Systematic Reviews and the Health Technology Assessment database were searched from inception to May 11, 2016. A sample search strategy is available in Supplementary File 3. Animal studies, case reports, comments, editorials, and letters were excluded; no other limitations were applied. The references lists of identified systematic reviews were also hand-searched for relevant articles not found through database searches.

Selection of Literature

Studies were included if they: reported original data; examined the impact of a behaviour modification intervention on healthcare provider RBC transfusion practices; had a comparator group (e.g. no intervention or another intervention); and were designed as either a randomized controlled trial (RCT) or non-randomized study. A non-randomized study involves the selection of groups each exposed to a different intervention without random assignment.[18 19] Common non-randomized designs in behaviour modification studies include non-randomized trials (also referred to as between subjects or between group trials), time series studies, and uncontrolled and controlled before and after studies.[19 20] No fixed definition of a behaviour modification

intervention was applied; thus, any definition used within the included studies was accepted. Included interventions were grouped using an inductive approach based on descriptors and labels provided from the studies themselves. Studies were excluded if they did not meet any of the above criteria, including if they only assessed transfusion of other blood products (i.e. fresh frozen plasma, platelets, cryoprecipitate) and not in conjunction with RBCs. Detailed inclusion and exclusion criteria are provided in Supplementary File 4. Abstract and full-text screening were completed in duplicate (LJJS; LED; HMH) and any disagreement was resolved through discussion and consensus, or through consultation with a third reviewer. Agreement between reviewers was calculated using a kappa statistic.

Data Extraction

Data extraction was completed in duplicate using a standardized data extraction form (LJJS and KM). Data on publication date, country, healthcare setting, study design, follow-up period, type of intervention and comparator(s) groups, intervention characteristics, RBC transfusion criteria, definition of an "inappropriate" transfusion, number of patients treated in each group, and the primary outcome of interest (the proportion of patients transfused) were extracted. Secondary outcomes, including the proportion of inappropriate transfusions, mean RBC units transfused per patient, in-hospital mortality, hospital LOS, pre-transfusion hemoglobin, and changes in costs (e.g. RBC unit costs) were also extracted where available.

Quality Assessment

Risk of bias and quality assessments of included studies were completed in duplicate (LJJS and KM). The Cochrane Risk of Bias tool was used to evaluate the risk of bias among included RCTs.[21] Quality of non-randomized studies were assessed using the Downs and Black Checklist.[22] Typically scored out of 28 points, the Downs and Black Checklist was modified

because several items do not apply to the non-randomized studies (e.g. randomization), thereby reducing the denominator to 22 for uncontrolled before and after studies, and 23 for controlled before and after and non-randomized trials.

Data Analysis

Meta-analyses were conducted using a random-effects model. Pooled odds ratio (OR) and the weighted mean difference (WMD), and their respective 95% confidence intervals (95% CI), were calculated for categorical and continuous outcomes, respectively. Stratified analyses by intervention type and study design were completed. Statistical heterogeneity was examined using both the I^2 (percentage of total inter-study variation due to heterogeneity rather than chance) and Q statistic *p*-value (test of homogeneity). An I^2 greater than 50% was considered as evidence for significant heterogeneity.[23] In cases of moderate to high heterogeneity, random effects meta-regression was performed with the year of publication, the number of interventions per study, having a multi-modal intervention, a study setting in a single unit or clinical service, follow-up period (greater than 1 year), and each of the identified intervention types as covariates. A regression coefficient with a $p<0.10$ was considered a significant predictor of the outcome. Publication bias was examined using Begg's funnel plot and Egger's regression test. In the case of funnel plot asymmetry, the trim-and-fill method was used to impute estimates from potentially suppressed publications. This method assumes that studies that do not demonstrate a desired effect (e.g. decrease in proportion transfused) were not likely published [24]. All statistical analyses were completed using Stata/IC 13.1.

RESULTS

Search Results

The flow chart of included studies is provided in Figure 1. Four-thousand six-hundred and sixty-one unique abstracts were identified, of which 236 proceeded to full-text review. Three systematic reviews[13-15] were hand-searched and 12 additional relevant studies were identified. One hundred and seventy-three studies were excluded during full-text review, resulting in 75 articles included in the final analysis (Kappa = 87.6%, 95% CI 81.3-93.9%).

Characteristics of Included Studies

The characteristics of included studies are summarized in Supplementary File 5. The 75 included articles were comprised of 74 unique study populations, as two articles[25 26] reported different outcomes for the same population. In addition, one article[27] reported outcomes from two unique study studies; thus, the non-overlapping findings from both studies were included. The included studies were published between 1983[28] and 2016,[29-31] with the majority of studies conducted in the United States (n=46). Only 3 studies were RCTs;[27 32 33] the remaining 72 were non-randomized studies, specifically uncontrolled before and after (n=66);[25-27 29-31 34-93] controlled before and after (n=2);[94 95] and non-randomized trial (n=4)[28 96-98] designs.

In all cases, an intervention was compared to either historical controls or standard of care. Most studies were conducted in a single acute care facility, often an academic hospital. Follow-up periods varied considerably from 2 weeks[73] to 6 years[41] post-intervention. Targeted populations included primarily physicians (e.g. intensivists, anesthesiologists, surgeons) ordering RBC transfusions, as well as medical trainees (e.g. residents), other healthcare providers (e.g. nurses), and hospital staff (e.g. hospital laboratory and blood bank technologists) involved in the care of patients receiving transfusions. The unit of intervention was the individual healthcare provider, ward or unit, or institution (i.e. not patients themselves).

Types of interventions

The effectiveness of either a single (n=31) or multiple interventions (n=44) in combination (referred to as multi-modal interventions) was evaluated. The following single intervention categories were identified: education sessions or materials (n=9);[33 71-77 96] protocols or algorithms (n=7);[30 32 81-85] guidelines (n=4);[78-80 97] computerized physician order entry (CPOE) systems and decision support (n=4);[27 87-89] reminders (n=2);[90 95] audit and feedback (n=2);[91 98] audit approval (n=2);[92 93] and a clinical policy (n=1).[86] Descriptions of each, along with examples from the included studies, are provided in Table 1.

Multi-modal interventions included between 2 and 5 strategies, applied concurrently or in sequence. Combinations of multi-modal interventions are summarized in Supplementary File 6. The interventions most commonly included in multi-modal interventions were: education (n=31);[25-29 31 34 35 40-44 46-48 50-53 55-57 59-61 63 65-68 94] guidelines (n=22);[27 31 35 37 38 43 46-49 51 52 54 55 57 59 60 63 64 66 67 94] and audit and feedback (n=20).[28 29 31 37 39 42 45-48 50-53 59 60 62-64 68] Some multi-modal interventions applied additional interventions not examined among the single intervention studies, including paper order forms (n=4),[54 59 62 64] retrospective or prospective audit (n=6),[29 38 49 55 66 70] and financial incentives (n=1).[29]

Quality of Included Studies

All three RCTs[27 32 33] incorporated study elements that were deemed to be of high, low, and unclear risk of bias (Supplementary File 7). Due to the nature of the interventions, treatment allocation was not concealed, nor could the participants, personnel, or outcome assessors be blinded; thus, risk of bias was consistently high in these areas. In contrast, risk of bias was low across all studies with respect to both attrition and reporting bias.

The majority of non-randomized studies (n=54) were of moderate quality, where quality assessment scores ranged from 12-15; twelve studies[28 35 37 40 44 45 49 72 79 83 94 96] were of low

quality (scores from 0-11) and no studies were deemed to be of high quality (score > 17) (Supplementary File 8). Most studies were found to have low scores due to poor reporting (Q1-Q10), particularly of the characteristics of the targeted population and distribution of principal confounders. External validity (Q11 and Q13) was moderate for most studies; however, Q12 (i.e. subjects prepared to participate representative of the entire population) was deemed "unable to determine" for all studies. The internal validity was low to moderate across studies (Q16 to Q26). Adequate adjustment for confounding (Q25) and whether losses to follow-up were taken into account (Q26) were also deemed "unable to determine" for all studies.

Impact of Behaviour Modification Interventions on RBC Usage and Patient Outcomes

A summary of the pooled analyses is provided in Table 2. The primary outcome, the proportion of patients transfused, was reported in 29 studies. Patients treated in the intervention group were at least 29% less likely to receive a transfusion compared to those treated in the control group (pooled OR: 0.63 [95% CI: 0.56 to 0.71]; n=29) (Figure 2; Table 2). There was strong evidence of heterogeneity (I^2= 90%, Q-statistic p=0.00), although this was not apparent upon visual inspection as a number of studies crossed the null value. Sorting studies by year of publication showed that, with the exception of the two earliest studies,[28 80] the associated decrease in the odds of transfusion was fairly consistent over time (Supplementary File 9).

All 29 studies included in this analysis were non-randomized studies. A stratified analysis by non-randomized study design (Supplementary File 10) revealed high subgroup heterogeneity between the uncontrolled before and after studies (I^2= 89.0%, p=0.00). However, the variability between the two non-randomized trials was much lower (I^2= 18.7%) was likely due to chance alone (i.e. not due to heterogeneity) (Q-statistic p=0.267), suggesting that differences in study

design might have contributed to some of the observed heterogeneity in the crude pooled estimate.

Further, stratification by intervention category revealed that differences in techniques across studies might have also contributed to study heterogeneity (Figure 2; Table 2). Among these interventions, the use of a protocol or algorithm (pooled OR: 0.34 [95% CI: 0.19 to 0.60]; n=3) and a multi-modal intervention (pooled OR: 0.63 [95% CI: 0.54 to 0.74]; n=16) were associated with significantly decreased odds of patients being transfused. CPOE and decision support,[88] audit approval,[93] and policy interventions[86] were also associated with decreases in the odds of transfusion to a lesser degree; these point estimates, however, were derived from a single study in each subgroup (Figure 2; Table 2). No significant differences were observed between groups following the use of education (pooled OR: 0.74 [94% CI: 0.44 to 1.24]; n=3) and guidelines (pooled OR: 0.17 [95% CI: 0.01-3.15]; n=3), or reminders (OR: 1.51 [95%: 0.86-2.66]; n=1).

Among secondary outcomes (Table 2; Supplementary Files 11-15), use of any intervention was associated with a decreased odds of inappropriate transfusion (pooled OR: 0.46 [95% CI: 0.36 to 0.59; I^2= 97.6%, Q-statistic p=0.00; n=11), commonly defined as a transfusion initiated at a pre-transfusion hemoglobin above 7 g/dL to 9 g/dL. The mean RBC units transfused per patient (WMD: -0.50 units [95% CI: -0.85 to -0.16]; I^2= 99.8%, Q-statistic p=0.00; n=12) and mean patient LOS (WMD: -1.14 days [95% CI: -2.12 to -0.16]; I^2= 82.2%, Q-statistic p=0.00; n=8) also decreased following the use of an intervention (Table 2). The change in mean pre-transfusion hemoglobin level was only examined among studies of multi-modal interventions and was associated with a WMD of -0.28 g/dL (95% CI: -0.48 to -0.08; I^2= 95.5%, Q-statistic p=0.00; n=5).

There was also significant heterogeneity in the pooled analyses of secondary outcomes (I^2 ranging from 57.4 to 99.8%). It was unclear whether differences in interventions contributed to the heterogeneity, as stratification by intervention category left many subgroups with only one study; this precluded calculation of all subgroup I^2 values (Supplementary Files 11-15). Single modality interventions were associated with greater impacts on RBC usage, compared to multi-modality interventions (Table 2). Specifically, implementation of a guideline in one study resulted in the lowest odds of inappropriate transfusion (OR: 0.07 (95% CI: 0.02 to 0.19) and the greatest decrease in mean RBC units transfused (WMD: -1.42 units [95% CI: -1.67 to -1.17]).[80] Another study examining a treatment algorithm reported the largest decrease in hospital LOS, however there was marked variability in this estimate (WMD: -6.30 days [95% CI: -14.43 to 1.83]).[32] A significant increase in the odds of inappropriate transfusion (OR: 1.74 [95% CI: 1.39-2.19]) was observed following audit and feedback in one study.[91]

There was no significant difference in the odds of in-hospital mortality (pooled OR: 0.90 (95% CI: 0.80 to 1.02; I^2= 57.4%, Q-statistic p=0.001; n=19) (Table 2). The stratified meta-analysis (by intervention type) suggested that the observed heterogeneity in the pooled estimate was likely attributed to the variability in interventions examined across studies (Supplementary File 15).

Potential Predictors of RBC Usage

Studies published on or after 1995, the year in which evidence of efficacy and safety of restrictive transfusion practices were first published,[99] were included in the meta-regression. The year of publication, number of interventions, having a multi-modal intervention, a single unit or clinical service setting, follow-up greater than 1 year, and the individual component interventions in a given study were not identified as significant predictors of RBC transfusion (Supplementary

File 16). For the remaining outcomes, small study sample sizes (n<10 studies) precluded meta-regression.[100]

Publication bias

Evidence for publication bias among included studies (open circle symbols) was indicated by the asymmetry in the funnel plot (Figure 3) and Egger's regression test (p=0.006). Eight studies were imputed using the trim-and-fill method (square with circle symbols) resulting in a pooled OR of 0.765 (95% CI: 0.598 to 0.979) for the primary outcome of patients being transfused. This suggests that studies of smaller patient sample size, reporting an increased likelihood of transfusion post-intervention, may have been suppressed from publication.

DISCUSSION

Efforts to modify transfusion practices are not novel and have been described internationally for over four decades. We identified 75 studies, primarily non-randomized studies of low to moderate quality, examining the impact of a behaviour modification intervention, compared to no intervention, on RBC transfusion practices. Among single modality interventions examined, eight categories were identified: education, protocol/algorithm, guidelines, CPOE and decision support, reminders, audit and feedback, audit approval, and clinical policy. The majority of studies used multi-modal interventions. Most studies reported reduced RBC use and improvements in patient and system outcomes, regardless of the intervention or combination of interventions. The pooled odds ratio of patients being transfused decreased by at least 29% and, on average, patients received 0.50 fewer RBC units post-intervention. The pooled average pre-transfusion hemoglobin levels also decreased by 0.28 g/dL and the proportion of inappropriate transfusion (above a hemoglobin of 7 g/dL to 9 g/dL) decreased by approximately 40%. As

expected, given the increasing body of evidence suggesting similar safety profiles between restrictive and liberal transfusion practices,[10] there was no effect on in-hospital mortality. Among all interventions examined, the protocol/algorithm and multi-modal interventions were associated with the greatest decreases in the odds of transfusion.

The present study represents the most up-to-date collection of published literature and the first meta-analysis of interventional studies in this field. Therefore, the analytical investigations performed in our study represent a substantial and novel contribution to the existing knowledge of how to achieve restricted RBC transfusion practices. Across all pooled estimates we observed significant statistical heterogeneity, which was only partly attributed to the variability between interventions. Context-specific factors, not easily discernable from the available evidence, are also likely contributing to the observed heterogeneity among included studies. These may include variability in physician experience, clinical practice or flow, perceived ease of an intervention, and/or organizational capacity or receptivity for change.[101] Work from the audit and feedback literature—which is among the most extensive in the area of behaviour modification interventions—has also reported variability in effect size of the intervention based on differences in baseline performance of the targeted behaviour as well as nuances in delivery of the intervention (i.e. how feedback is provided).[102] Collectively, this information suggests that the decision to adopt a given intervention should, therefore, not only consider evidence of effectiveness, but also the factors related to the context and implementation. For instance, a labour-intensive intervention such as a CPOE and decision support system will be more feasible and efficient to implement in a setting with electronic ordering systems already in place, rather than in a one without. Explicit methodology to first identify relevant determinants to change and selection of an intervention(s) to address such determinants, such as through theory-based

frameworks, might prove useful in tailoring an appropriate intervention to a given clinical setting.[103 104]

Our findings are consistent with the evidence from the broader knowledge translation literature.[105] In one of the most comprehensive systematic reviews, Grimshaw *et al.*[105] identified over 200 studies examining the impact of interventions on a wide range of healthcare provider behaviours and settings. The authors identified a similar array of interventions (e.g. education, audit and feedback, reminders) that were all were effective to varying degrees, and their observed effectiveness was not associated with the number of interventions implemented within a given study.[105] The results of our meta-regression analysis further support that a multi-modal intervention and the number of component interventions are not predictive of the effectiveness of the interventions.

Our results are also in line with the qualitative findings of previous systematic reviews of interventions to modify transfusion practices more broadly.[13-15] Identified interventions were similarly found to be effective at reducing transfusion use, however the previous reviews were unable to comment on their comparative effectiveness due to the dearth of direct comparisons between intervention types and reported heterogeneity among studies.[13 14] With our updated review of the literature, meta-analysis was feasible given the high prevalence of common study designs, as well as frequent reporting of our primary and secondary outcomes. While the comparator groups among included studies were also restricted to historical controls or standard of care, our stratified meta-analyses still enabled crude comparisons of effectiveness between interventions.

Limitations

The majority of included studies were non-randomized studies of low to moderate quality and susceptible to bias. For example, most studies employed an uncontrolled before and after study design and, in the absence of a concomitant control group, these studies were at high risk of bias due to both secular trends and maturation bias.[106] Due to the lack of randomization, such studies can also be susceptible to selection bias.[19] In addition, we found limited to no reporting of participant characteristics and it is unclear whether and to what extent these characteristics led to confounding of the reported outcomes. The non-randomized studies were also deemed to have moderate external validity, thus generalizability of findings across all clinical settings and/or international healthcare systems is unclear.

Our stratified meta-analysis resulted in very limited number of studies (or even one study) often of moderate quality, in many of the single modality subgroups. This limited our ability to make inferences of comparative effectiveness across all intervention types and precluded our ability perform further statistical techniques, such as network meta-analysis.[107] While meta-regression was permitted for the primary outcome, similar analyses were underpowered for the remaining outcomes (n<10 studies). Finally, the findings from our meta-analyses must be interpreted with caution given the evidence for publication bias. Previous reviews similarly suggested of publication bias among earlier included studies due to the tendency of outcomes to favour the intervention group.[13 14]

Given such limitations of the non-randomized studies, particularly the uncontrolled before and after studies, and meta-analytic efforts, it is difficult to state with certainty which intervention is the most effective at modifying RBC transfusion practice.

Future Research

Further comparative effectiveness studies, designed as large, high-quality RCTs are recommended to determine the effectiveness of the present interventions. However, the prevalence of low to moderate quality non-randomized studies included in this present review may indicate the logistical difficulty in evaluating these interventions through such trials. As such, pragmatic trial designs may be considered to aid in balancing issues of feasibility with methodological rigor.[108] Also, none of the included studies evaluated the effectiveness of a behaviour modification intervention to that of another behaviour modification intervention (of either single or multi-modality). Such direct comparisons would not only aid in confirming effectiveness of interventions, but also help determine the comparative effectiveness of interventions. In the case of multi-modal interventions, further research should also attempt to address which elements of the intervention are key to affecting the desired change. This information may better and more appropriately advise healthcare organizations seeking to implement the most effective behaviour modification intervention.

Lastly, we did not identify any studies that performed a concomitant economic evaluation. This information is critical to selecting an intervention that is also efficient within a given healthcare budget. Eleven of the included studies did report of changes in healthcare costs, primarily cost savings in RBC usage, following either a single or multi-modal intervention.[26 38 50 54 63 66 71 77 81 88 93] Only one study factored in the cost of implementing the intervention into their estimate, resulting in a relatively modest savings.[88] Given the often costly, labour-intensive nature of many interventions, future cost-effectiveness studies should include the cost of implementation to determine whether true savings are realized from a given intervention.

CONCLUSIONS

We found a large body of literature that suggests that the majority of behaviour modification interventions are safe and effective at modifying RBC transfusion practices. The types of interventions are diverse—including single and multi-modality interventions—and the quality of studies was low to moderate. The protocol or algorithm and multi-modal interventions were associated with the greatest reductions in RBC transfusion. These results must be interpreted with caution due to the prevalence of uncontrolled before and after studies, extensive statistical heterogeneity, limited study sample size within intervention groups, and evidence for publication bias. Given these limitations, further large, high-quality randomized trials are required to not only confirm, but also directly compare effectiveness and cost-effectiveness of different types of behaviour modification interventions. This shift in the field from simply understanding "does it work", towards investigating "what works best" and "at what cost" is required as healthcare organizations respond to meet the transfusion guideline recommendations.

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REFERENCE LIST

1. Shander A, Hofmann A, Gombotz H, et al. Estimating the cost of blood: past, present, and future directions. *Best Pract Res Clin Anaesthesiol* 2007;21(2):271-89.

2. Delaney M, Wendel S, Bercovitz RS, et al. Transfusion reactions: prevention, diagnosis, and treatment. *Lancet* 2016;388(10061):2825-36.

3. Toy P, Gajic O, Bacchetti P, et al. Transfusion-related acute lung injury: incidence and risk factors. *Blood* 2012;119(7):1757-67.

4. Bolton-Maggs PH, Moon I. Assessment of UK practice for management of acute childhood idiopathic thrombocytopenic purpura against published guidelines. *Lancet* 1997;350(9078):620-3.

5. Carson JL, Stanworth SJ, Roubinian N, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev* 2016;10:Cd002042. doi: 10.1002/14651858.CD002042.pub4 [published Online First: 2016/11/02]

6. Holst LB, Petersen MW, Haase N, et al. Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis. *Bmj* 2015;350:h1354.

7. Docherty AB, O'Donnell R, Brunskill S, et al. Effect of restrictive versus liberal transfusion strategies on outcomes in patients with cardiovascular disease in a non-cardiac surgery setting: systematic review and meta-analysis. *Bmj* 2016;352:i1351.

8. Fominskiy E, Putzu A, Monaco F, et al. Liberal transfusion strategy improves survival in perioperative but not in critically ill patients. A meta-analysis of randomised trials. *Br J Anaesth* 2015;115(4):511-19.

9. Brunskill SJ, Millette SL, Shokoohi A, et al. Red blood cell transfusion for people undergoing hip fracture surgery. *Cochrane Database Syst Rev* 2015(4)

10. Carson JL, Guyatt G, Heddle NM, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. *Jama* 2016;316(19):2025-35.

11. Grimshaw JM, Eccles MP, Lavis JN, et al. Knowledge translation of research findings. *Implement Sci* 2012;7(1):1.

12. Grimshaw JM, Eccles MP. Is evidence-based implementation of evidence-based care possible? *Med J Aust* 2004;180(6):S50.

13. 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. *Arch Intern Med* 2005;165(8):845-52.

14. Wilson K, MacDougall L, Fergusson D, et al. 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):1224-9.

15. Hibbs SP, Nielsen ND, Brunskill S, et al. The Impact of Electronic Decision Support on Transfusion Practice: A Systematic Review. *Transfus Med Rev* 2015;29(1):14-23. doi: http://dx.doi.org/10.1016/j.tmrv.2014.10.002

16. 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.

17. Soril LJJ, Sparling M, Gill S, et al. The effectiveness of behavioural interventions targeting inappropriate physician transfusion practices: a systematic review protocol: University of York: Centre for Reviews and Dissemination; 2015 [cited 2016 November 25]. Available from: http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015024757 accessed November 25 2016.

18. Cook TD, Campbell DT. Quasi-experimentation: Design & analysis issues for field settings. Chicago: Rand McNally 1979.

19. Shadish WR, Cook TD, Campbell DT. Experimental and quasi-experimental designs for generalized causal inference: Wadsworth Cengage learning 2002.

20. Grimshaw J, Campbell M, Eccles M, et al. Experimental and quasi-experimental designs for evaluating guideline implementation strategies. *Fam Pract* 2000;17(90001):11-16.

21. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* 2011;343:d5928.

22. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;52(6):377-84.

23. Higgins J, Thompson SG. Quantifying heterogeneity in a meta‐analysis. *Stat Med* 2002;21(11):1539-58.

24. Duval S, Tweedie R. Trim and fill: a simple funnel‐plot‐based method of testing and adjusting for publication bias in meta‐analysis. *Biometrics* 2000;56(2):455-63.

25. Goodnough LT, Shieh L, Hadhazy E, et al. Improved blood utilization using real-time clinical decision support. *Transfusion* 2014;54(5):1358-65. doi: http://dx.doi.org/10.1111/trf.12445

26. Goodnough LT, Maggio P, Hadhazy E, et al. Restrictive blood transfusion practices are associated with improved patient outcomes. *Transfusion* 2014;54(10 Pt 2):2753-9. doi: http://dx.doi.org/10.1111/trf.12723

27. Rothschild JM, McGurk S, Honour M, et al. Assessment of education and computerized decision support interventions for improving transfusion practice. *Transfusion* 2007;47(2):228-39.

28. Handler S. Does continuing medical education affect medical care. A study of improved transfusion practices. *Minn Med* 1983;66(3):167.

29. Murphy DJ, Lyu PF, Gregg SR, et al. Using Incentives to Improve Resource Utilization: A Quasi-Experimental Evaluation of an ICU Quality Improvement Program. *Crit Care Med* 2016;44(1):162-70.

30. Rineau E, Chaudet A, Chassier C, et al. Implementing a blood management protocol during the entire perioperative period allows a reduction in transfusion rate in major orthopedic surgery: a before–after study. *Transfusion* 2016

31. Markel DC, Allen MW, Zappa NM. Can an Arthroplasty Registry Help Decrease Transfusions in Primary Total Joint Replacement? A Quality Initiative. *Clin Orthop Relat Res* 2016;474(1):126-31.

32. Despotis GJ, Grishaber JE, Goodnough LT. The effect of an intraoperative treatment algorithm on physicians' transfusion practice in cardiac surgery. *Transfusion* 1994;34(4):290-6.

33. Soumerai SB, Salem-Schatz S, Avorn J, et al. A controlled trial of educational outreach to improve blood transfusion practice. *Jama* 1993;270(8):961-6.

34. Alavi-Moghaddam M, Bardeh M, Alimohammadi H, et al. Blood transfusion practice before and after implementation of type and screen protocol in emergency

department of a university affiliated hospital in iran. *Emerg Med Int* 2014;2014(316463) doi: http://dx.doi.org/10.1155/2014/316463

35. Andreasen JJ, Sindby JE, Brocki BC, et al. Efforts to change transfusion practice and reduce transfusion rates are effective in coronary artery bypass surgery. *J Cardiothorac Vasc Anesth* 2012;26(4):545-49. doi: http://dx.doi.org/10.1053/j.jvca.2012.02.006

36. Annan E, Fless KG, Jasani N, et al. Red Blood Cell Transfusion Practices: Can High-Intensity ICU Staffing Stem the Tide? *ICU Director* 2013;4(1):11-14. doi: http://dx.doi.org/10.1177/1944451612467534

37. Ansari S, Szallasi A. Blood management by transfusion triggers: when less is more. *Blood Transfus* 2012;10(1):28-33. doi: http://dx.doi.org/10.2450/2011.0108-10

38. Baer VL, Henry E, Lambert DK, et al. Implementing a program to improve compliance with neonatal intensive care unit transfusion guidelines was accompanied by a reduction in transfusion rate: a pre‐post analysis within a multihospital health care system. *Transfusion* 2011;51(2):264-69.

39. Beaty CA, Haggerty KA, Moser MG, et al. Disclosure of physician-specific behavior improves blood utilization protocol adherence in cardiac surgery. *Ann Thorac Surg* 2013;96(6):2168-74. doi: http://dx.doi.org/10.1016/j.athoracsur.2013.06.080

40. Brandis K, Richards B, Ghent A, et al. A strategy to reduce inappropriate red blood cell transfusion. *Med J Aust* 1994;160(11):721-2.

41. Brandt MM, Rubinfeld I, Jordan J, et al. Transfusion insurgency: practice change through education and evidence-based recommendations. *Am J Surg* 2009;197(3):279-83. doi: http://dx.doi.org/10.1016/j.amjsurg.2008.10.004

42. Butler CE, Noel S, Hibbs SP, et al. Implementation of a clinical decision support system improves compliance with restrictive transfusion policies in hematology patients. *Transfusion* 2015;55(8):1964-71.

43. Corwin HL, Theus JW, Cargile CS, et al. Red blood cell transfusion: Impact of an education program and a clinical guideline on transfusion practice. *J Hosp Med* 2014;9(12):745-49. doi: http://dx.doi.org/10.1002/jhm.2237

44. Gallagher-Swann M, Ingleby B, Cole C, et al. Improving transfusion practice: ongoing education and audit at two tertiary speciality hospitals in Western

Australia. *Transfus Med* 2011;21(1):51-6. doi: http://dx.doi.org/10.1111/j.1365-3148.2010.01041.x

45. Gardner RM, Christiansen PD, Tate KE, et al. Computerized continuous quality improvement methods used to optimize blood transfusions. *Proc Annu Symp Comput Appl Med Care* 1993:166-70.

46. Garrioch M, Sandbach J, Pirie E, et al. Reducing red cell transfusion by audit, education and a new guideline in a large teaching hospital. *Transfus Med* 2004;14(1):25-31. doi: http://dx.doi.org/10.1111/j.0958-7578.2004.00476.x

47. Geissler RG, Kosters C, Franz D, et al. Utilisation of blood components in trauma surgery: A single-centre, retrospective analysis before and after the implementation of an educative PBM initiative. *Transfus Med Hemother* 2015;42(2):83-89. doi: http://dx.doi.org/10.1159/000377735

48. Gutsche JT, Kornfield ZN, Speck RM, et al. Impact of guideline implementation on transfusion practices in a surgical intensive care unit. *J Cardiothorac Vasc Anesth* 2013;27(6):1189-93. doi: http://dx.doi.org/10.1053/j.jvca.2013.05.040

49. Haldiman L, Zia H, Singh G. Improving appropriateness of blood utilization through prospective review of requests for blood products: the role of pathology residents as consultants. *Lab Med* 2014;45(3):264-71. doi: http://dx.doi.org/10.1309/LMSKRN7ND12ZOORW

50. Harrison BT, Chen J, Der Vartanian C, et al. Improving red cell transfusion in the elective surgical setting: An improvement collaborative with evaluation. *Vox Sang* 2015;108(4):393-402. doi: http://dx.doi.org/10.1111/vox.12237

51. King R, Michelman M, Curran V, et al. Patient-centered approach to ensuring appropriateness of care through blood management. *South Med J* 2013;106(6):362-8. doi: http://dx.doi.org/10.1097/SMJ.0b013e318296d9fa

52. Leahy MF, Roberts H, Mukhtar SA, et al. A pragmatic approach to embedding patient blood management in a tertiary hospital. *Transfusion* 2014;54(4):1133-45. doi: http://dx.doi.org/10.1111/trf.12362

53. Likosky DS, Surgenor SD, Dacey LJ, et al. Rationalising the treatment of anaemia in cardiac surgery: short and mid-term results from a local quality improvement initiative. *Qual Saf Health Care* 2010;19(5):392-8. doi: http://dx.doi.org/10.1136/qshc.2009.033456

54. Littenberg B, Corwin H, Gettinger A, et al. A practice guideline and decision aid for blood transfusion. *Immunohematology* 1995;11(3):88-94.

55. Lucas RE, Oberli H. An audit to assess the impact of a strategy to reduce inappropriate red cell transfusions at Honiara Hospital. *Trop Doct* 1997;27(2):97-9.

56. Mahar FK, Moiz B, Khurshid M, et al. Implementation of Maximum Surgical Blood Ordering Schedule and an Improvement in Transfusion Practices of Surgeons subsequent to Intervention. *Indian J* 2013;29(3):129-33. doi: http://dx.doi.org/10.1007/s12288-012-0169-4

57. Marconi M, Almini D, Pizzi MN, et al. Quality assurance of clinical transfusion practice by implementation of the privilege of blood prescription and computerized prospective audit of blood requests. *Transfus Med* 1996;6(1):11-9.

58. McCrory MC, Strouse JJ, Takemoto CM, et al. Computerized physician order entry improves compliance with a manual exchange transfusion protocol in the pediatric intensive care unit. *J Pediatr Hematol Oncol* 2014;36(2):143-7. doi: http://dx.doi.org/10.1097/MPH.0b013e31828e55e6

59. Morrison JC, Sumrall DD, Chevalier SP, et al. The effect of provider education on blood utilization practices. *Am J Obstet Gynecol* 1993;169(5):1240-45.

60. Oliver JC, Griffin RL, Hannon T, et al. The success of our patient blood management program depended on an institution-wide change in transfusion practices. *Transfusion* 2014;54(10 Pt 2):2617-24. doi: http://dx.doi.org/10.1111/trf.12536

61. Rana R, Afessa B, Keegan MT, et al. Evidence-based red cell transfusion in the critically ill: quality improvement using computerized physician order entry. *Crit Care Med* 2006;34(7):1892-7.

62. Rehm JP, Otto PS, West WW, et al. Hospital-wide educational program decreases red blood cell transfusions. *J Surg Res* 1998;75(2):183-6.

63. Rosen N, Bates L, Herod G. Transfusion therapy: improved patient care and resource utilization. *Transfusion* 1993;33(4):341-47.

64. Spencer J, Thomas SRYW, Yardy G, et al. Are we overusing blood transfusing after elective joint replacement? - A simple method to reduce the use of a scarce resource. *Ann R Coll Surg Engl* 2005;87(1):28-30. doi: http://dx.doi.org/10.1308/1478708051379

65. Tavares MM, Diquattro PJ, Sweeney JD. Reduction in red blood cell transfusion associated with engagement of the ordering physician. *Transfusion* 2014;54(10 Pt 2):2625-30. doi: http://dx.doi.org/10.1111/trf.12552

66. Ternstrom L, Hyllner M, Backlund E, et al. A structured blood conservation programme reduces transfusions and costs in cardiac surgery. *Interact Cardiovasc Thorac Surg* 2014;19(5):788-94. doi: http://dx.doi.org/10.1093/icvts/ivu266

67. Vos J, Gumodoka B, van Asten HA, et al. Changes in blood transfusion practices after the introduction of consensus guidelines in Mwanza region, Tanzania. *Aids* 1994;8(8):1135-40.

68. Yeh DD, Naraghi L, Larentzakis A, et al. Peer-to-peer physician feedback improves adherence to blood transfusion guidelines in the surgical intensive care unit. *J Trauma Acute Care Surg* 2015;79(1):65-70.

69. Yerrabothala S, Desrosiers KP, Szczepiorkowski ZM, et al. Significant reduction in red blood cell transfusions in a general hospital after successful implementation of a restrictive transfusion policy supported by prospective computerized order auditing. *Transfusion* 2014;54(10pt2):2640-45.

70. Zelinka ES, Brevig J, McDonald J, et al. The perfusionist's role in a collaborative multidisciplinary approach to blood transfusion reduction in cardiac surgery. *J Extra Corporeal Technol* 2010;42(1):45-51.

71. Boral LI, Bernard A, Hjorth T, et al. How do I implement a more restrictive transfusion trigger of hemoglobin level of 7g/dL at my hospital? *Transfusion* 2015;55(5):937-45. doi: http://dx.doi.org/10.1111/trf.12982

72. Hillman RS, Helbig S, Howes S, et al. The effect of an educational program on transfusion practices in a regional blood program. *Transfusion* 1979;19(2):153-7.

73. Joubert J, Joubert S, Raubenheimer J, et al. The long-term effects of training interventions on transfusion practice: A follow-up audit of red cell concentrate utilisation at Kimberley Hospital, South Africa. *Transfus Apher Sci* 2014;51(3):25-32. doi: http://dx.doi.org/10.1016/j.transci.2014.10.013

74. Leão SC, Gomes MAB, Aragão MCdA, et al. Practices for rational use of blood components in a universitary hospital. *Rev Assoc Med Bras* 2015;61(4):355-61.

75. Paone G, Brewer R, Likosky DS, et al. Transfusion rate as a quality metric: Is blood conservation a learnable skill? *Ann Thorac Surg* 2013;96(4):1279-84. doi: http://dx.doi.org/10.1016/j.athoracsur.2013.05.045

76. Valentine SL, Lightdale JR, Tran CM, et al. Assessment of hemoglobin threshold for packed RBC transfusion in a medical-surgical PICU. *Pediatr Crit Care Med* 2014;15(2):e89-94. doi: http://dx.doi.org/10.1097/PCC.0000000000000033

77. Yaffee DW, Smith IDE, Ursomanno PA, et al. Management of blood transfusion in aortic valve surgery: Impact of a blood conservation strategy. *Ann Thorac Surg* 2014;97(1):95-101. doi: http://dx.doi.org/10.1016/j.athoracsur.2013.09.057

78. Hoeg RT, Leinoe EB, Andersen P, et al. Measuring the impact of a restrictive transfusion guideline in patients with acute myeloid leukaemia. *Vox Sang* 2013;105(1):81-4. doi: http://dx.doi.org/10.1111/vox.12017

79. Horowitz PE, Lorenzen CM, Rhydderch RD. Limiting the usage of blood products in cardiovascular surgery. *Ann Saudi Med* 1991;11(2):213-7.

80. McSwiney M, O'Farrell D, Joshi G, et al. Blood transfusion in total hip arthroplasty: guidelines to eliminate overtransfusion. *Can J Anaesth* 1993;40(3):222-26.

81. Muller U, Exadaktylos A, Roeder C, et al. Effect of a flow chart on use of blood transfusions in primary total hip and knee replacement: prospective before and after study.[Erratum appears in BMJ. 2005 Feb;14(1):72], [Erratum appears in BMJ. 2004 Oct 9;329(7470):837]. *Bmj* 2004;328(7445):934-8.

82. Ciccocioppo A, Walker M, Taylor F, et al. Protocol management for patients presenting with lower GI haemorrhage saves costs and maintains outcomes. *ANZ J Surg* 2011;81(6):451-55. doi: http://dx.doi.org/10.1111/j.1445-2197.2010.05603.x

83. Lee Q-J, Mak W-P, Yeung S-T, et al. Blood management protocol for total knee arthroplasty to reduce blood wastage and unnecessary transfusion. *J Orthop Surg* 2015;23(1):66.

84. Vrotsos E, Gonzalez B, Goldszer RC, et al. Improving blood transfusion practice by educational emphasis of the Blood Utilization Committee: experience of one hospital. *Transfus Clin Biol* 2015;22(1):1-4. doi: http://dx.doi.org/10.1016/j.tracli.2014.07.002

85. Whitney G, Daves S, Hughes A, et al. Implementation of a transfusion algorithm to reduce blood product utilization in pediatric cardiac surgery. *Paediatr Anaesth* 2013;23(7):639-46. doi: http://dx.doi.org/10.1111/pan.12126

86. Torella F, Haynes SL, Bennett J, et al. Can hospital transfusion committees change transfusion practice? *J R Soc Med* 2002;95(9):450-52.

87. Adams ES, Longhurst CA, Pageler N, et al. Computerized physician order entry with decision support decreases blood transfusions in children. *Pediatrics* 2011;127(5):e1112-e19.

88. Fernandez Perez ER, Winters JL, Gajic O. The addition of decision support into computerized physician order entry reduces red blood cell transfusion resource utilization in the intensive care unit. *Am J Hematol* 2007;82(7):631-3.

89. McWilliams B, Triulzi DJ, Waters JH, et al. Trends in RBC ordering and use after implementing adaptive alerts in the electronic computerized physician order entry system. *Am J Clin Pathol* 2014;141(4):534-41. doi: http://dx.doi.org/10.1309/AJCPEN6VHT0ECAFI

90. Pentti J, Syrjälä M, Pettilä V. Computerized quality assurance of decisions to transfuse blood components to critically ill patients. *Acta Anaesthesiol Scand* 2003;47(8):973-78.

91. Lewis CM, Monroe MM, Roberts DB, et al. An audit and feedback system for effective quality improvement in head and neck surgery: Can we become better surgeons? *Cancer* 2015;121(10):1581-7. doi: http://dx.doi.org/10.1002/cncr.29238

92. Tuckfield A, Haeusler MN, Grigg AP, et al. Reduction of inappropriate use of blood products by prospective monitoring of transfusion request forms. *Med J Aust* 1997;167(9):473-76.

93. Politsmakher A, Doddapaneni V, Seeratan R, et al. Effective reduction of blood product use in a community teaching hospital: when less is more. *Am J Med* 2013;126(10):894-902. doi: http://dx.doi.org/10.1016/j.amjmed.2013.06.013

94. Eindhoven GB, Diercks RL, Richardson FJ, et al. Adjusted transfusion triggers improve transfusion practice in orthopaedic surgery. *Transfus Med* 2005;15(1):13-8.

95. Lam HT, Schweitzer SO, Petz L, et al. Effectiveness of a prospective physician self-audit transfusion-monitoring system. *Transfusion* 1997;37(6):577-84.

96. Joyce KM, Byrne D, O'Connor P, et al. An evaluation of the use of deliberate practice and simulation to train interns in requesting blood products. *Simul Healthc* 2015;10(2):92-97.

97. Hassan NE, Winters J, Winterhalter K, et al. Effects of blood conservation on the incidence of anemia and transfusions in pediatric parapneumonic effusion: a

hospitalist perspective. *J Hosp Med* 2010;5(7):410-3. doi: http://dx.doi.org/10.1002/jhm.700

98. Lam H, Schweitzer S, Petz L, et al. Are retrospective peer-review transfusion monitoring systems effective in reducing red blood cell utilization? *Arch Pathol Lab Med* 1996;120:810-16.

99. Hébert PC, Wells G, Marshall J, et al. Transfusion requirements in critical care: a pilot study. *Jama* 1995;273(18):1439-44.

100. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0; The Cochrane Collaboration March 2015 [cited 2016 November 25]. Available from: http://www.handbook.cochrane.org accessed November 25 2016.

101. Tinmouth A. Reducing the amount of blood transfused by changing clinicians' transfusion practices. *Transfusion* 2007;47(s2):132S-36S.

102. Ivers N, Jamtvedt G, Flottorp S, et al. Audit and feedback: effects on professional practice and healthcare outcomes. *Cochrane Database Syst Rev* 2012(7)

103. Michie S, Johnston M, Abraham C, et al. Making psychological theory useful for implementing evidence based practice: a consensus approach. *Qual Saf Health Care* 2005;14(1):26-33.

104. Colquhoun HL, Squires JE, Kolehmainen N, et al. Methods for designing interventions to change healthcare professionals' behaviour: a systematic review. *Implement Sci* 2017;12(1):30.

105. Grimshaw JM, Thomas RE, MacLennan G, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health technology assessment (Winchester, England)* 2004;8(6):iii-iv, 1-72. [published Online First: 2004/02/13]

106. Fergusson D, Hebert P, Shapiro S. The before/after study design in transfusion medicine: methodologic considerations. *Transfus Med Rev* 2002;16(4):296-303.

107. Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. *Bmj* 2013;346:f2914.

108. Ford I, Norrie J. Pragmatic trials. *New England Journal of Medicine* 2016;375(5):454-63.

Figure 1. PRISMA Flow Diagram of Included Studies

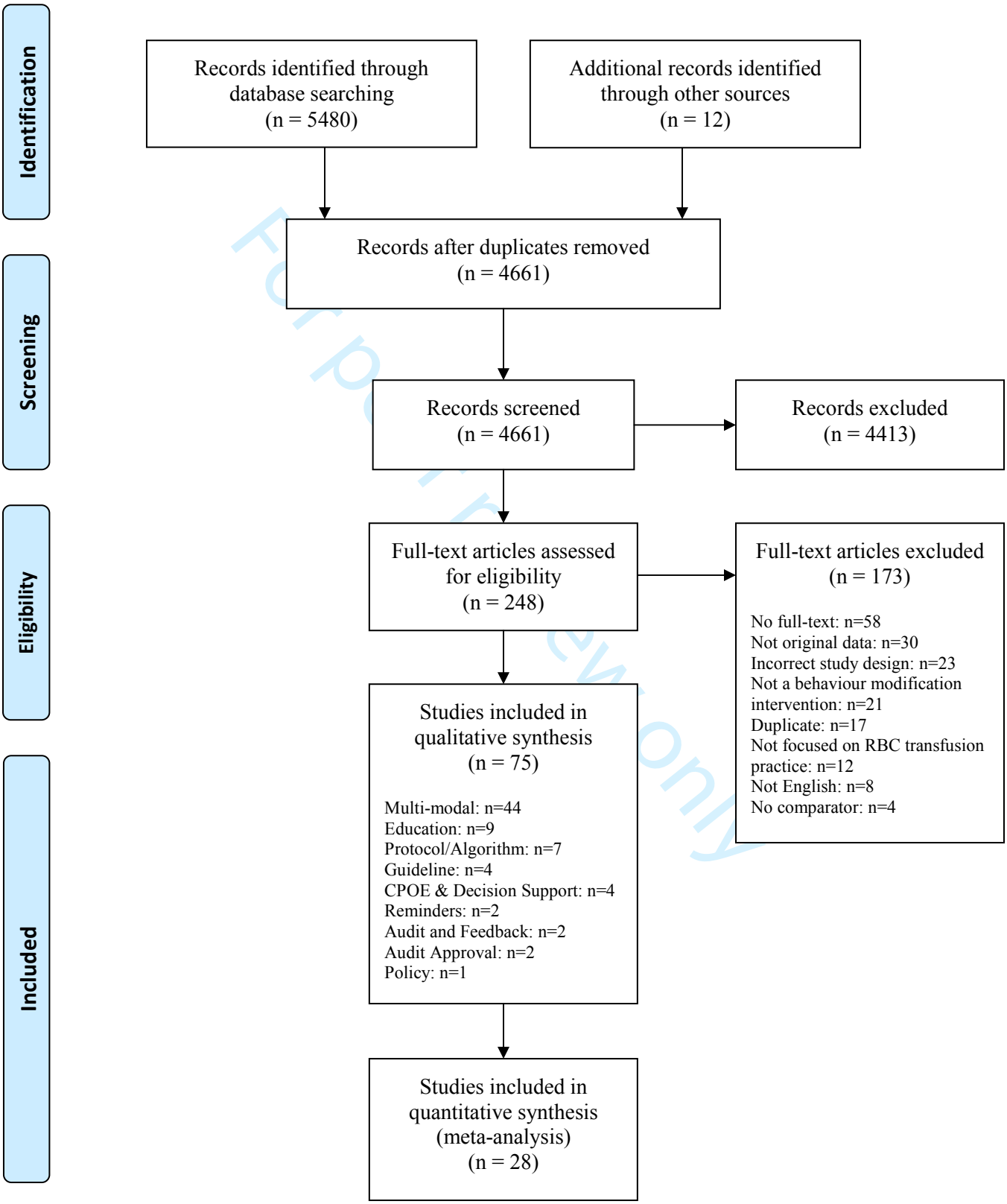

Figure 2. Forest Plot of Odds of Patients Being Transfused

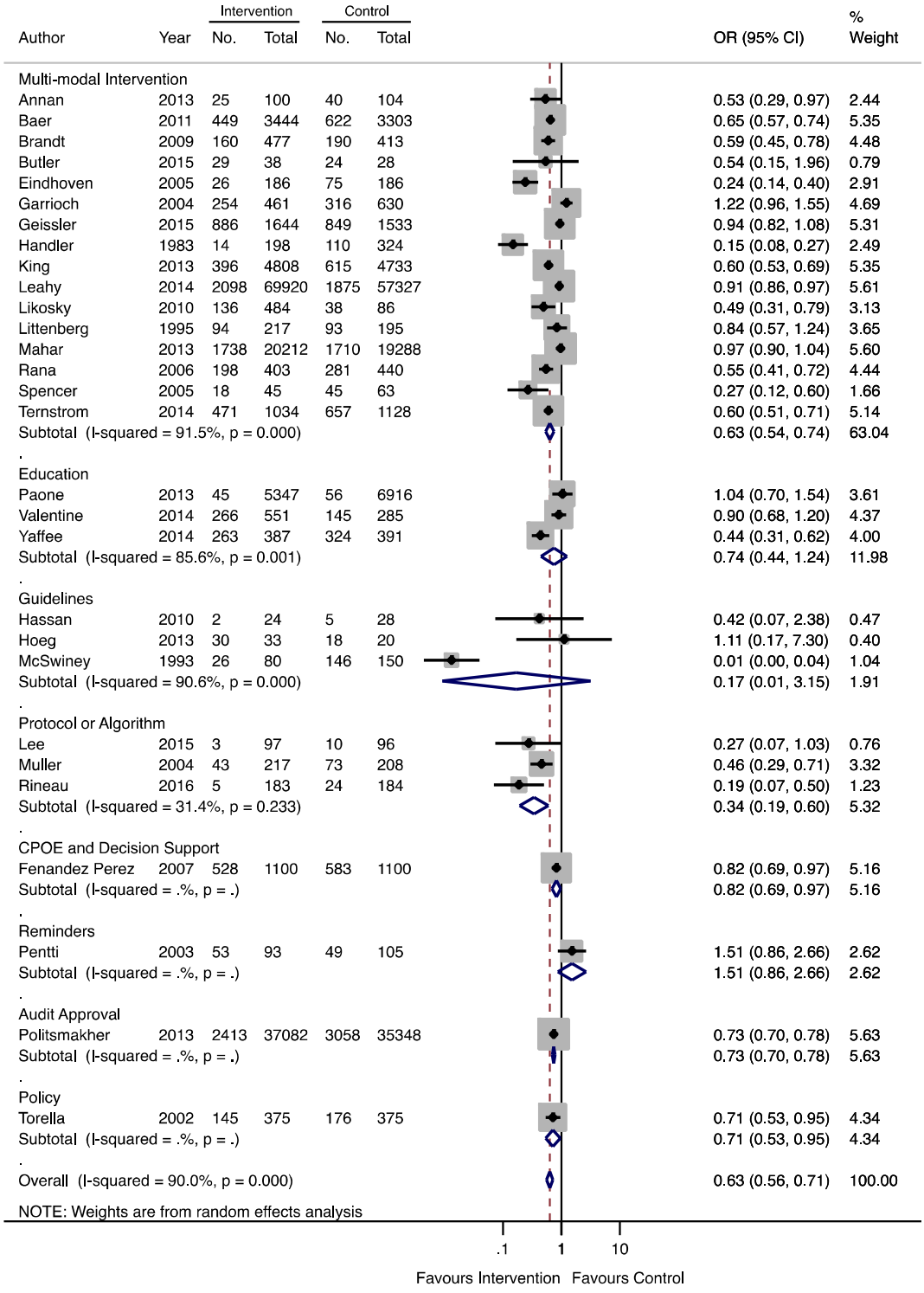

Figure 3. Filled Funnel Plot with Pseudo 95% Confidence Limits

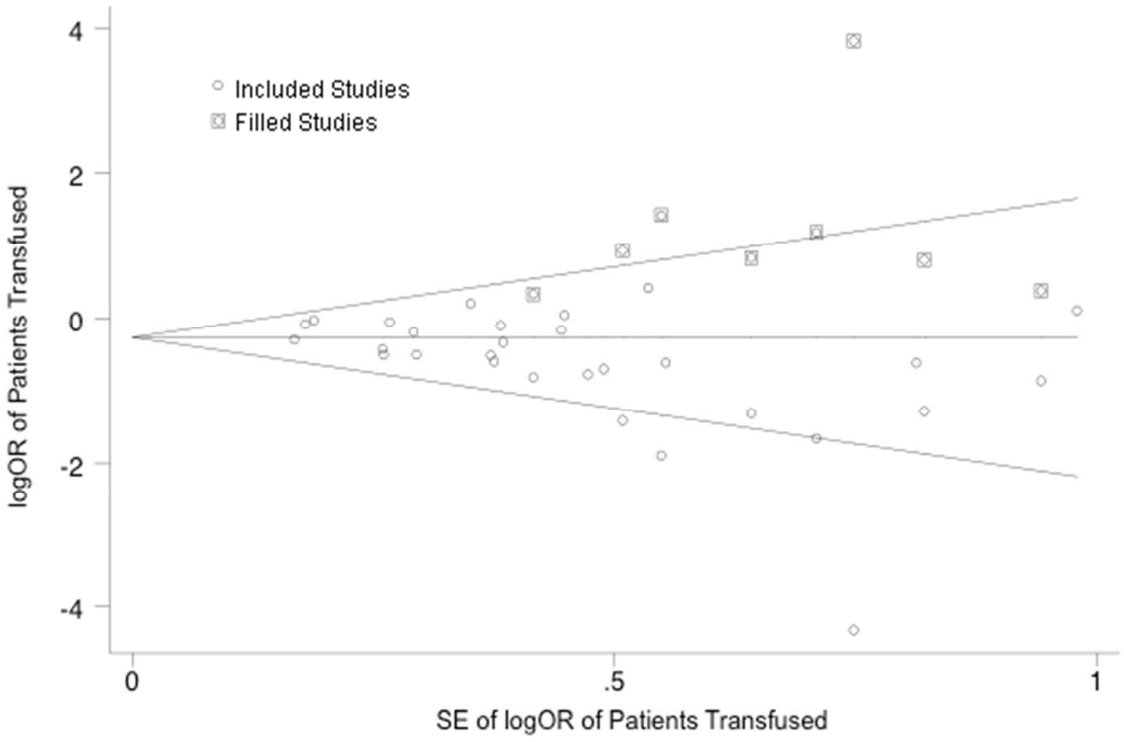

Table 1. Categories of Single and Multi-modal Behavior Modification Interventions

Description of Techniques	Examples from Included Studies
Education Educational materials or group sessions to disseminate: a) Specific medical evidence, such as etiology and pathophysiology of anaemia, indications for transfusion, risks of RBC transfusions, and other evidence from relevant trials (e.g. TRICC trial).; or b) Compiled materials or recommendations from clinical practice guidelines, transfusion protocols or algorithms.	• Formal didactic group sessions • Adaptation of existing departmental or institutional rounds sessions or clinical staff meetings • One-on-one training sessions • Printed education materials distributed to participants or displayed in clinical settings (e.g. graphics and posters)
Protocol or Algorithm Document with a comprehensive outline of steps and detailed criteria to follow for the treatment of specific patient groups or clinical setting; considered more rigid or specific than guidelines.	• Visual map or flow chart depicting clinical scenarios for management of anaemia • Clinical protocols to manage hemorrhaging • Patient blood management protocol with indications for RBC transfusions
Guideline Development and/or adoption of evidence-based clinical practice guidelines (i.e. statements that include recommendations) intended to optimize care of patients.	• *De novo* institutional guidelines for RBC transfusions, appropriate management of anaemia, or RBC/blood conservation • Adoption of guidelines developed by other institutions or expert clinical organizations
Computerized Physician Order Entry (CPOE) and Decision Support Electronic order entry system for healthcare providers to directly enter medication, treatments or other requests for a patient; the system is programmed to prompt with alerts (e.g. of guidelines) or other content to support clinical decision-making.	• Replacement of paper orders to electronic system that consolidates laboratory orders (e.g. RBC orders) information with other patient chart information • Decision support algorithm incorporated into electronic order entry of RBC/blood products sent to blood banks or laboratories
Reminders Direct notification to healthcare providers of either institutional clinical criteria, recommended use of medications or other treatments, or ordering processes.	• Paper forms provided when RBC/blood products are issued reminding healthcare providers of transfusion criteria and encouraging self-audit of practice • Alerts (electronic or by telephone) to healthcare provider

	when RBC transfusion orders placed outside of specified clinical indications (e.g. higher hemoglobin level of patient) or existing guidelines
Audit and Feedback Process to measure performance of healthcare providers or patient outcome data over a specified period of time and to provide a summary (verbal or written) of this information back to those healthcare providers in order to reach a specified goal.	• Transfusion practices were retrospectively audited and the ordering healthcare providers were presented with his or her individual results in the context of the clinical department as a whole and with other department faculty anonymized.
Audit Approval Medication, laboratory, or other treatment orders are audited and for any not meeting pre-specified institutional criteria, an approval is required before the order is approved.	• RBC transfusions orders audited by blood bank or laboratory staff; those placed outside of recommended criteria were not issued and ordering healthcare providers were notified that requests were sent directly to departmental reviewers (e.g. transfusion medicine specialists) for approval.
Policy Compulsory clinical and/or administrative directives for prescribing of medications, laboratory tests, other treatments.	• RBC ordering policy that enforcing standard blood product ordering schedule and adherence to specific hemoglobin triggers.
Paper Order Form Mandatory completion of a paper form order specific medications, laboratory tests, or other treatments.	• Healthcare providers required to complete *de novo* institutional paper order form for RBC transfusions and provide clinical rationale from pre-specified list.
Audit Prospective or retrospective review of clinical performance or patient outcomes; the data is often of electronically collected.	• Retrospective review of RBC transfusions orders outside of recommended clinical criteria (e.g. hemoglobin trigger)
Financial Incentive Provision of financial reward provided to individual or groups of healthcare providers upon attainment of specific clinical performance goal.	• Group-based financial rewards, scaled based on number of healthcare providers, were issued if a 20% reduction in the mean number of RBC transfusions orders per patient-day compared to the previous year was obtained.

Table 2. Results of Meta-Analysis for RBC Usage and Patient Outcomes

Outcome Measures	Multi-modal	Education	Protocol/ Algorithm	Guideline	CPOE & Decision Support	Reminders	Audit and Feedback	Audit Approval	Policy	Pooled Estimate** (95% CI)	I^2 (%); Q-statistic (*p* value)
Odds of patients being transfused (OR, 95% CI)	0.63 (0.54-0.74)	0.74 (0.44-1.24)	0.34 (0.19-0.60)	0.17 (0.01-3.15)	0.82* (0.69-0.97)	1.51* (0.86-2.66)	--	0.73* (0.70-0.78)	0.71* (0.53-0.95)	0.63 (0.56-0.71)	90.0%; p=0.0001
Odds of patients being inappropriately transfused (OR, 95% CI)	0.54 (0.41-0.71)	--	0.25* (0.16-0.39)	0.07* (0.02-0.19)	--	0.13* (0.05-0.30)	1.74* (1.39-2.19)	0.16* (0.07-0.40)	--	0.46 (0.36-0.59)	97.6%; p=0.0001
Difference in RBC units transfused (WMD, 95% CI)	-0.47 (-0.88- -0.07)	--	-0.13* (-0.35- 0.09)	-1.42* (-1.67- -1.17)	-0.20* (-0.35- -0.05)	--	--	--	--	-0.50 (-0.85- -0.16)	99.8%; p=0.0001
Odds of patient in-hospital mortality (OR, 95% CI)	0.88 (0.74-1.04)	0.88 (0.67-1.14)	0.35 (0.06-2.20)	--	1.33* (1.02-1.73)	1.15* (0.51-2.62)	--	0.81* (0.73-0.90)	--	0.90 (0.80-1.02)	57.4%; p=0.001
Difference in hospital LOS (WMD, 95% CI)	-0.75 (-1.84- 0.35)	--	-6.30* (-14.43- 1.83	-3.00* (-5.74- -0.26)	-1.66* (-2.80- -0.52)	--	--	--	--	-1.14 (-2.12- -0.16)	82.2%; p=0.0001
Difference in pre-transfusion Hgb level (WMD, 95% CI)	-0.28 (-0.48- -0.08)	--	--	--	--	--	--	--	--	-0.28 (-0.48- -0.08)	95.5%; p=0.0001

OR: odds ratio; WMD: weighted mean difference; *Point estimate derived from a single study; **Pooled estimate from both single intervention and multi-modal intervention studies.

Supplementary File 1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page # of Manuscript File (unless otherwise indicated)
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	8
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8-9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary File 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8-9

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9-10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-12, Supplementary File 5-6, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12-13, Supplementary Files 7-8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13-15, Table 2, Figure 2, Supplementary

			Files 9-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-15, Table 2, Figure 2, Supplementary Files 9-15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	16, Figure 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	15-16, Supplementary File 16
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18, 20-21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplementary File 2. Study Protocol

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

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Supplementary File 2. Study Protocol

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.

Supplementary File 2. Study Protocol

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)

Supplementary File 2. Study Protocol

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

Supplementary File 2. Study Protocol

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.

Supplementary File 2. Study Protocol

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.

Supplementary File 2. Study Protocol

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

Supplementary File 3. Sample Search Strategy

MEDLINE May 2016
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

Supplementary File 4. Inclusion and Exclusion Criteria for Review of Full-text Articles

Inclusion Criteria	Exclusion Criteria
Full-text articles	Articles not available in full-text (i.e. title or abstracts only)
Original data	Non-original data
Peer-reviewed articles	Grey literature
Physicians and other healthcare providers prescribing/ordering transfusions (any healthcare setting)	Animal studies
RCT or quasi-experimental studies	Case studies, commentaries, editorials, letters, opinions
Primary objective: efficacy/effectiveness of intervention to modify RBC transfusion practices	Not focused on primary objective
Interventions: behaviour modification intervention targeted at healthcare provider RBC transfusion practice (e.g. education, guidelines, audit and feedback, order entry systems, etc.)	Not a behaviour modification intervention
Comparator: any intervention including no intervention (i.e. standard of care, historical controls)	No comparator
Any outcomes (e.g. physician compliance or patient outcomes)	

Supplementary File 5. Characteristics of Included Studies

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
Multi-modal Interventions									
Alavi-Moghaddam[34] (2014) Iran	ED in one academic and general medical/surgical hospital	All ED staff and blood bank technicians	Blood	Before and After	Historical Control	3 months	NR	NR	Protocol, Education
Andreasen[35] (2012) Denmark	Cardiac surgeries in one academically-affiliated hospital	Anesthesiol-gists, surgeons, intensivists, and nurses	RBC, FFP, platelets	Before and After	Historical Control	24 months	NR	Defined over-transfusion as proportion of patients transfused with RBCs discharged with hemoglobin 7 mmol/L (11.3 g/dL)	Education, Guideline, Algorithm
Annan[36] (2013) United States	ICU in one academically-affiliated community hospital	All ICU staff	RBC	Before and After	Historical Control	1 month	NR	NR	"High-intensity ICU staffing (HIS)", including: changes in Protocols, CPOE and Decision Support
Ansari[37] (2012) United States	One community hospital	All physicians ordering transfusions	RBC	Before and After	Historical Control	12 months	1) Acute bleeding (blood loss of >30%) with tachycardia and low blood pressure; 2) Hgb <9 g/dL in	Transfusions that did not meet established criteria, including pre-transfusion hgb level greater	Guideline, Audit & Feedback

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
							high-risk patients; 3) Hgb <7 g/dL in patients with symptomatic chronic anaemia; 4) Special circumstances (e.g. sickle cell crisis and other causes of poor oxygen delivery)	than 9 g/dL	
Baer[38] (2011) United States	Four neonatal ICUs in one healthcare system	All neonatal ICU staff	RBC	Before and After	Historical Control	12 months	Hematocrit falls below: • 40% for a patient on extracorporeal membrane oxygenation, • 35% for a patient on mechanical ventilation 27% for a patient on supplemental oxygen or with signs of anemia but not on mechanical ventilation, • 20% in any neonatal ICU patient	NR	Guideline, CPOE and Decision Support, and Audit

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
Beaty[39] (2013) United States	Cardiac surgical ICU in one academic hospital	Cardiac surgery attendings, cardiac residents, and ICU providers (intensivists, surgery residents, and mid-level providers)	RBC	Before and After	Historical Control	17 weeks	Hgb level of less than 8 g/dL	Transfusion trigger of hgb >8 g/dL	Protocol, Audit and Feedback
Brandis[40] (1994) Australia	One acute care hospital	All medical staff that order transfusions in anesthetics, surgery and ICU	RBC	Before and After	Historical Control	6 months	Hgb level 7 g/dL	NR	Education, Protocol, Policies
Brandt[41] (2009) United States	Surgical ICU in one hospital	Intensivists, fellows, and residents	RBC	Before and After	Historical Control	6 years	Hgb level 8 g/dL	NR	Protocol, Education (to residents)
Butler[42] (2015) United Kingdom	Inpatient hematology services in one academic hospital	Clinical hematolog-ists treating patients receiving intensive chemotherap	RBC, platelets	Before and After	Historical Control	10 months	1) Massive bleeding with blood pressure instability; 2) Hgb 7 g/dL in a stable ICU patient;	Above the recommended trigger of 8 g/dL	Education, CPOE and Decision Support, Audit and Feedback

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
		y or hematopoie-tic stem cell transplants					3) Hgb 8.0 g/dL in a non-ICU patient with signs/symptoms of anemia; 4) Hgb 10 g/dL with acute cardiac ischemia; 5) Surgical blood loss anticipated		
Corwin[43] (2014) United States	One level 1 trauma centre	Clinical staff in all major clinical departments, high-volume transfusing services, and residents	RBC	Before and After	Historical Control	18 months	1) Acute hemorrhage or hemorrhagic shock; 2) Hgb <7–8 g/dL; 3) Acute MI, Hgb 8 g/dL; 4) Acute coronary syndrome Hgb 8 g/dL; Use of the hgb concentration alone as a trigger for RBC transfusion was recommended against; decision to order an RBC transfusion should also consider a patient's intravascular	NR	Education, Guideline, CPOE and Decision Support

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
							volume status, evidence of shock, duration and extent of anemia, and cardiopulmonary physiologic parameters as well as other symptomatology.		
Eindhoven[94] (2005) Netherlands	Two hospitals	All physicians and nurses treating patients undergoing elective, primary total hip replacement	RBC	Controlled Before and After	Standard of care in one hospital (i.e. patients transfused at a Hgb level below 10g/dL or haematocr-it level below 30%)	12 months	1) Presence of anaemia-related symptoms and signs; 2) Diminished oxygen uptake in the lungs due to respiratory disease; 3) Inability of the patient to compensate for the effects of haemodilution; 4) Estimated blood loss and increased risk of re-bleeding; 5) Enhanced need for oxygen delivery (high body temperature, shivering and sepsis); and	NR	Education, Guideline (referred to as "6-8-10 Flexinorm")

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
							(6) Presence of symptoms or signs of atherosclerosis of heart, brain or renal vessels.		
Gallagher-Swann[44] (2011) Australia	Two hospitals: one tertiary maternity and gynaecologi-cal hospital; and one tertiary paediatric hospital	All medical staff in adult, neonatal, and antenatal, and pediatric settings	Blood	Before and After	Historical Control	28 months	NR	NR	Protocol, Education, Reminders
Gardner[45] (1993) United States	One tertiary hospital	All physicians and nurses ordering blood	Blood	Before and After	Historical Control	3 months	If ordering for anemia for packed cells: hgb < 10 g/dL or hematocrit below 30%	Defined over-transfusions as those that did not meet the transfusion criteria	CPOE and Decision Support, Audit and Feedback
Garrioch[46] (2004) United Kingdom (Scotland)	One academic hospital	All physicians	RBC	Before and After	Historical Control	3 months	NR	NR	Education, Guideline, Audit and Feedback, Reminders
Geissler[47] (2015) Germany	One trauma centre	All medical staff involved in cardiac surgeries (e.g. heart	RBC, FFP, platelets	Before and After	Historical Control	12 months	NR	NR	"Patient Blood Management (PBM) Initiative", including Education, Guidelines Audit

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
		transplantation, aortic surgery, valve surgery)							and Feedback, and Policies
Goodnough[25,26] (2014a; 2014b) United States	One academic hospital	All physicians ordering transfusions	RBC	Before and After	Historical Control	36 months	Hgb level of 7 g/dL stable medical and surgical inpatients who were not bleeding, or 8 g/dL for patients with acute coronary syndromes	NR	Education, CPOE and Decision Support
Gutsche[48] (2013) United States	Surgical ICU in one academic hospital	Cardiologists, cardiac surgeons, anesthesiologists, and intensivists involved in the care of cardiac surgery patients	RBC	Before and After	Historical Control	6 months	Transfusion associated with a pre-transfusion hgb <7.0 mg/dL	Transfusion associated with a hgb from 7 mg/dL to 7.9 mg/dL without evidence of organ ischemia, shock, pressor requirement, or hemorrhage	Education, Guideline, Audit and Feedback
Haldiman[49] (2014) United States	One tertiary-care, Level I trauma hospital	All physicians ordering transfusions	RBC, FFP, platelets, cryoprecipitate	Before and After	Historical Control	36 months	Hgb level of 8 gm/dL or less and a hematocrit level of 24% or less as a trigger point	Transfusions not compliant with guideline	Guideline, Audit
Handler[28] (1983) United States	One community	Surgeons	RBC	Between groups	Standard of care in four hospitals	12 months	NR	NR	Education, Audit and Feedback

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
	hospital								
Harrison[50] (2015) Australia	Regional healthcare system comprised of 232 public hospitals	Surgeons in five surgical groups: cardio-thoracic, colorectal, gynaecology and obstetrics, Orthopaedic, and general surgery	RBC	Before and After	Historical Control	12 months	NR	When the Hgb min ≥ 100 g/dl post-operation; when Hgb min ≥ 70 g/l and ≤100 g/l and when no clinical indications are present; and when Hgb max levels ≤70 g/l when clinically indicated	"Blood Watch Program" that involved 21 different system and behaviour modifying interventions, including Education, Audit and Feedback
King[51] (2013) United States	One community hospital	All physicians	RBC	Before and after	Historical Control	8 months	Hgb level 7 g/dL	NR	Education, Guideline, Audit and Feedback
Leahy[52] (2014) Australia	One academic hospital	All physicians	RBC	Before and After	Historical Control	36 months	NR	NR	"Patient Blood Management Programme", including Protocol, Education, Guideline, Audit and Feedback, CPOE and decision support
Likosky[53] (2010) United States	Departments of medicine, surgery, anesthesia, and	Surgeons treating non-emergent isolated coronary	RBC	Before and After	Historical Control	27 months	1) Intra-operative patients: when haematocrit falls below 19% on cardiopulmonary	NR	Protocol, Education, Audit and Feedback

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
	pathology, and disciplines from nursing, cardiothorac -ic surgery, anaesthesia, perfusion, quality improve- ment, transfusion medicine and epidemiolog y in one hospital	artery bypass graft surgery					bypass 2) Post-operative patients <75 years: when haematocrit falls below 21% after the procedure until the patient was discharged from the hospital 3) Patients >75 years: when haematocrit falls below 24% after the procedure until the patient was discharged from the hospital		
Littenberg[54] (1995) United States	ICU in one hospital	Intensivists	RBC	Before and After	Historical Control	3 months	During intervention period: Hgb < 8.6 g/dL or hematocrit < 26% During follow-up period: Hgb <= 7 g/dL or hematocrit <=21%	NR	Guideline, Order Form and Decision Support, Audit
Lucas[55] (1997) Australia	One hospital	All physicians	Blood	Before and After	Historical Control	3 months	Hgb level 80 g/L	NR	Education, Guideline
Mahar[56] (2013)	One tertiary care,	All physicians	RBC	Before and	Historical Control	12 months	NR	NR	Protocol,

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
Pakistan	academic hospital			After					Education
Marconi[57] (1996) Italy	One academic hospital	All physicians	RBC	Before and After	Historical Control	6 months	NR	Post-operative haematocrit above 36%	Protocol, Education, Guideline, CPOE and Decision Support
Markel[31] (2016) United States	Orthopedic services in two "peer" hospitals	Orthopaedic service line practitioners treating patients with primary total joint arthroplasty	RBC	Before and After	Historical Control	6 months	In post-operative patients: pre-transfusion hgb of 8 g/dL or less or for symptoms of chest pain, orthostatic hypotension, tachycardia unresponsive to fluid resuscitation, congestive heart failure	NR	Education, Guideline, Audit and Feedback
McCrory[58] (2014) United States	Pediatric ICU in one children's hospital	Pediatric ICU and pediatric hematology attending physicians	RBC	Before and After	Historical Control	24 months	NR	NR	Protocol, CPOE and Decision Support
Morrison[59] (1993) United States	Department of Obstetrics and Gynecology in one	All staff physicians and residents	RBC, FFP, platelets	Before and After	Historical Control	10 months	NR	NR	Education, Guideline, Audit and Feedback, Paper Order Form

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
	academic hospital								
Murphy[29] (2016) United States	Seven ICUs in an academic healthcare system	Intensivists, advanced practice providers (APPs) (i.e. nurse practitioners and physician assistants), and physicians in training	RBC	Before and After	Historical Control	12 months	NR	NR	Education, Audit and Feedback, and Unit-based Provider Financial Incentives
Oliver[60] (2014) United States	One academic hospital	All physicians	RBC, FFP, platelets	Before and After	Historical Control	6 months	Hgb 7 g/dL or less in nonbleeding patients (as per TRICC trial) • Transfuse 1 unit and reassess unless ongoing blood loss (1500 - 2000ml) or hemodynamic instability • Exceptions: active coronary ischemia, ongoing blood loss, severe	NR	Education, Guideline, Audit and Feedback

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
							sepsis/septic shock		
Rana[61] (2006) United States	Multidisciplinary ICU (medical, surgical, and mixed) in one tertiary academic hospital	All ICU physicians and nurses	RBC	Before and After	Historical Control	3 months	Hgb level 7g/dL	Pre-transfusion hgb >7 g/dL in the absence of active bleeding, early septic shock, or ischemia	Education, CPOE and Decision Support, Algorithm
Rehm[62] (1998) United States	One Veteran Affairs hospital	All staff and residents in medical and surgical specialties from two local university programmes	RBC	Before and After	Historical Control	12 months	Hgb level <7 g/dL	Hgb level >10 g/dL	Paper order form and Decision Support, Audit and Feedback, Audit Approval, Reminders
Rosen[63] (1993) United States	One private tertiary care hospital	All staff	RBC, FFP, platelets, cryoprecipitate	Before and After	Historical Control	36 months	Hgb level <8g/dL	Transfusions not meeting transfusion criteria	Education, Guideline, CPOE and Decision Support, Audit and Feedback
Rothschild[27] (2007) United States	One academic hospital	All staff	RBC, FFP, platelets	Before and After	Historical Control	3 months	Hematocrit <21%	Transfusions not meeting transfusion criteria	Education, Guideline
Spencer[64] (2005) United States	One hospital	All anesthetic and surgical	RBC	Before and After	Historical Control	12 months	Signs of cardiovascular instability from	Transfusions not meeting transfusion	Guideline, Paper Order Form and Decision Support,

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
		staff treating patients undergoing hip and knee arthroplasty					excessive intra-operative blood loss, was symptomatically anaemic postoperatively, or the hgb level fell below 8 g/dL	criteria	Audit and Feedback, Reminders
Tavares[65] (2014) United States	One academic tertiary care hospital	All staff	RBC	Before and After	Historical Control	9 years	Hgb level between 8-9 g/dL	Hgb level >9g/dL recommended for cancellation	Education, Audit Approval
Ternstrom[66] (2014) Sweden	Cardiac surgery services in one academic hospital	All staff particularly surgeons, anaesthetis-ts, residents, OR-, ICU- and ward nurses, nurse helpers, physiothera-pists and perfusionists	RBC, plasma, platelets	Before and after	Historical Control	24 months	Hgb level <6 g/dL	NR	"Blood Conservation Programme" consisting of Education, Guidelines, and Self-Audit
Vos[67] (1994) Tanzania	Eight hospitals: four government hospitals and three missions hospitals	All physicians	All blood components	Before and After	Historical Control	24 months	1) Operated patients: hgb >10 g/dL; 2) Pregnancy: hgb >7 g/dL when >36 weeks, hgb >6 g/dL when <36 weeks; 3) children: hgb	NR	Education, Guideline

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
							>4 g/dL; other: hgb >5 g/dL		
Yeh[68] (2015) United States	Surgical ICU in one tertiary care hospital	Residents, fellows, attending physicians of both ICU and surgical teams	RBC	Before and After	Historical Control	6 months	Hgb level <8 g/dL	Hgb level >8 g/dL	Education, Audit and Feedback
Yerrabothala[69] (2014) United States	One academic tertiary care hospital	All staff	RBC	Before and After	Historical Control	6 months	Hgb level < 7g/dL	Transfusions not meeting transfusion criteria	CPOE and Decision Support, Policy
Zelinka[70] (2010) United States	Cardiac surgery services in one community hospital	All medical staff involved in cardiac surgeries	RBC	Before and After	Historical Control	4 years	NR	NR	
Single Interventions									
Boral[71] (2015) United States	One tertiary care hospital	All medical, surgical, nursing and blood bank staff	RBC	Before and After	Historical Control	36 months	Hgb level of 7 g/dL or Hct of 21%	NR	Education
Hillman[72] (1979) United States	Twenty-two area hospitals	All physicians	RBC, whole blood	Before and After	Historical Control	6 months	NR	NR	Education
Joubert[73] (2014) South Africa	Departments of internal medicine, intensive	All physicians	RBC	Before and After	Historical Control	2 weeks	Usually appropriate when Hgb ≤ 6.9 g/dL; When Hb 7.0–9.9	Not required when Hgb level >= 10g/dL	Education

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
	care, obstetrics & gynaecology and general surgery in one hospital						g/dL depends on clinical picture		
Joyce[96] (2015) Ireland	One academic hospital	Interns	All blood components	Between Groups	Standard of Care	3 months	NR	NR	Education
Leão[74] (2015) Brazil	One academic hospital	All physicians, nurses, and nursing technicians	RBC	Before and After	Historical Control	6 months	NR	NR	Education
Paone[75] (2013) United States	Thirty-three hospitals in one state	Cardiac surgeons	RBC, FFP, platelets	Before and After	Historical Control	4 years	NR	NR	Education
Soumerai[33] (1993) United States	Surgical and medical services from two academic and two community hospitals	Surgeons in orthopedic, vascular, and general surgery and general medicine attending physicians	RBC	RCT	Standard of Care	6 months	1) Hematocrit <24%, a fall in hematocrit of 6 percentage points or more within 24 hours, or 2) A pre-transfusion hematocrit between 24% and 30% in the presence of one of the following: angina within 24 hours prior to	Transfusions not meeting transfusion criteria	Education

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
							transfusion, myocardial infarction within 6 weeks prior to transfusion, an electrocardiogram indicating acute ischemia or acute infarction, or 3) Blood loss of 1000 mL or greater prior to transfusion		
Valentine[76] (2014) United States	Medical-surgical pediatric ICU in one children's hospital	Pediatric intensivists	RBC, whole blood	Before and After	Historical Control	24 months	Hgb level <7 g/dL	NR	Education
Yaffee[77] (2014) United States	Cardiac surgery services in one hospital	Surgeons, surgical residents, anesthesiol-ogists, perfusionis-ts, and recovery room and intensive care unit nurses, operating on aortic valve	RBC	Before and After	Historical Control	24 months	Hgb level <8 g/dL	NR	Education

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
		replacement patients							
Hassan[97] (2010) United States	One children's hospital	General pediatricians and hospitalists	Blood	Between Groups	Standard of Care	36 months	NR	NR	Guideline
Hoeg[78] (2013) Denmark	Hematology department in one university hospital	All medical staff treating patients with acute myeloid leukemia	RBC	Before and After	Historical Control	36 months	Hgb level between 7.3 and 9.7 g/dL and only in the presence of symptomatic anaemia, coronary artery disease, ongoing blood loss or sepsis	NR	Guideline
Horowitz[79] (1991) Saudi Arabia	One hospital	All physicians treating cardiac surgery patients	RBC, FFP, platelets, cryoprecipitate	Before and After	Historical Control	6 months	NR	Transfusions not justified by the results of hgb levels (not specified) and coagulation tests	Guideline
McSwiney[80] (1993) Ireland	Anesthesia department in one hospital	All physicians treating patients undergoing total hip arthroplasty	Blood	Before and After	Historical Control	NR	Hematocrit less than 30 in men and 27 in women	Discharge hematocrit exceeding 36%	Guideline
Ciccocioppo[82] (2011) Australia	One hospital	All medical staff treating patients with lower GI bleed	RBC	Before and After	Historical Control	30 months	NR	NR	Protocol

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
Despotis[32] (1994) United States	One hospital	Anesthesiol-ogy and surgery staff physicians treating cardiac surgery patients	RBC, FFP, platelets	RCT	Standard of Care	NR	NR	NR	Algorithm
Lee[83] (2015) China	One hospital	Physicians treating patients for total knee replacement	Blood	Before and After	Historical Control	4 months	NR	NR	Protocol
Muller[81] (2004) Switzerland	Orthopedic unit and intensive care unit in tertiary care hospital	Nurses and physicians in orthopaedic, anaesthesio-logy, and intensive care treating patients underoing total joint replacement	RBC	Before and After	Historical Control	NR	Multi-criteria based on implemented guideline	NR	Algorithm
Rineau[30] (2016) France	Orthopaedic surgery service in one academic hospital	All physicians treating patients undergoing total hip arthroplasty or total knee arthroplasty	Blood	Before and After	Historical Control	6 months	Hgb level <7 or 8 g/dL depending on cormobidities	NR	Protocol

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
Vrotsos[84] (2015) United States	Cardiac unit in one hospital	All physicians	Blood	Before and After	Historical Control	6 months	NR	NR	Protocol
Whitney[85] (2013) United States	Pediatric operating rooms and ICU in one tertiary care children's hospital	All physicians treating pediatric cardiac surgery patients	RBC, plasma, platelets, cryoprecipitate	Before and After	Historical Control	12 months	NR	NR	Protocol
Torella[86] (2002) United Kingdom	One academic hospital	All physicians treating patients undergoing coronary artery bypass graft surgery, total hip replacement, colectomy, and transurethral prostatect-omy.	RBC	Before and After	Historical Control	6 months	Hgb level <8g/dL in the absence of symptoms	NR	Policy
Adams[87] (2011) United States	Acute care and Pediatric ICU wards in one children's hospital	Pediatricians and pediatric intensivists	RBC	Before and After	Historical Control	12 months	NR	NR	CPOE and Decision Support

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
Fernandez Perez[88] (2007) United States	Three multi-disciplinary ICUs in one hospital	Intensivists	RBC	Before and After	Historical Control	12 months	Hgb level >7 g/dL in the presence of active bleeding, ischemia or early septic shock	NR	CPOE and Decision Support
McWilliams[89] (2014) United States	Eleven hospitals in a regional healthcare system, including level 1 trauma centers, a cancer treatment hospital, and one centre specializing in women's health	All physicians	RBC	Before and After	Historical Control	10 months	1) Hgb level of 8.0 g/dL or lower in a non–ICU patient with signs and symptoms of anemia 2) Hgb level of 7.5 g/dL or lower in a stable ICU patient 3) Hgb level of 10 g/dL or lower with acute cardiac ischemia 4) Surgical blood loss anticipated 5) Acute bleeding with blood pressure (BP) instability	NR	CPOE and Decision Support
Rothschild[27] (2007) United States	One academic hospital	All staff	RBC, FFP, platelets	RCT	Standard of Care	4 months	Hematocrit <21%	Transfusions not meeting transfusion criteria	CPOE and Decision Support
Lam[95] (1997) United States	Two "peer" non-academic hospitals	All physicians	RBC, FFP, platelets	Controlled Before and After	Standard of Care	4 months	NR	NR	Reminders (through self-audit)

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
Pentti [90] (2003) Finland	Medical-surgical ICU in one academic hospital	All physicians	RBC, FFP, platelets	Before and After	Historical Control	3 months	Hgb level <80 g/L	Transfusions above the recommended transfusion criteria	Reminders (through electronic audit)
Lam[98] (1996) United States	Five hospitals including three academic and two non-academic	All physicians	RBC	Between Groups	Standard of Care	34 months	Hgb level >= 90g/L	NR	Audit and Feedback
Lewis[91] (2015) United States	Cancer centre in one academic hospital	All physicians treating patients with head and neck cancer	RBC	Before and After	Historical Control	24 months	NR	NR	Audit and Feedback
Tuckfield[92] (1997) Australia	One hospital	All medical staff	RBC, FFP, platelets	Before and After	Historical Control	3 months	1) Hgb <7 g/dL for severe anemia; 2) Hgb between 7-10 g/dL for anemia, bone marrow failure, anemia and sepsis, continuing blood loss, and abnormal bleeding during an operation; 3) Hgb <8 g/dL for perioperative period	Transfusions not meeting transfusion criteria	Audit Approval

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
Politsmakher[93] (2013) United States	Departments of medicine, surgery, obstetrics/ gynecology, pediatrics, and emergency medicine in one community-based academic hospital	All physicians	RBC, FFP, platelets, cryo-precipitate	Before and After	Historical Control	24 months	1) Symptomatic anemia Hgb <7 g/dL; 2) Active bleeding, blood loss 15% of blood volume; 3) Chronic transfusion in sickle cell/ thalassemia patients; 4) Before major elective procedure Hgb <8 g/dL 5) Red cell exchange in sickle cell patients to attain Hgb ¼ 10g/dL and Hgb S <30%	Transfusions not meeting transfusion criteria	Audit Approval

ED: emergency department; CPOE: computerized physician order entry; FFP: fresh frozen plasma; GI: gastrointestinal; Hgb: hemoglobin; ICU: intensive care unit; NR: not reported; RBC: red blood cell; RCT: randomized controlled trial;

*Sample size based on blood orders, not patients

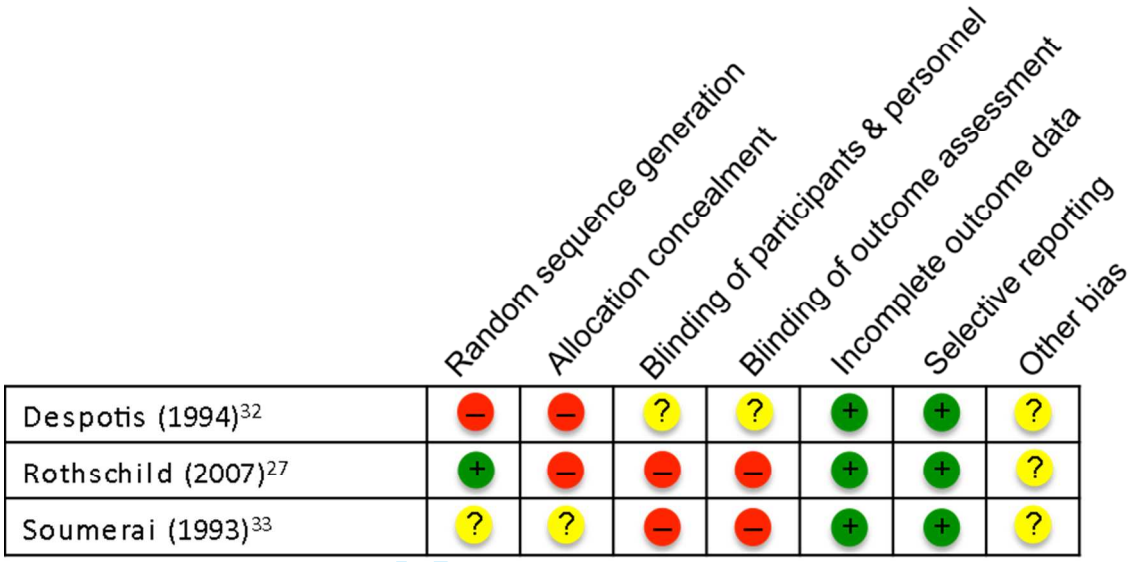
Supplementary File 6. Composition of Multi-modal Interventions

Study	Interventions										
	Education	Guideline	Audit and Feedback	CPOE & Decision Support	Protocol/ Algorithm	Paper Order Form	Reminder	Policy	Audit Approval	Audit	Financial Incentive
Alavi-Moghaddam (2014) [34]	✓				✓						
Andreasen (2012) [35]	✓	✓			✓						
Annan (2013) [36]				✓	✓						
Ansari (2012) [37]		✓	✓								
Baer (2011) [38]		✓		✓						✓	
Beaty (2013) [39]			✓		✓						
Brandis (1994) [40]	✓				✓			✓			
Brandt (2009) [41]	✓				✓						
Butler (2015) [42]	✓		✓	✓							
Corwin (2014) [43]	✓	✓		✓							
Eindhoven (2005) [94]	✓	✓									
Gallagher-Swann (2011) [44]	✓				✓		✓				
Gardner (1993) [45]			✓	✓							
Garrioch (2004) [46]	✓	✓	✓				✓				
Geissler (2015) [47]	✓	✓	✓					✓			
Goodnough (2014a; 2014b) [25,26]	✓			✓							
Gutsche (2013) [48]	✓	✓	✓								
Haldiman (2014) [49]		✓								✓	
Handler (1983) [28]	✓		✓								

Study	Interventions										
	Education	Guideline	Audit and Feedback	CPOE & Decision Support	Protocol/ Algorithm	Paper Order Form	Reminder	Policy	Audit Approval	Audit	Financial Incentive
Harrison (2015) [50]	✓		✓								
King (2013) [51]	✓	✓	✓								
Leahy (2014) [52]	✓	✓	✓	✓	✓						
Likosky (2010) [108]	✓		✓		✓						
Littenberg (1995) [54]		✓				✓					
Lucas (1997) [55]	✓	✓								✓	
Mahar (2013)[56]	✓				✓						
Marconi (1996) [57]	✓	✓		✓	✓						
Markel (2016) [31]	✓	✓	✓								
McCrory (2014) [58]				✓	✓						
Morrison (1993) [59]	✓	✓	✓			✓					
Murphy (2016) [29]	✓		✓							✓	✓
Oliver (2014) [60]	✓	✓	✓								
Rana (2006) [61]	✓			✓	✓						
Rehm (1998) [62]			✓			✓	✓		✓		
Rosen (1993) [63]	✓	✓	✓	✓							
Rothschild (2007) [27]	✓	✓									
Spencer (2005) [64]		✓	✓			✓	✓				
Tavares (2014) [65]	✓								✓		
Ternstrom (2014) [66]	✓	✓								✓	
Vos (1994) [67]	✓	✓									

Study	Interventions										
	Education	Guideline	Audit and Feedback	CPOE & Decision Support	Protocol/ Algorithm	Paper Order Form	Reminder	Policy	Audit Approval	Audit	Financial Incentive
Yeh (2015) [68]	✓		✓								
Yerrabothala (2014) [69]				✓				✓			
Zelinka (2010) [70]					✓					✓	
TOTAL	**31**	**22**	**20**	**12**	**14**	**4**	**4**	**3**	**2**	**6**	**1**

Supplementary File 7. Risk of Bias in RCTs Assessed with Cochrane Risk of Bias Tool



Supplementary File 8. Quality Assessment of Quasi-Experimental Studies Using Adapted Downs and Black Checklist

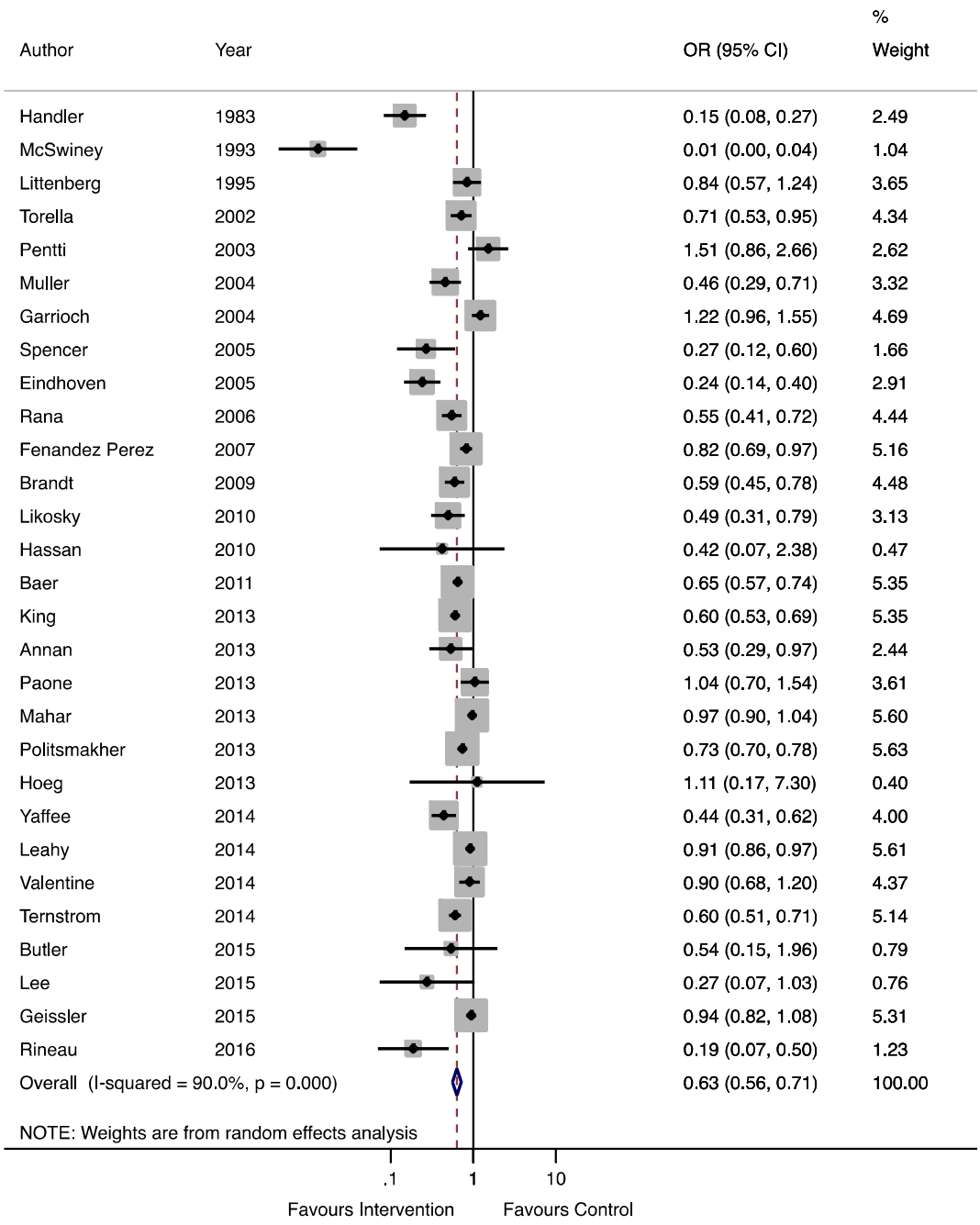
Study	REPORTING										EXTERNAL VALIDITY			INTERNAL VALIDITY – BIAS AND CONFOUNDING								Total /22
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q16	Q17	Q18	Q19	Q20	Q21	Q22	Q25	Q26	
Adams [87]	1	0	1	1	0	1	1	0	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Alavi-Moghaddam [34]	1	1	0	0	0	1	1	0	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	13
Andreasen [35]	1	0	0	1	0	1	0	0	0	0	1	UTD	1	1	0	0	1	1	1	n/a	UTD	UTD	9
Annan [36]	1	1	1	1	0	1	0	0	0	0	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	12
Ansari [37]	1	0	0	1	0	1	0	1	0	0	1	UTD	1	UTD	0	1	1	0	1	n/a	UTD	UTD	9
Baer [38]	0	0	1	1	0	1	1	1	0	1	1	UTD	1	1	1	0	1	1	1	n/a	UTD	UTD	13
Beaty [39]	1	1	1	1	0	1	0	1	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	14
Boral [71]	1	0	0	1	0	1	1	1	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	13
Brandis [40]	0	0	0	1	0	1	0	1	0	0	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	10
Brandt [41]	1	0	0	1	0	1	0	1	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	12
Butler [42]	0	1	0	0	1	1	0	1	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	12
Ciccocioppo [82]	0	1	0	1	0	1	1	1	0	0	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	12
Corwin [43]	0	1	0	1	0	1	1	1	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	13
Eindhoven [94]	1	0	0	1	0	1	1	1	0	1	1	UTD	1	0	1	1	UTD	1	0	UTD	UTD	UTD	11/23
Fernandez Perez [88]	1	1	0	0	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Gallagher-Swann [44]	1	0	1	1	0	1	0	0	0	n/a	UTD	UTD	1	UTD	1	n/a	1	1	1	n/a	UTD	UTD	9
Gardner [45]	1	1	0	1	0	1	0	1	0	0	1	UTD	1	UTD	0	1	1	1	1	n/a	UTD	UTD	11

Study	REPORTING										EXTERNAL VALIDITY			INTERNAL VALIDITY – BIAS AND CONFOUNDING									Total /22
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q16	Q17	Q18	Q19	Q20	Q21	Q22	Q25	Q26	
Garrioch [46]	1	1	0	1	0	1	1	1	0	0	1	UTD	1	UTD	0	1	1	1	1	n/a	UTD	UTD	12
Geissler [47]	1	0	0	1	0	1	1	1	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	13
Goodnough [26]	1	1	0	1	0	1	0	1	0	1	1	UTD	1	0	0	1	1	1	1	n/a	UTD	UTD	12
Goodnough [25]	1	1	0	1	0	1	0	1	0	0	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	12
Gutsche [48]	1	0	0	1	0	1	1	1	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	13
Haldiman [49]	1	1	0	1	0	1	0	0	0	n/a	1	UTD	1	UTD	1	n/a	1	1	1	n/a	UTD	UTD	10
Handler [28]	0	1	0	1	0	0	0	0	0	n/a	1	UTD	1	1	1	n/a	UTD	1	0	1	UTD	UTD	8/23
Harrison [50]	1	1	0	1	0	1	0	1	0	0	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	12
Hassan [97]	1	1	0	0	0	1	1	1	0	1	1	UTD	1	1	1	0	1	1	0	1	UTD	UTD	13/23
Hillman [72]	1	0	0	0	0	1	1	0	0	0	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	10
Hoeg [78]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	UTD	1	1	1	1	1	n/a	UTD	UTD	14
Horowitz [79]	1	0	0	1	0	1	0	0	0	0	1	UTD	1	1	1	1	1	UTD	1	n/a	UTD	UTD	10
Joubert [73]	1	1	0	1	0	1	0	0	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	13
Joyce [96]	1	0	0	1	0	1	1	0	1	0	UTD	UTD	1	1	1	1	UTD	1	1	UTD	UTD	UTD	11/23
King [51]	1	1	0	1	0	1	0	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	13
Lam [95]	1	1	1	0	0	1	0	0	0	1	1	UTD	1	1	1	0	1	1	0	1	UTD	UTD	13/23
Lam [98]	1	1	0	1	0	1	0	0	0	1	1	UTD	1	1	UTD	1	UTD	1	1	1	UTD	UTD	12/23
Leahy [52]	0	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14

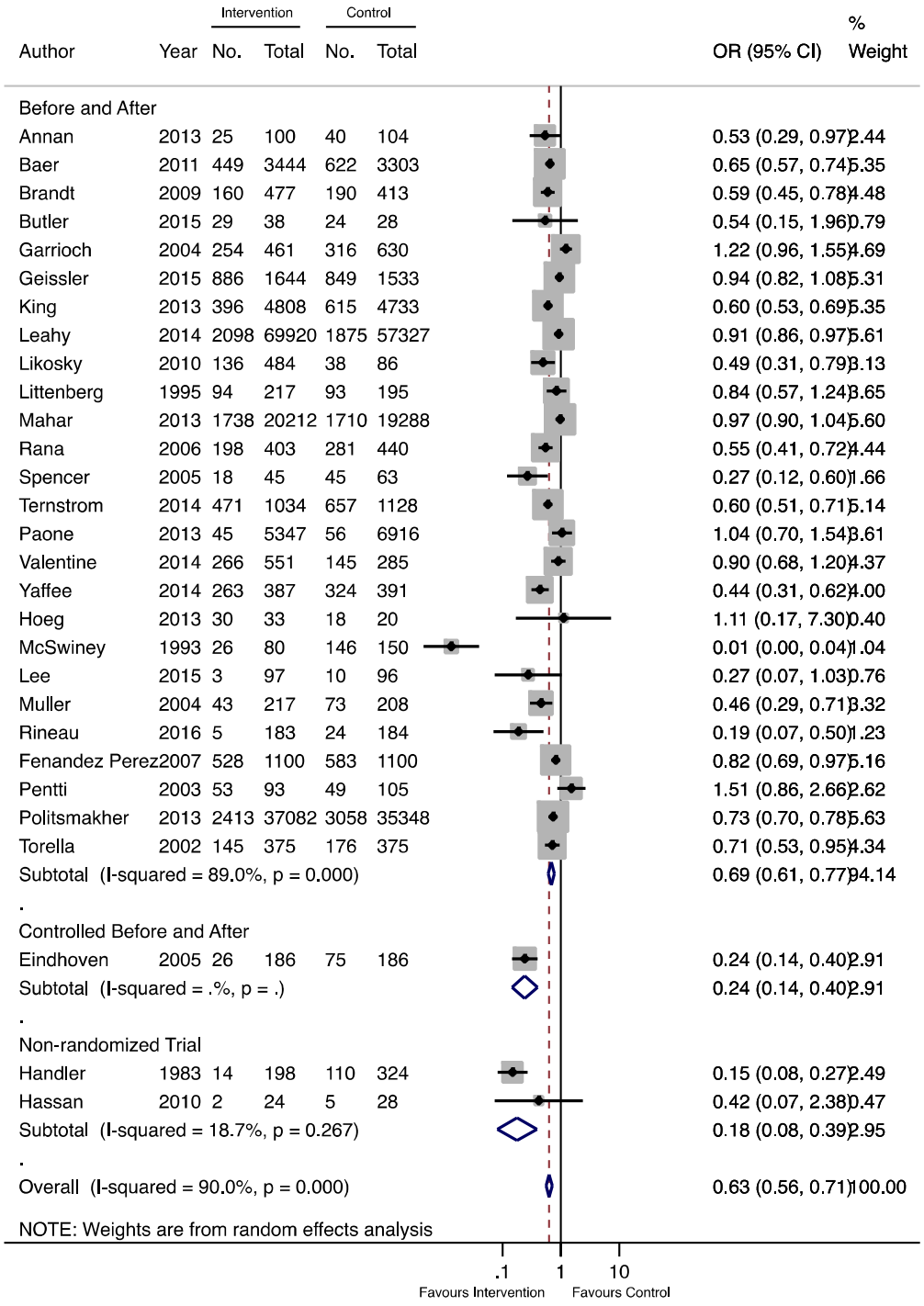
Study	REPORTING										EXTERNAL VALIDITY			INTERNAL VALIDITY – BIAS AND CONFOUNDING								Total /22
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q16	Q17	Q18	Q19	Q20	Q21	Q22	Q25	Q26	
Leão [74]	1	1	0	1	0	1	0	0	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	13
Lee [83]	0	1	0	1	0	1	0	0	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	11
Lewis [91]	0	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Likosky [53]	1	1	0	1	0	1	0	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Littenberg [54]	1	1	0	1	0	1	0	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Lucas [55]	0	1	0	1	0	1	0	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	12
Mahar [56]	1	1	0	1	0	1	0	0	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	12
Markel [31]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
McCrory [58]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
McSwiney [80]	1	1	0	1	0	1	1	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
McWilliams [89]	1	0	0	1	0	1	0	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	13
Morrison [59]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
Muller [81]	1	1	0	1	0	1	1	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Murphy [29]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
Oliver [60]	1	1	0	1	0	1	0	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Paone [75]	1	1	0	1	0	1	0	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Pentti [90]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
Politsmakher [93]	0	1	0	1	0	1	0	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	12

Study	REPORTING										EXTERNAL VALIDITY			INTERNAL VALIDITY – BIAS AND CONFOUNDING								Total /22
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q16	Q17	Q18	Q19	Q20	Q21	Q22	Q25	Q26	
Rana [61]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
Rehm [62]	0	1	0	1	0	1	0	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	12
Rineau [30]	1	1	0	1	0	1	0	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Rothschild [27]	1	1	1	1	0	1	1	1	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	15
Rosen [63]	1	0	0	1	0	1	0	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	12
Spencer [64]	1	1	0	1	0	1	0	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	13
Tavares [65]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
Ternstrom [66]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
Torella [86]	0	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Tuckfield [92]	1	1	0	1	0	1	0	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Valentine [76]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	UTD	1	1	1	1	1	n/a	UTD	UTD	14
Vos [67]	1	1	0	1	0	1	0	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	13
Vrotsos [84]	0	1	0	1	0	1	0	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	12
Whitney [85]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
Yaffee [77]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	14
Yeh [68]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
Yerrabothala [69]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
Zelinka [70]	0	1	0	1	0	1	0	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	12

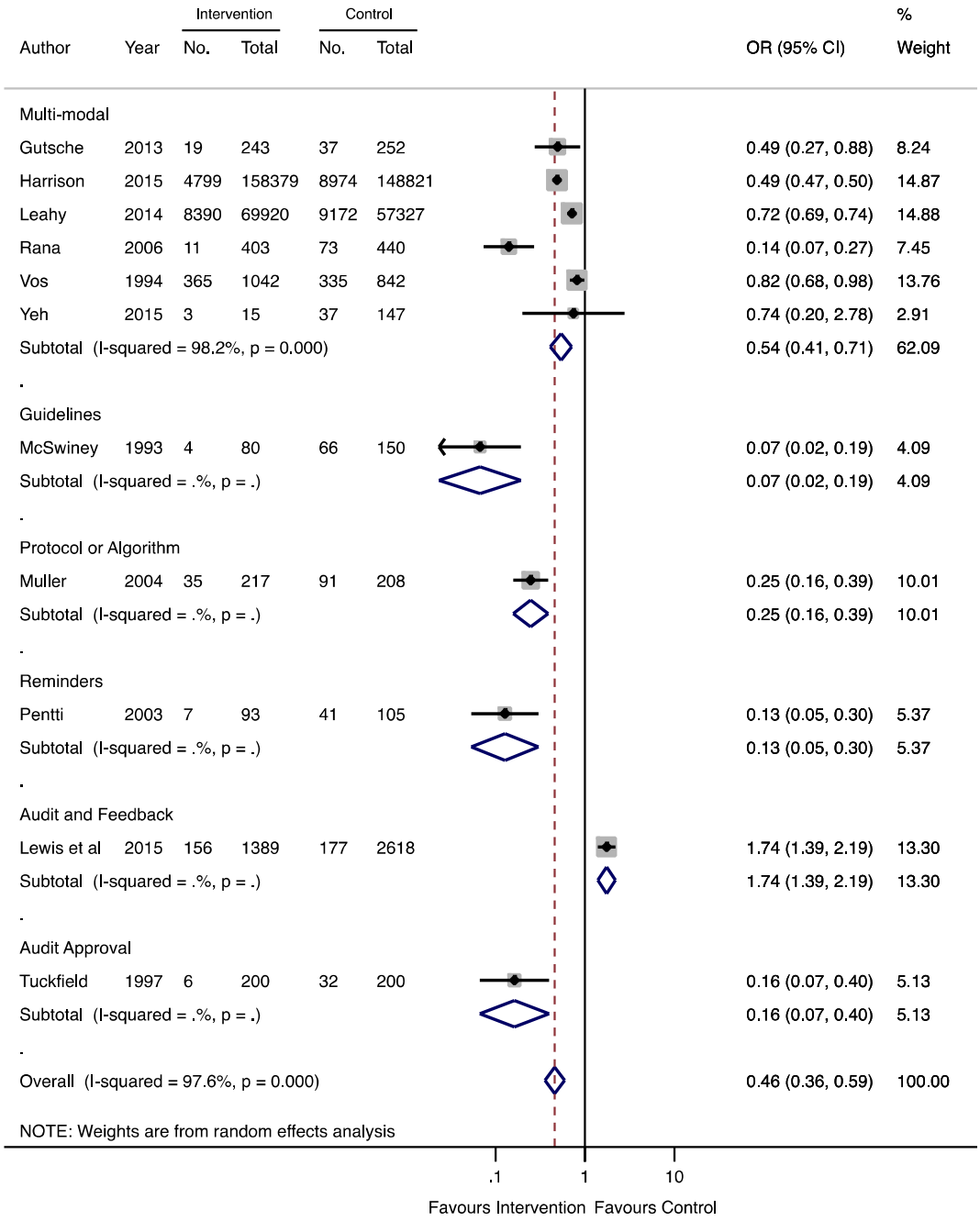
Supplementary File 9. Forest Plot for Odds of Patients Being Transfused Sorted by Year of Publication



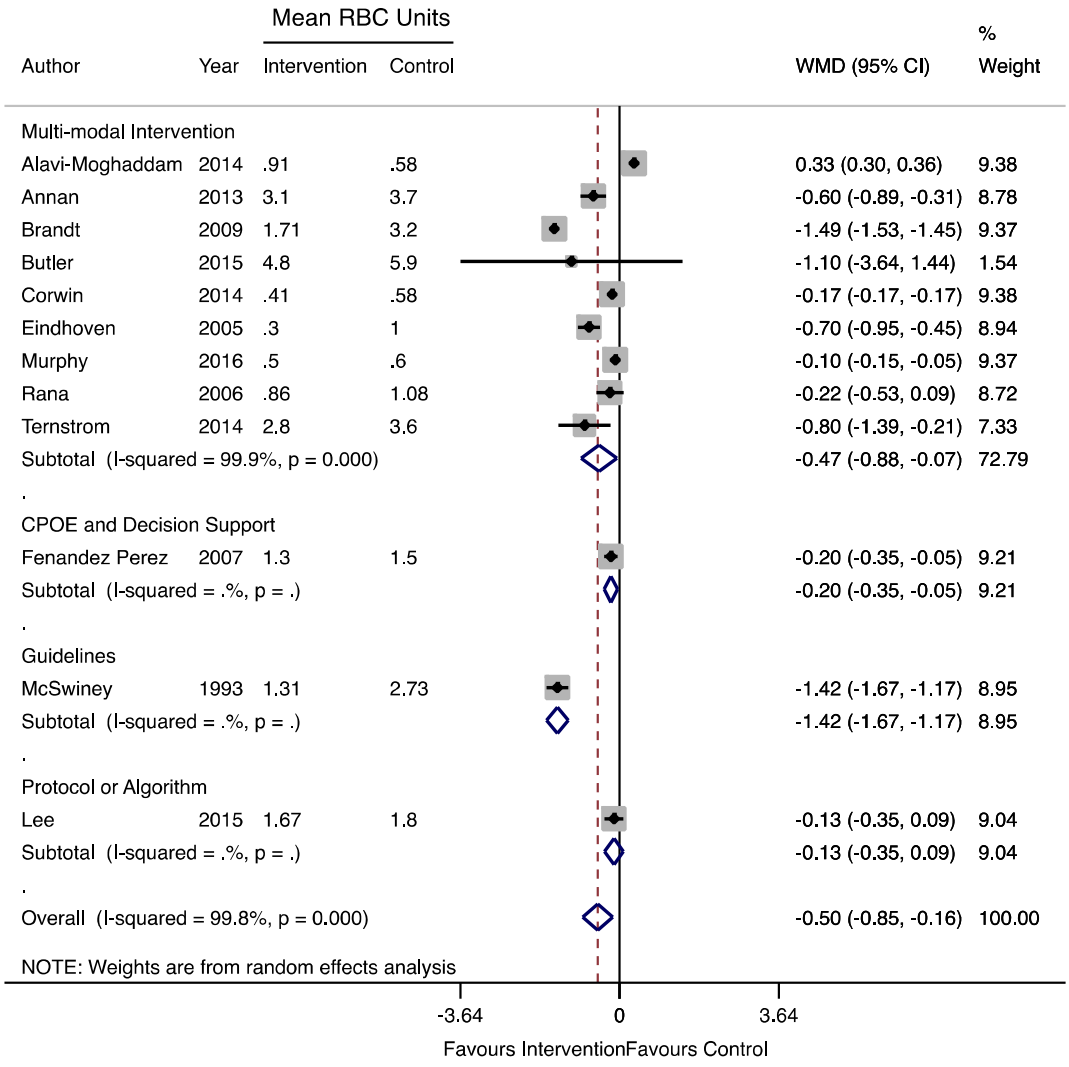
Supplementary File 10. Forest Plot of Odds of Patients Being Transfused, Stratified by Study Design



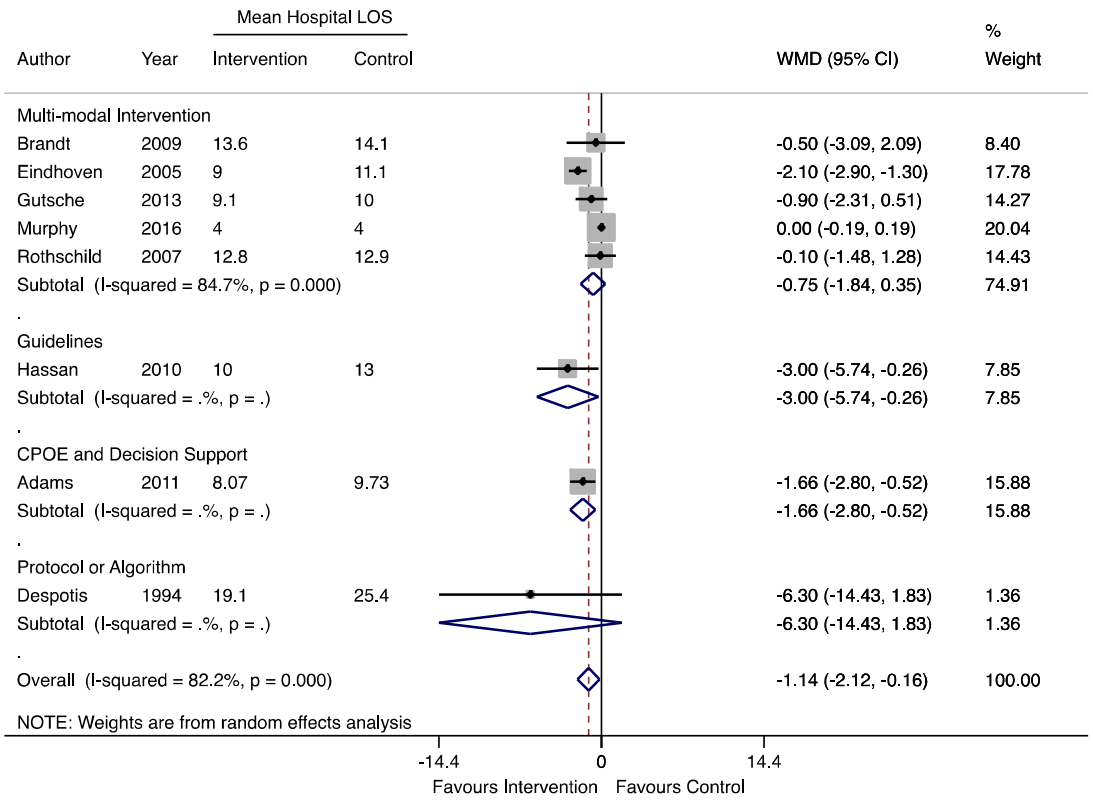
Supplementary File 11. Forest Plot for the Odds of Patients Being Inappropriately Transfused



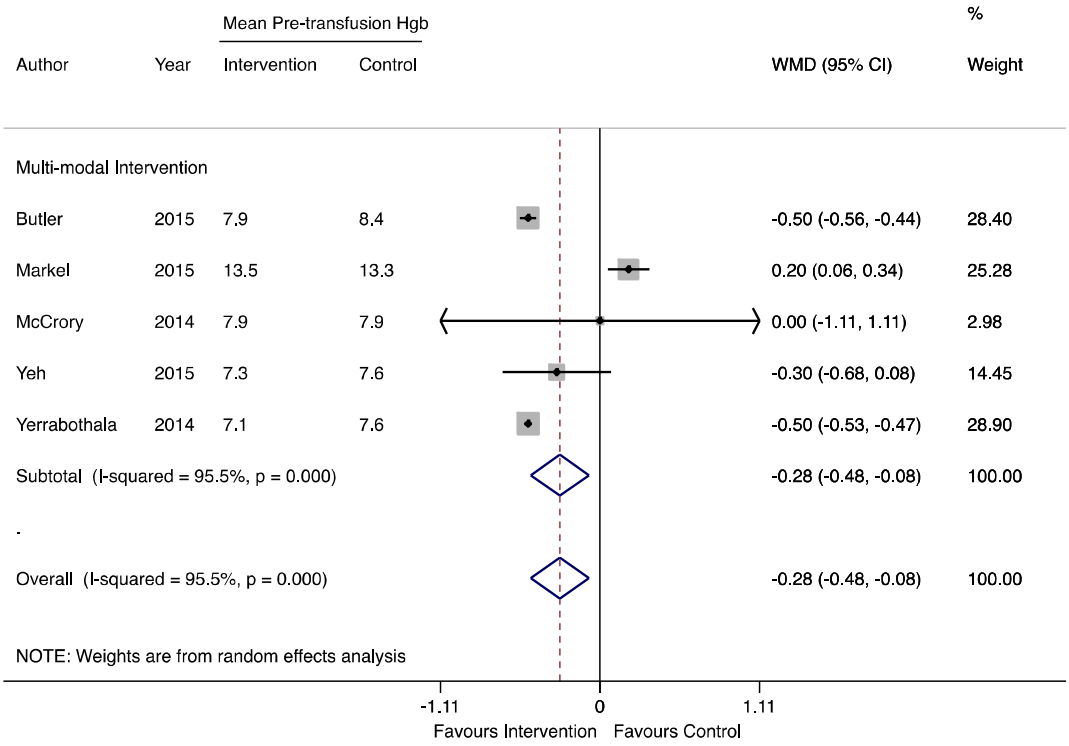
Supplementary File 12. Forest Plot for the Mean Number of RBC Units Transfused Per Patient



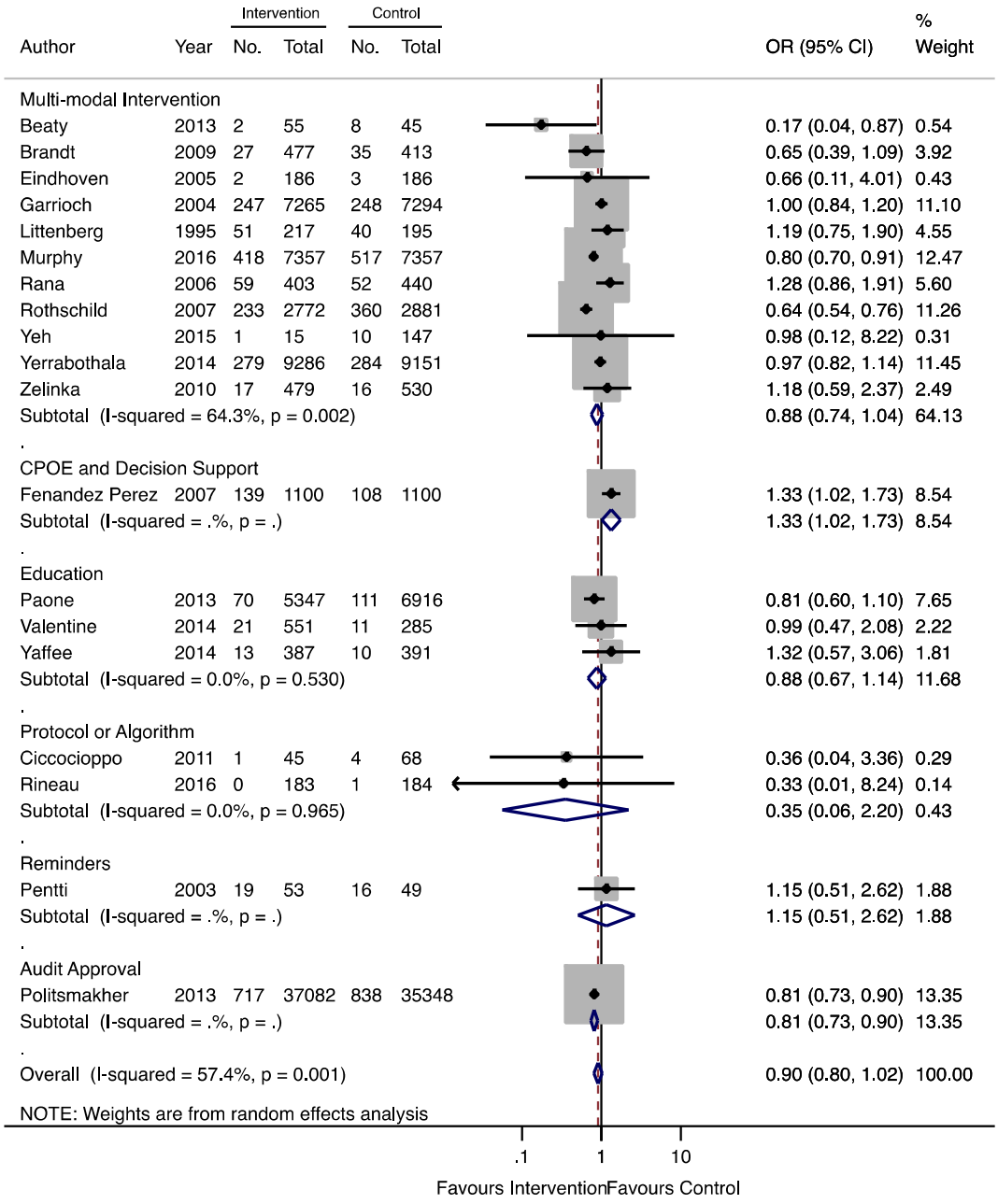
Supplementary File 13. Forest Plot for the Mean Hospital Length of Stay (days)



Supplementary File 14. Forest Plot for the Mean Pre-transfusions Hemoglobin Level (g/dL)



Supplementary File 15. Forest Plot for the Odds of In-hospitality Mortality



Supplementary File 16. Results of Meta-Regression Analysis

Covariate	Patients Transfused	
	Coefficient of logOR (SE)	*p* value
Year of Publication	0.0086 (0.071)	0.689
Number of Interventions	0.0358 (0.017)	0.617
Multi-Modal Intervention	-0.0475 (0.179)	0.794
Setting in Single Unit/ Clinical Service	-0.0717 (0.181)	0.695
Follow-up ≥ 1 year	-0.0270 (0.189)	0.888
Education	0.0918 (0.177)	0.609
Guideline	-0.0424 (0.176)	0.811
Audit and Feedback	0.1172 (0.194)	0.553
CPOE and Decision Support	0.0384 (0.205)	0.853
Protocol/ Algorithm	-0.1411 (0.191)	0.467
Reminder	0.3805 (0.277)	0.182
Policy	0.2377 (0.294)	0.426
Audit Approval	0.1056 (0.396)	0.792
Audit	0.0995 (0.244)	0.687
Paper Order Entry	-0.1948 (0.359)	0.592

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Behaviour modification interventions to optimize red blood cell transfusion practices: A systematic review and meta-analysis

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Behaviour modification interventions to optimize red blood cell transfusion practices: A systematic review and meta-analysis

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ABSTRACT

Objective: To assess the impact of behaviour modification interventions to promote restrictive red blood cell (RBC) transfusion practices.

Design: Systematic review and meta-analysis.

Setting, participants, interventions: Six electronic databases were searched to January 2018. Published randomized controlled trials (RCTs) or non-randomized studies examining an intervention to modify healthcare providers' RBC transfusion practice in any healthcare setting were included.

Primary and secondary outcomes: The primary outcome was the proportion of patients transfused. Secondary outcomes included the proportion of inappropriate transfusions, RBC units transfused per patient, in-hospital mortality, length of stay (LOS), pre-transfusion hemoglobin, and healthcare costs. Meta-analysis was conducted using a random-effects model and meta-regression was performed in cases of heterogeneity. Publication bias was assessed by Begg's funnel plot.

Results: Eighty-four low to moderate quality studies were included: 3 were RCTs, and 81 were non-randomized studies. Thirty-one studies evaluated a single intervention, 44 examined a multi-modal intervention. The comparator in all studies was standard of care or historical control. In 33 non-randomized studies, use of an intervention was associated with reduced odds of transfusion (OR: 0.63 [95% CI 0.56−0.71]), odds of inappropriate transfusion (OR: 0.46 [95% CI 0.36−0.59]), RBC units/patient (WMD: -0.50 units [95% CI -0.85−-0.16]), LOS (WMD: -1.14 days [95% CI -2.12−-0.16]), and pre-transfusion hemoglobin (-0.28 g/dL [95% CI -0.48−-0.08]). There was no difference in odds of mortality (OR: 0.90 [95% CI 0.80−1.02]). Protocol/algorithm

and multi-modal interventions were associated with the greatest decreases in the primary outcome. There was high heterogeneity among estimates and evidence for publication bias.

Conclusions: The literature examining the impact of interventions on RBC transfusions is extensive, albeit, most studies are non-randomized. Despite this, pooled analysis of 33 studies revealed improvement in the primary outcome. Future work needs to shift from asking, "does it work?", to "what works best and at what cost?".

Registration: PROSPERO 2015:CRD42015024757

STRENGTHS AND LIMITATIONS OF STUDY

- In this systematic review and meta-analysis, 84 studies examining single and multi-modal interventions to modify red blood cell transfusion practices were identified.
- This is the most comprehensive systematic review and the first meta-analysis of these interventions to date.
- Included studies were of low to moderate quality and almost all were designed as non-randomized, before and after studies.
- No studies examined the comparative effectiveness between behaviour modification interventions, nor the cost-effectiveness of interventions.
- There was significant statistical heterogeneity and evidence for publication bias.

INTRODUCTION

Blood transfusions are commonly administered as a life-saving therapy to restore hemoglobin levels among severely anaemic patients.[1-3] Blood and blood products, such as red blood cells (RBC), are, however, scarce and expensive health resources that must be managed carefully to ensure judicious use and availability for those most in need of transfusions.[4] Beyond blood conservation, transfusion safety and reducing the adverse events associated with transfusion must be considered. RBC transfusions have been associated with increased risk of infections, acute transfusion reactions, and, in certain cases, mortality.[5-7] High-quality evidence has accumulated over the past two decades in support of reducing patient exposure to RBC transfusions, through the adoption of more restrictive RBC transfusion thresholds.[8-12] A number of guidelines, such as those most recently released by the AABB (formerly the American Association of Blood Banks),[13] have also recommended against transfusion if hemoglobin levels are above 7 g/dL to 8 g/dL for most patients groups.

It is well documented that publication of such evidence alone is insufficient for affecting change.[14] Clinical practice is influenced by a myriad of social, cultural, and environmental factors that are not necessarily considered in guidelines.[15] Concerted change management efforts are, therefore, commonly undertaken to actively address these factors in order to implement recommended guidelines and achieve the desired practice change.

Interventions to specifically modify provider transfusion practices, such as education, audit and feedback, and computerized or paper order entry systems, have been described in prior studies.[16-19] Previous systematic reviews have examined the impact of these interventions, alone or in combination, on transfusion practices for various blood components (e.g. RBCs, fresh frozen plasma, platelets, cryoprecipitate). The findings of these syntheses report variability in

outcomes—including a paucity of economic outcomes—and limitations in both the quality of evidence and breadth of interventions examined.[16-18] With the exception of one systematic review published in 2015 that exclusively focused on the impacts of electronic decision support,[18] these previous reviews are dated (last published in 2005).[16 17]

Therefore, a *de novo* systematic review synthesizing the current literature in this area, concentrating on all behaviour modification interventions targeting RBC transfusion practices, is useful as healthcare organizations respond to meet recent RBC transfusion guideline recommendations. The objective of this study was to determine the effectiveness of behaviour modification interventions that change RBC transfusion practices, specifically, the effects of interventions on the proportion of patients transfused, as well as patient and healthcare system outcomes.

MATERIALS AND METHODS

A systematic review of the published literature was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Supplementary File 1).[20] The protocol for this systematic review is registered on the PROSPERO website (2015:CRD42015024757; Supplementary File 2).[21]

Search Strategy

The electronic search strategy was developed by an Information Specialist (DLL). MEDLINE, PubMed, EMBASE, the Cochrane Central Registry of Controlled Trials, the Cumulative Index to Nursing and Allied Health, the Cochrane Database of Systematic Reviews and the Health Technology Assessment database were searched from inception to January 12, 2018. A sample search strategy is available in Supplementary File 3. Animal studies, case

reports, comments, editorials, and letters were excluded; no other limitations were applied. The references lists of identified systematic reviews were also hand-searched for relevant articles not found through database searches.

Selection of Literature

Studies were included if they: reported original data; examined the impact of a behaviour modification intervention on healthcare provider RBC transfusion practices; had a comparator group (e.g. no intervention or another intervention); and were designed as either a randomized controlled trial (RCT) or non-randomized study. A non-randomized study involves the selection of groups each exposed to a different intervention without random assignment.[22 23] Common non-randomized designs in behaviour modification studies include non-randomized trials (also referred to as between subjects or between group trials), time series studies, and uncontrolled and controlled before and after studies.[23 24] No fixed definition of a behaviour modification intervention was applied; thus, any definition used within the included studies was accepted. Included interventions were grouped using an inductive approach based on descriptors and labels provided from the studies themselves. Studies were excluded if they did not meet any of the above criteria, including if they only assessed transfusion of other blood products (i.e. fresh frozen plasma, platelets, cryoprecipitate) and not in conjunction with RBCs. Detailed inclusion and exclusion criteria are provided in Supplementary File 4. Abstract and full-text screening were completed in duplicate (LJJS; LED; HMH; KM) and any disagreement was resolved through discussion and consensus, or through consultation with a third reviewer. Agreement between reviewers was calculated using a kappa statistic.

Data Extraction

Data extraction was completed in duplicate using a standardized data extraction form (LJJS and KM). Data on publication date, country, healthcare setting, study design, follow-up period, type of intervention and comparator(s) groups, intervention characteristics, RBC transfusion criteria, definition of an "inappropriate" transfusion, number of patients treated in each group, and the primary outcome of interest (the proportion of patients transfused) were extracted. Secondary outcomes, including the proportion of inappropriate transfusions, mean RBC units transfused per patient, in-hospital mortality, hospital LOS, pre-transfusion hemoglobin, and changes in costs (e.g. RBC unit costs) were also extracted where available.

Quality Assessment

Risk of bias and quality assessments of included studies were completed in duplicate (LJJS and KM). The Cochrane Risk of Bias tool was used to evaluate the risk of bias among included RCTs.[25] Quality of non-randomized studies were assessed using the Downs and Black Checklist.[26] Typically scored out of 28 points, the Downs and Black Checklist was modified because several items do not apply to the non-randomized studies (e.g. randomization), thereby reducing the denominator to 22 for uncontrolled before and after studies, and 23 for controlled before and after and non-randomized trials.

Data Analysis

Meta-analyses were conducted using a random-effects model. Pooled odds ratio (OR) and the weighted mean difference (WMD), and their respective 95% confidence intervals (95% CI), were calculated for categorical and continuous outcomes, respectively. Stratified analyses by intervention type and study design were completed. Statistical heterogeneity was examined using both the I^2 (percentage of total inter-study variation due to heterogeneity rather than chance) and Q statistic *p*-value (test of homogeneity). An I^2 greater than 50% was considered as evidence for

significant heterogeneity.[27] Random effects meta-regression was performed with the year of publication, the number of interventions per study, having a multi-modal intervention, a study setting in a single unit or clinical service, follow-up period (greater than 1 year), and each of the identified intervention types as covariates. A regression coefficient with a $p<0.10$ was considered a significant predictor of the primary outcome. Publication bias was examined using Begg's funnel plot and Egger's regression test. In the case of funnel plot asymmetry, the trim-and-fill method was used to impute estimates from potentially suppressed publications. This method assumes that studies that do not demonstrate a desired effect (e.g. decrease in proportion transfused) were not likely published [28]. All statistical analyses were completed using Stata/IC 13.1.

RESULTS

Search Results

The flow chart of included studies is provided in Figure 1. Five-thousand four-hundred and twenty unique abstracts were identified, of which 270 proceeded to full-text review. Thirteen additional relevant studies were identified through hand-searching. One hundred and eighty-six studies were excluded during full-text review, resulting in 84 articles included in the final analysis (Kappa = 87.0%, 95% CI 80.8-93.1%).

Characteristics of Included Studies

The characteristics of included studies are summarized in Supplementary File 5. The 84 included articles were comprised of 83 unique study populations, as two articles[29 30] reported different outcomes for the same population. In addition, one article[31] reported outcomes from two unique study studies; thus, the non-overlapping findings from both studies were included.

The included studies were published between 1983[32] and 2017,[33-38] with the majority of studies conducted in the United States (n=50). Only 3 studies were RCTs (1 cluster RCT, 2 randomized at the individual-level);[31 39 40] the remaining 81 were non-randomized studies, specifically uncontrolled before and after (n=74);[29-31 33-36 38 41-106] controlled before and after (n=2);[107 108] interrupted time series (n=1);[37] and non-randomized trial (n=4)[32 109-111] designs.

In all cases, an intervention was compared to either historical controls or standard of care. Most studies were conducted in a single acute care facility, often an academic hospital. Follow-up periods varied considerably from 2 weeks[82] to 6 years[48] post-intervention. Targeted populations included primarily physicians (e.g. intensivists, anesthesiologists, surgeons) ordering RBC transfusions, as well as medical trainees (e.g. residents), other healthcare providers (e.g. nurses), and hospital staff (e.g. hospital laboratory and blood bank technologists) involved in the care of patients receiving transfusions. The unit of intervention was the individual healthcare provider, ward or unit, or institution (i.e. not patients themselves).

Types of interventions

The effectiveness of either a single (n=32) or multiple interventions (n=52) in combination (referred to as multi-modal interventions) was evaluated. The following single intervention categories were identified: education sessions or materials (n=9);[40 80-86 109] protocols or algorithms (n=7);[39 90-95] guidelines (n=4);[87-89 110] computerized physician order entry (CPOE) systems and decision support (n=4);[31 97-99] reminders (n=2);[100 108] audit and feedback (n=2);[101 111] audit approval (n=2);[102 103] a clinical policy (n=1);[96] and prospective audit of transfusion practices.[37] Descriptions of each, along with examples from the included studies, are provided in Table 1.

Table 1. Categories of Single and Multi-modal Behavior Modification Interventions

Description of Techniques	Examples from Included Studies
Education Educational materials or group sessions to disseminate: a) Specific medical evidence, such as etiology and pathophysiology of anaemia, indications for transfusion, risks of RBC transfusions, and other evidence from relevant trials (e.g. TRICC trial).; or b) Compiled materials or recommendations from clinical practice guidelines, transfusion protocols or algorithms.	• Formal didactic group sessions • Adaptation of existing departmental or institutional rounds sessions or clinical staff meetings • One-on-one training sessions • Printed education materials distributed to participants or displayed in clinical settings (e.g. graphics and posters)
Protocol or Algorithm Document with a comprehensive outline of steps and detailed criteria to follow for the treatment of specific patient groups or clinical setting; considered more rigid or specific than guidelines.	• Visual map or flow chart depicting clinical scenarios for management of anaemia • Clinical protocols to manage hemorrhaging • Patient blood management protocol with indications for RBC transfusions
Guideline Development and/or adoption of evidence-based clinical practice guidelines (i.e. statements that include recommendations) intended to optimize care of patients.	• *De novo* institutional guidelines for RBC transfusions, appropriate management of anaemia, or RBC/blood conservation • Adoption of guidelines developed by other institutions or expert clinical organizations
Computerized Physician Order Entry (CPOE) and Decision Support Electronic order entry system for healthcare providers to directly enter medication, treatments or other requests for a patient; the system is programmed to prompt with alerts (e.g. of guidelines) or other content to support clinical decision-making.	• Replacement of paper orders to electronic system that consolidates laboratory orders (e.g. RBC orders) information with other patient chart information • Decision support algorithm incorporated into electronic order entry of RBC/blood products sent to blood banks or laboratories
Reminders Direct notification to healthcare providers of either institutional clinical criteria, recommended use of medications or other treatments, or ordering processes.	• Paper forms provided when RBC/blood products are issued reminding healthcare providers of transfusion criteria and encouraging self-audit of practice • Alerts (electronic or by telephone) to healthcare provider when RBC transfusion orders placed outside of specified clinical indications (e.g. higher hemoglobin level of patient) or existing guidelines
Audit and Feedback	• Transfusion practices were retrospectively audited and the

Process to measure performance of healthcare providers or patient outcome data over a specified period of time and to provide a summary (verbal or written) of this information back to those healthcare providers in order to reach a specified goal.	ordering healthcare providers were presented with his or her individual results in the context of the clinical department as a whole and with other department faculty anonymized.
Audit Approval Medication, laboratory, or other treatment orders are audited and for any not meeting pre-specified institutional criteria, an approval is required before the order is approved.	• RBC transfusions orders audited by blood bank or laboratory staff; those placed outside of recommended criteria were not issued and ordering healthcare providers were notified that requests were sent directly to departmental reviewers (e.g. transfusion medicine specialists) for approval.
Policy Compulsory clinical and/or administrative directives for prescribing of medications, laboratory tests, other treatments.	• RBC ordering policy that enforcing standard blood product ordering schedule and adherence to specific hemoglobin triggers.
Paper Order Form Mandatory completion of a paper form order specific medications, laboratory tests, or other treatments.	• Healthcare providers required to complete *de novo* institutional paper order form for RBC transfusions and provide clinical rationale from pre-specified list.
Audit Prospective or retrospective review of clinical performance or patient outcomes; the data is often of electronically collected.	• Retrospective review of RBC transfusions orders outside of recommended clinical criteria (e.g. hemoglobin trigger)
Financial Incentive Provision of financial reward provided to individual or groups of healthcare providers upon attainment of specific clinical performance goal.	• Group-based financial rewards, scaled based on number of healthcare providers, were issued if a 20% reduction in the mean number of RBC transfusions orders per patient-day compared to the previous year was obtained.
Order Sets Groups of related medical orders, such as laboratory/diagnostic test orders, patient care orders, and medication orders, that are combined electronically or on paper; can be targeted to align current practice with guidelines or recommended best practice.	• RBC transfusion order set implement hospital-wide that included prompts for transfusion rate and ordering of pre-transfusion oral and intravenous diuretics.
Checklists Comprehensive list of items and/or activities (paper or electronic form) to be completed by healthcare providers for a given clinical encounter.	• Paper checklist affixed to transfusion order set and used to inform and/or remind healthcare providers a) of risk factors associated with transfusion, and b) to document consent for transfusion.

Multi-modal interventions included between 2 and 5 strategies, applied concurrently or in sequence. Combinations of multi-modal interventions are summarized in Supplementary File 6. The interventions most commonly included in multi-modal interventions were: education (n=31);[29-32 41 42 47-51 53-55 57-60 62-65 67-70 72 74-77 107] guidelines (n=22);[31 42 44 45 50 53-56 58 59 61 62 64 65 67 69 72 73 75 76 107] and audit and feedback (n=20).[32 44 46 49 52-55 57-60 65 67-69 71-73 77] Some multi-modal interventions applied additional interventions not examined among the single intervention studies, including paper order forms (n=4),[61 67 71 73] financial incentives (n=1),[68] and physician checklists and order sets (n=1).[106]

Quality of Included Studies

All three RCTs[31 39 40] incorporated study elements that were deemed to be of high, low, and unclear risk of bias (Supplementary File 7). Due to the nature of the interventions, treatment allocation was not concealed, nor could the participants, personnel, or outcome assessors be blinded; thus, risk of bias was consistently high in these areas. In contrast, risk of bias was low across all studies with respect to both attrition and reporting bias.

The majority of non-randomized studies (n=63) were of moderate quality, where quality assessment scores ranged from 12-15; twelve studies[32 42 44 47 51 52 56 81 88 92 107 109] were of low quality (scores from 0-11) and no studies were deemed to be of high quality (score > 17) (Supplementary File 8). Most studies were found to have low scores due to poor reporting (Q1-Q10), particularly of the characteristics of the targeted population and distribution of principal confounders. External validity (Q11 and Q13) was moderate for most studies; however, Q12 (i.e. subjects prepared to participate representative of the entire population) was deemed "unable to determine" for all studies. The internal validity was low to moderate across studies (Q16 to

Q26). Adequate adjustment for confounding (Q25) and whether losses to follow-up were taken into account (Q26) were also deemed "unable to determine" for all studies.

Impact of Behaviour Modification Interventions on RBC Usage and Patient Outcomes

A summary of the pooled analyses is provided in Table 2. The primary outcome, the proportion of patients transfused, was reported in 33 studies. The pooled odds of a patient receiving a RBC transfusion was 0.70 (95% CI: 0.65 to 0.76]; n=33) (Figure 2; Table 2). There was strong evidence of heterogeneity in this estimate (I^2= 90.5%, Q-statistic p=0.00), although this was not apparent upon visual inspection as a number of studies crossed the null value. Sorting studies by year of publication showed that, with the exception of the two earliest studies,[32 89] the associated decrease in the odds of transfusion was fairly consistent over time (Supplementary File 9).

All 33 studies included in this analysis were non-randomized studies. A stratified analysis by non-randomized study design (Supplementary File 10) revealed high subgroup heterogeneity between the uncontrolled before and after studies (I^2= 89.6%, p=0.00). However, the variability between the two non-randomized trials was much lower (I^2= 18.7%) and was likely due to chance alone (i.e. not due to heterogeneity) (Q-statistic p=0.267), suggesting that differences in study design might have contributed to some of the observed heterogeneity in the crude pooled estimate.

Further, stratification by intervention category revealed that differences in techniques across studies might have also contributed to study heterogeneity (Figure 2; Table 2). Among these interventions, the use of a protocol or algorithm (pooled OR: 0.34 [95% CI: 0.19 to 0.60]; n=3) and a multi-modal intervention (pooled OR: 0.73 [95% CI: 0.67 to 0.79]; n=20) were associated with significantly decreased odds of patients being transfused. CPOE and decision

Table 2. Results of Meta-Analysis for RBC Usage and Patient Outcomes

Outcome Measures	Multi-modal	Education	Protocol/ Algorithm	Guidelines	CPOE & Decision Support	Reminders	Audit and Feedback	Audit Approval	Policy	Pooled Estimate** (95% CI)	I^2 (%); Q-statistic (*p* value)
Odds of patients being transfused (OR, 95% CI)	0.73 (0.67-0.79)	0.74 (0.44-1.24)	0.34 (0.19-0.60)	0.17 (0.01-3.15)	0.82* (0.69-0.97)	1.51* (0.86-2.66)	--	0.73* (0.70-0.78)	0.71* (0.53-0.95)	0.70 (0.65-0.76)	90.5%; p=0.0001
Odds of patients being inappropriately transfused (OR, 95% CI)	0.54 (0.41-0.71)	--	0.25* (0.16-0.39)	0.07* (0.02-0.19)	--	0.13* (0.05-0.30)	1.74* (1.39-2.19)	0.16* (0.07-0.40)	--	0.46 (0.36-0.59)	97.6%; p=0.0001
Difference in RBC units transfused (WMD, 95% CI)	-0.34 (-0.37- -0.31)	--	-0.13* (-0.35- 0.09)	-1.42* (-1.67- -1.17)	-0.20* (-0.35- -0.05)	--	--	--	--	-0.35 (-0.38- -0.32)	99.9%; p=0.0001
Odds of patient in-hospital mortality (OR, 95% CI)	0.91 (0.81-1.03)	0.88 (0.67-1.14)	0.35 (0.06-2.20)	--	1.33* (1.02-1.73)	1.15* (0.51-2.62)	--	0.81* (0.73-0.90)	--	0.92 (0.84-1.02)	64.8%; p=0.001
Difference in hospital LOS (WMD, 95% CI)	-0.42 (-0.79- -0.06)	--	-6.30* (-14.43- 1.83	-3.00* (-5.74- -0.26)	-1.66* (-2.80- -0.52)	--	--	--	--	-0.63 (-1.02- -0.24)	79.7%; p=0.0001
Difference in pre-transfusion Hgb level (WMD, 95% CI)	-0.28 (-0.48- -0.08)	--	--	--	--	--	--	--	--	-0.28 (-0.48- -0.08)	95.5%; p=0.0001

OR: odds ratio; WMD: weighted mean difference; *Point estimate derived from a single study; **Pooled estimate from both single intervention and multi-modal intervention studies.

support (OR: 0.82 [95% CI: 0.69 to 0.97]; n=1),[98] audit approval (OR: 0.73 [95% CI: 0.70 to 0.78]; n=1),[103] and policy interventions (OR: 0.71 [95% CI: 0.53 to 0.95]; n=1)[96] were also associated with decreases in the odds of transfusion; these point estimates, however, were derived from a single study in each subgroup (Figure 2; Table 2). No significant differences were observed between groups following the use of education (pooled OR: 0.74 [94% CI: 0.44 to 1.24]; n=3) and guidelines (pooled OR: 0.17 [95% CI: 0.01-3.15]; n=3), or reminders (OR: 1.51 [95%: 0.86-2.66]; n=1).

The impacts of behaviour modification interventions on secondary outcomes are summarized in Table 2 and Supplementary Files 11-15. An "inappropriate" transfusion was defined by the included studies as a RBC transfusion initiated at a pre-transfusion hemoglobin above 7 g/dL to 9 g/dL for most, non-bleeding adult patients.[55 57 59 70 76 77 89 90 100-102] Use of an intervention was associated with a decrease in the pooled odds of inappropriate transfusion (pooled OR: 0.46 [95% CI: 0.36 to 0.59; I^2= 97.6%, Q-statistic *p*=0.00; n=11), The mean RBC units transfused per patient (WMD: -0.35 units [95% CI: -0.38 to -0.32]; I^2= 99.9%, Q-statistic *p*=0.00; n=14) and mean patient LOS (WMD: -0.63 days [95% CI: -1.02 to -0.24]; I^2= 79.7%, Q-statistic *p*=0.00; n=9) also decreased following the use of an intervention (Table 2). The change in mean pre-transfusion hemoglobin level was only examined among studies of multi-modal interventions and was associated with a WMD of -0.28 g/dL (95% CI: -0.48 to -0.08; I^2= 95.5%, Q-statistic *p*=0.00; n=5).

There was also significant heterogeneity in the pooled analyses of secondary outcomes (I^2 ranging from 57.4 to 99.9%). It was unclear whether differences in interventions contributed to the heterogeneity, as stratification by intervention category left many subgroups with only one study; this precluded calculation of all subgroup I^2 values (Supplementary Files 11-15). Single

modality interventions were associated with greater impacts on RBC usage, compared to multi-modality interventions (Table 2). Specifically, implementation of a guideline in one study resulted in the lowest odds of inappropriate transfusion (OR: 0.07 (95% CI: 0.02 to 0.19) and the greatest decrease in mean RBC units transfused (WMD: -1.42 units [95% CI: -1.67 to -1.17]).[89] Another study examining a treatment algorithm reported the largest decrease in hospital LOS, however there was marked variability in this estimate (WMD: -6.30 days [95% CI: -14.43 to 1.83]).[39] A significant increase in the odds of inappropriate transfusion (OR: 1.74 [95% CI: 1.39-2.19]) was observed following audit and feedback in one study.[101]

There was no significant difference in the odds of in-hospital mortality (pooled OR: 0.92 (95% CI: 0.84 to 1.02; I^2= 64.8%, Q-statistic p=0.00; n=19) (Table 2). The stratified meta-analysis (by intervention type) suggested that the observed heterogeneity in the pooled estimate was likely attributed to the variability in interventions examined across studies (Supplementary File 15).

Potential Predictors of RBC Usage

Studies published on or after 1995, the year in which evidence of efficacy and safety of restrictive transfusion practices were first published,[112] were included in the meta-regression. The year of publication, number of interventions, having a multi-modal intervention, a single unit or clinical service setting, follow-up greater than 1 year, and the individual component interventions in a given study were not identified as significant predictors of RBC transfusion (Supplementary File 16).

Publication bias

Evidence for publication bias among included studies (open circle symbols) was indicated by the asymmetry in the funnel plot (Figure 3) and Egger's regression test (p=0.001).

Ten studies were imputed using the trim-and-fill method (square with circle symbols) resulting in a pooled OR of 0.803 (95% CI: 0.663 to 0.972) for the primary outcome of patients being transfused. This suggests that studies of smaller patient sample size, reporting an increased likelihood of transfusion post-intervention, may have been suppressed from publication.

DISCUSSION

Efforts to modify transfusion practices are not novel and have been described internationally for over four decades. We identified 84 studies, primarily non-randomized studies of low to moderate quality, examining the impact of a behaviour modification intervention, compared to no intervention, on RBC transfusion practices. Among single modality interventions examined, eight categories were identified: education, protocol/algorithm, guidelines, CPOE and decision support, reminders, audit and feedback, audit approval, and clinical policy. The majority of studies used multi-modal interventions. Meta-analysis was permitted for a small subset of only non-randomized studies (n=33). On average, the pooled odds of patients being transfused decreased by 30% (pooled OR: 0.70; 95% CI: 0.65 to 0.76) and patients received 0.35 fewer RBC units post-intervention. In addition, the pooled average pre-transfusion hemoglobin levels decreased by 0.28 g/dL and the proportion of inappropriate transfusion (above a hemoglobin of 7 g/dL to 9 g/dL) decreased by approximately 54% (pooled OR: 0.46; 95% CI: 0.36 to 0.59). As expected, given the increasing body of evidence suggesting similar safety profiles between restrictive and liberal transfusion practices,[13] there was no difference pooled odds of in-hospital mortality between intervention and comparator groups. Among all interventions examined, the protocol/algorithm and multi-modal interventions were associated with the greatest decreases in the pooled odds of patients being transfused.

The present study represents the most up-to-date collection of published literature and the first meta-analysis of interventional studies in this field. Therefore, the analytical investigations performed in our study represent a substantial and novel contribution to the existing knowledge of how to achieve restricted RBC transfusion practices. Across all pooled estimates we observed significant statistical heterogeneity, which was only partly attributed to the variability between interventions. Context-specific factors, not easily discernable from the available evidence, are also likely contributing to the observed heterogeneity among included studies. These may include variability in physician experience, clinical practice or flow, perceived ease of an intervention, and/or organizational capacity or receptivity for change.[113] Work from the audit and feedback literature—which is among the most extensive in the area of behaviour modification interventions—has also reported variability in effect size of the intervention based on differences in baseline performance of the targeted behaviour as well as nuances in delivery of the intervention (i.e. how feedback is provided).[114] Collectively, this information suggests that the decision to adopt a given intervention should, therefore, not only consider evidence of effectiveness, but also the factors related to the context and implementation. For instance, a labour-intensive intervention such as a CPOE and decision support system will be more feasible and efficient to implement in a setting with electronic ordering systems already in place, rather than in a one without. Explicit methodology to first identify relevant determinants to change and selection of an intervention(s) to address such determinants, such as through theory-based frameworks, might prove useful in tailoring an appropriate intervention to a given clinical setting.[115 116]

Our findings are consistent with the evidence from the broader knowledge translation literature.[117] In one of the most comprehensive systematic reviews, Grimshaw *et al.*[117] identified

over 200 studies examining the impact of interventions on a wide range of healthcare provider behaviours and settings. The authors identified a similar array of interventions (e.g. education, audit and feedback, reminders) that were all were effective to varying degrees, and their observed effectiveness was not associated with the number of interventions implemented within a given study.[117] The results of our meta-regression analysis further support that a multi-modal intervention and the number of component interventions are not predictive of the impact of the interventions on the primary outcome.

Our results are also in line with the qualitative findings of previous systematic reviews of interventions to modify transfusion practices more broadly.[16-18] Identified interventions were similarly found to be effective at reducing transfusion use, however the previous reviews were unable to comment on their comparative effectiveness due to the dearth of direct comparisons between intervention types and reported heterogeneity among studies.[16 17] With our updated review of the literature, meta-analysis was feasible given the high prevalence of common study designs, as well as frequent reporting of our primary and secondary outcomes. While the comparator groups among included studies were also restricted to historical controls or standard of care, our stratified meta-analyses still enabled crude comparisons of effectiveness between interventions.

Limitations

The majority of included studies were non-randomized studies of low to moderate quality and susceptible to bias. For example, most studies employed an uncontrolled before and after study design and, in the absence of a concomitant control group, these studies were at high risk of bias due to both secular trends and maturation bias.[118] Due to the lack of randomization, such studies can also be susceptible to selection bias.[23] In addition, we found limited to no reporting of

participant characteristics and it is unclear whether and to what extent these characteristics led to confounding of the reported outcomes. The non-randomized studies were also deemed to have moderate external validity, thus generalizability of findings across all clinical settings and/or international healthcare systems is unclear.

Despite the large number of studies included in the systematic review, the primary outcome was only available for a minority of non-randomized studies (n=33). Our stratified meta-analysis also resulted in a very limited number of studies (or even one study) often of moderate quality, in many of the single modality subgroups. Taken together, these limited our ability to make inferences of comparative effectiveness across all intervention types and precluded our ability perform further statistical techniques, such as network meta-analysis.[119] While meta-regression was permitted for the primary outcome, similar analyses were underpowered for most secondary outcomes.[120] Finally, the findings from our meta-analyses must be interpreted with caution given the evidence for publication bias. Previous reviews similarly suggested of publication bias among earlier included studies due to the tendency of outcomes to favour the intervention group.[16 17]

Given such limitations of the non-randomized studies (particularly the uncontrolled before and after studies) and the meta-analytic efforts, it is difficult to state with certainty which intervention is the most effective at modifying RBC transfusion practice.

Future Research

Further comparative effectiveness studies, designed as large, high-quality RCTs are recommended to determine the effectiveness of the present interventions. However, the prevalence of low to moderate quality non-randomized studies included in this present review may indicate the logistical difficulty in evaluating these interventions through RCTs. As such,

pragmatic trial designs may be considered to aid in balancing issues of feasibility with methodological rigor.[121] Also, none of the included studies evaluated the effectiveness of a behaviour modification intervention to that of another behaviour modification intervention (of either single or multi-modality). Such direct comparisons would not only aid in confirming effectiveness of interventions, but also help determine the comparative effectiveness of interventions. In the case of multi-modal interventions, further research should also attempt to address which elements of the intervention are key to affecting the desired change. This information may better and more appropriately advise healthcare organizations seeking to implement the most effective behaviour modification intervention.

Lastly, we did not identify any studies that performed a concomitant economic evaluation. This information is critical to selecting an intervention that is also efficient within a given healthcare budget. Sixteen of the included studies did report of changes in healthcare costs, primarily cost savings in RBC usage, following either a single or multi-modal intervention.[30 34-37 45 57 61 72 75 80 86 90 98 103 104] Only two studies factored in the cost of implementing the intervention into their estimate.[34 98] Given the often costly, labour-intensive nature of many interventions, future cost-effectiveness studies should include the cost of implementation to determine whether true savings are realized from a given intervention.

CONCLUSIONS

We found a large body of literature evaluating the impact of behaviour modification interventions on RBC transfusion practices. The types of interventions are diverse, including single and multi-modality interventions. The quality of included studies was low to moderate and the proportion of non-randomized studies was high (n=81). The protocol or algorithm and multi-

modal interventions were associated with statistically significant reductions in the pooled odds of RBC transfusion. These results must be interpreted with caution due to the prevalence of uncontrolled before and after studies, statistical heterogeneity, limited study sample size within intervention groups, and evidence for publication bias. Given these limitations, further large, high-quality pragmatic trials would aid to not only confirm, but also directly compare effectiveness and cost-effectiveness of different types of behaviour modification interventions. This shift in the field from simply understanding "does it work", towards investigating "what works best" and "at what cost" is required as healthcare organizations respond to meet the transfusion guideline recommendations.

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REFERENCE LIST

1. Carson JL, Noveck H, Berlin JA, et al. Mortality and morbidity in patients with very low postoperative Hb levels who decline blood transfusion. *Transfusion* 2002;42(7):812-8. [published Online First: 2002/10/12]

2. Weiskopf RB, Beliaev AM, Shander A, et al. Addressing the unmet need of life-threatening anemia with hemoglobin-based oxygen carriers. *Transfusion* 2017;57(1):207-14. doi: 10.1111/trf.13923 [published Online First: 2016/11/20]

3. Beliaev AM, Marshall RJ, Gordon M, et al. Clinical benefits and cost-effectiveness of allogeneic red-blood-cell transfusion in severe symptomatic anaemia. *Vox Sang* 2012;103(1):18-24. doi: 10.1111/j.1423-0410.2011.01573.x [published Online First: 2011/12/14]

4. Shander A, Hofmann A, Gombotz H, et al. Estimating the cost of blood: past, present, and future directions. *Best Pract Res Clin Anaesthesiol* 2007;21(2):271-89.

5. Delaney M, Wendel S, Bercovitz RS, et al. Transfusion reactions: prevention, diagnosis, and treatment. *Lancet* 2016;388(10061):2825-36.

6. Toy P, Gajic O, Bacchetti P, et al. Transfusion-related acute lung injury: incidence and risk factors. *Blood* 2012;119(7):1757-67.

7. Bolton-Maggs PH, Moon I. Assessment of UK practice for management of acute childhood idiopathic thrombocytopenic purpura against published guidelines. *Lancet* 1997;350(9078):620-3.

8. Carson JL, Stanworth SJ, Roubinian N, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev* 2016;10:Cd002042. doi: 10.1002/14651858.CD002042.pub4 [published Online First: 2016/11/02]

9. Holst LB, Petersen MW, Haase N, et al. Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis. *Bmj* 2015;350:h1354.

10. Docherty AB, O'Donnell R, Brunskill S, et al. Effect of restrictive versus liberal transfusion strategies on outcomes in patients with cardiovascular disease in a non-cardiac surgery setting: systematic review and meta-analysis. *Bmj* 2016;352:i1351.

11. Fominskiy E, Putzu A, Monaco F, et al. Liberal transfusion strategy improves survival in perioperative but not in critically ill patients. A meta-analysis of randomised trials. *Br J Anaesth* 2015;115(4):511-19.

12. Brunskill SJ, Millette SL, Shokoohi A, et al. Red blood cell transfusion for people undergoing hip fracture surgery. *Cochrane Database Syst Rev* 2015(4)

13. Carson JL, Guyatt G, Heddle NM, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. *Jama* 2016;316(19):2025-35.

14. Grimshaw JM, Eccles MP, Lavis JN, et al. Knowledge translation of research findings. *Implement Sci* 2012;7(1):1.

15. Grimshaw JM, Eccles MP. Is evidence-based implementation of evidence-based care possible? *Med J Aust* 2004;180(6):S50.

16. 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. *Arch Intern Med* 2005;165(8):845-52.

17. Wilson K, MacDougall L, Fergusson D, et al. 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):1224-9.

18. Hibbs SP, Nielsen ND, Brunskill S, et al. The Impact of Electronic Decision Support on Transfusion Practice: A Systematic Review. *Transfus Med Rev* 2015;29(1):14-23. doi: http://dx.doi.org/10.1016/j.tmrv.2014.10.002

19. Meybohm P, Richards T, Isbister J, et al. Patient Blood Management Bundles to Facilitate Implementation. *Transfus Med Rev* 2017;31(1):62-71. doi: 10.1016/j.tmrv.2016.05.012 [published Online First: 2016/06/19]

20. 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.

21. Soril LJJ, Sparling M, Gill S, et al. The effectiveness of behavioural interventions targeting inappropriate physician transfusion practices: a systematic review protocol: University of York: Centre for Reviews and Dissemination; 2015 [cited 2016 November 25]. Available from: http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015024757 accessed November 25 2016.

22. Cook TD, Campbell DT. Quasi-experimentation: Design & analysis issues for field settings. Chicago: Rand McNally 1979.

23. Shadish WR, Cook TD, Campbell DT. Experimental and quasi-experimental designs for generalized causal inference: Wadsworth Cengage learning 2002.

24. Grimshaw J, Campbell M, Eccles M, et al. Experimental and quasi-experimental designs for evaluating guideline implementation strategies. *Fam Pract* 2000;17(90001):11-16.

25. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* 2011;343:d5928.

26. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;52(6):377-84.

27. Higgins J, Thompson SG. Quantifying heterogeneity in a meta‐analysis. *Stat Med* 2002;21(11):1539-58.

28. Duval S, Tweedie R. Trim and fill: a simple funnel‐plot–based method of testing and adjusting for publication bias in meta‐analysis. *Biometrics* 2000;56(2):455-63.

29. Goodnough LT, Shieh L, Hadhazy E, et al. Improved blood utilization using real-time clinical decision support. *Transfusion* 2014;54(5):1358-65. doi: http://dx.doi.org/10.1111/trf.12445

30. Goodnough LT, Maggio P, Hadhazy E, et al. Restrictive blood transfusion practices are associated with improved patient outcomes. *Transfusion* 2014;54(10 Pt 2):2753-9. doi: http://dx.doi.org/10.1111/trf.12723

31. Rothschild JM, McGurk S, Honour M, et al. Assessment of education and computerized decision support interventions for improving transfusion practice. *Transfusion* 2007;47(2):228-39.

32. Handler S. Does continuing medical education affect medical care. A study of improved transfusion practices. *Minn Med* 1983;66(3):167.

33. Abelow AG-G, A. Tadmor, B. Lahav, M. Shepshelovich, D. Educational interventions encouraging appropriate use of blood transfusions. *Vox Sang* 2017;112(2):150-55. doi: https://dx.doi.org/10.1111/vox.12493

34. Frank SMT, R. N. Podlasek, S. J. Ken Lee, K. H. Wintermeyer, T. L. Yang, W. W. Liu, J. Rotello, L. C. Fleury, T. A. Wachter, P. A. Ishii, L. E. Demski, R. Pronovost, P. J. Ness, P. M. Implementing a Health System-wide Patient Blood Management Program with a Clinical Community Approach. *Anesthesiology* 2017;127(5):754-64. doi: https://dx.doi.org/10.1097/ALN.0000000000001851

35. Heyes JK, P. A. Monaghan, K. Lawn, M. Dhesi, A. Mijovic, A. A single unit transfusion policy reduces red cell transfusions in general medical in-patients. *Qjm* 2017;110(11):735-39. doi: https://dx.doi.org/10.1093/qjmed/hcx150

36. Hicks CWL, J. Yang, W. W. DiBrito, S. R. Johnson, D. J. Brito, A. Higgins, R. S. D. Frank, S. M. Wick, E. C. A comprehensive Choosing Wisely quality improvement initiative reduces unnecessary transfusions in an Academic Department of Surgery. *Am J Surg* 2017;214(4):571-76. doi: https://dx.doi.org/10.1016/j.amjsurg.2017.06.020

37. Madrigal EP, S. Avadhani, V. Annen, K. Friedman, M. T. Adequacy of physician documentation and correlation with assessment of transfusion appropriateness: a follow-up study in the setting of prospective audits and patient blood management. *Transfusion* 2017;57(2):367-75. doi: https://dx.doi.org/10.1111/trf.13917

38. Norgaard AS, J. de Lichtenberg, T. H. White, J. O. Perner, A. Wanscher, M. Hillingso, J. Holm, M. L. Mau-Sorensen, M. Sillesen, H. Kjeldsen, L. Back, C. Nielsen, J. Seeberg, J. Hansen, M. B. Johansson, P. I. Three-year follow-up of implementation of evidence-based transfusion practice in a tertiary hospital. *Vox Sang* 2017;112(3):229-39. doi: https://dx.doi.org/10.1111/vox.12485

39. Despotis GJ, Grishaber JE, Goodnough LT. The effect of an intraoperative treatment algorithm on physicians' transfusion practice in cardiac surgery. *Transfusion* 1994;34(4):290-6.

40. Soumerai SB, Salem-Schatz S, Avorn J, et al. A controlled trial of educational outreach to improve blood transfusion practice. *Jama* 1993;270(8):961-6.

41. Alavi-Moghaddam M, Bardeh M, Alimohammadi H, et al. Blood transfusion practice before and after implementation of type and screen protocol in emergency department of a university affiliated hospital in iran. *Emerg Med Int* 2014;2014(316463) doi: http://dx.doi.org/10.1155/2014/316463

42. Andreasen JJ, Sindby JE, Brocki BC, et al. Efforts to change transfusion practice and reduce transfusion rates are effective in coronary artery bypass surgery. *J Cardiothorac Vasc Anesth* 2012;26(4):545-49. doi: http://dx.doi.org/10.1053/j.jvca.2012.02.006

43. Annan E, Fless KG, Jasani N, et al. Red Blood Cell Transfusion Practices: Can High-Intensity ICU Staffing Stem the Tide? *ICU Director* 2013;4(1):11-14. doi: http://dx.doi.org/10.1177/1944451612467534

44. Ansari S, Szallasi A. Blood management by transfusion triggers: when less is more. *Blood Transfus* 2012;10(1):28-33. doi: http://dx.doi.org/10.2450/2011.0108-10

45. Baer VL, Henry E, Lambert DK, et al. Implementing a program to improve compliance with neonatal intensive care unit transfusion guidelines was accompanied by a reduction in transfusion rate: a pre‐post analysis within a multihospital health care system. *Transfusion* 2011;51(2):264-69.

46. Beaty CA, Haggerty KA, Moser MG, et al. Disclosure of physician-specific behavior improves blood utilization protocol adherence in cardiac surgery. *Ann Thorac Surg* 2013;96(6):2168-74. doi: http://dx.doi.org/10.1016/j.athoracsur.2013.06.080

47. Brandis K, Richards B, Ghent A, et al. A strategy to reduce inappropriate red blood cell transfusion. *Med J Aust* 1994;160(11):721-2.

48. Brandt MM, Rubinfeld I, Jordan J, et al. Transfusion insurgency: practice change through education and evidence-based recommendations. *Am J Surg* 2009;197(3):279-83. doi: http://dx.doi.org/10.1016/j.amjsurg.2008.10.004

49. Butler CE, Noel S, Hibbs SP, et al. Implementation of a clinical decision support system improves compliance with restrictive transfusion policies in hematology patients. *Transfusion* 2015;55(8):1964-71.

50. Corwin HL, Theus JW, Cargile CS, et al. Red blood cell transfusion: Impact of an education program and a clinical guideline on transfusion practice. *J Hosp Med* 2014;9(12):745-49. doi: http://dx.doi.org/10.1002/jhm.2237

51. Gallagher-Swann M, Ingleby B, Cole C, et al. Improving transfusion practice: ongoing education and audit at two tertiary speciality hospitals in Western Australia. *Transfus Med* 2011;21(1):51-6. doi: http://dx.doi.org/10.1111/j.1365-3148.2010.01041.x

52. Gardner RM, Christiansen PD, Tate KE, et al. Computerized continuous quality improvement methods used to optimize blood transfusions. *Proc Annu Symp Comput Appl Med Care* 1993:166-70.

53. Garrioch M, Sandbach J, Pirie E, et al. Reducing red cell transfusion by audit, education and a new guideline in a large teaching hospital. *Transfus Med* 2004;14(1):25-31. doi: http://dx.doi.org/10.1111/j.0958-7578.2004.00476.x

54. Geissler RG, Kosters C, Franz D, et al. Utilisation of blood components in trauma surgery: A single-centre, retrospective analysis before and after the implementation of an educative PBM initiative. *Transfus Med Hemother* 2015;42(2):83-89. doi: http://dx.doi.org/10.1159/000377735

55. Gutsche JT, Kornfield ZN, Speck RM, et al. Impact of guideline implementation on transfusion practices in a surgical intensive care unit. *J Cardiothorac Vasc Anesth* 2013;27(6):1189-93. doi: http://dx.doi.org/10.1053/j.jvca.2013.05.040

56. Haldiman L, Zia H, Singh G. Improving appropriateness of blood utilization through prospective review of requests for blood products: the role of pathology residents as consultants. *Lab Med* 2014;45(3):264-71. doi: http://dx.doi.org/10.1309/LMSKRN7ND12ZOORW

57. Harrison BT, Chen J, Der Vartanian C, et al. Improving red cell transfusion in the elective surgical setting: An improvement collaborative with evaluation. *Vox Sang* 2015;108(4):393-402. doi: http://dx.doi.org/10.1111/vox.12237

58. King R, Michelman M, Curran V, et al. Patient-centered approach to ensuring appropriateness of care through blood management. *South Med J* 2013;106(6):362-8. doi: http://dx.doi.org/10.1097/SMJ.0b013e318296d9fa

59. Leahy MF, Roberts H, Mukhtar SA, et al. A pragmatic approach to embedding patient blood management in a tertiary hospital. *Transfusion* 2014;54(4):1133-45. doi: http://dx.doi.org/10.1111/trf.12362

60. Likosky DS, Surgenor SD, Dacey LJ, et al. Rationalising the treatment of anaemia in cardiac surgery: short and mid-term results from a local quality improvement initiative. *Qual Saf Health Care* 2010;19(5):392-8. doi: http://dx.doi.org/10.1136/qshc.2009.033456

61. Littenberg B, Corwin H, Gettinger A, et al. A practice guideline and decision aid for blood transfusion. *Immunohematology* 1995;11(3):88-94.

62. Lucas RE, Oberli H. An audit to assess the impact of a strategy to reduce inappropriate red cell transfusions at Honiara Hospital. *Trop Doct* 1997;27(2):97-9.

63. Mahar FK, Moiz B, Khurshid M, et al. Implementation of Maximum Surgical Blood Ordering Schedule and an Improvement in Transfusion Practices of Surgeons subsequent to Intervention. *Indian J* 2013;29(3):129-33. doi: http://dx.doi.org/10.1007/s12288-012-0169-4

64. Marconi M, Almini D, Pizzi MN, et al. Quality assurance of clinical transfusion practice by implementation of the privilege of blood prescription and computerized prospective audit of blood requests. *Transfus Med* 1996;6(1):11-9.

65. Markel DC, Allen MW, Zappa NM. Can an Arthroplasty Registry Help Decrease Transfusions in Primary Total Joint Replacement? A Quality Initiative. *Clin Orthop Relat Res* 2016;474(1):126-31.

66. McCrory MC, Strouse JJ, Takemoto CM, et al. Computerized physician order entry improves compliance with a manual exchange transfusion protocol in the pediatric intensive care unit. *J Pediatr Hematol Oncol* 2014;36(2):143-7. doi: http://dx.doi.org/10.1097/MPH.0b013e31828e55e6

67. Morrison JC, Sumrall DD, Chevalier SP, et al. The effect of provider education on blood utilization practices. *Am J Obstet Gynecol* 1993;169(5):1240-45.

68. Murphy DJ, Lyu PF, Gregg SR, et al. Using Incentives to Improve Resource Utilization: A Quasi-Experimental Evaluation of an ICU Quality Improvement Program. *Crit Care Med* 2016;44(1):162-70.

69. Oliver JC, Griffin RL, Hannon T, et al. The success of our patient blood management program depended on an institution-wide change in transfusion practices. *Transfusion* 2014;54(10 Pt 2):2617-24. doi: http://dx.doi.org/10.1111/trf.12536

70. Rana R, Afessa B, Keegan MT, et al. Evidence-based red cell transfusion in the critically ill: quality improvement using computerized physician order entry. *Crit Care Med* 2006;34(7):1892-7.

71. Rehm JP, Otto PS, West WW, et al. Hospital-wide educational program decreases red blood cell transfusions. *J Surg Res* 1998;75(2):183-6.

72. Rosen N, Bates L, Herod G. Transfusion therapy: improved patient care and resource utilization. *Transfusion* 1993;33(4):341-47.

73. Spencer J, Thomas SRYW, Yardy G, et al. Are we overusing blood transfusing after elective joint replacement? - A simple method to reduce the use of a scarce resource. *Ann R Coll Surg Engl* 2005;87(1):28-30. doi: http://dx.doi.org/10.1308/1478708051379

74. Tavares MM, Diquattro PJ, Sweeney JD. Reduction in red blood cell transfusion associated with engagement of the ordering physician. *Transfusion* 2014;54(10 Pt 2):2625-30. doi: http://dx.doi.org/10.1111/trf.12552

75. Ternstrom L, Hyllner M, Backlund E, et al. A structured blood conservation programme reduces transfusions and costs in cardiac surgery. *Interact Cardiovasc Thorac Surg* 2014;19(5):788-94. doi: http://dx.doi.org/10.1093/icvts/ivu266

76. Vos J, Gumodoka B, van Asten HA, et al. Changes in blood transfusion practices after the introduction of consensus guidelines in Mwanza region, Tanzania. *Aids* 1994;8(8):1135-40.

77. Yeh DD, Naraghi L, Larentzakis A, et al. Peer-to-peer physician feedback improves adherence to blood transfusion guidelines in the surgical intensive care unit. *J Trauma Acute Care Surg* 2015;79(1):65-70.

78. Yerrabothala S, Desrosiers KP, Szczepiorkowski ZM, et al. Significant reduction in red blood cell transfusions in a general hospital after successful implementation of a restrictive transfusion policy supported by prospective computerized order auditing. *Transfusion* 2014;54(10pt2):2640-45.

79. Zelinka ES, Brevig J, McDonald J, et al. The perfusionist's role in a collaborative multidisciplinary approach to blood transfusion reduction in cardiac surgery. *J Extra Corporeal Technol* 2010;42(1):45-51.

80. Boral LI, Bernard A, Hjorth T, et al. How do I implement a more restrictive transfusion trigger of hemoglobin level of 7g/dL at my hospital? *Transfusion* 2015;55(5):937-45. doi: http://dx.doi.org/10.1111/trf.12982

81. Hillman RS, Helbig S, Howes S, et al. The effect of an educational program on transfusion practices in a regional blood program. *Transfusion* 1979;19(2):153-7.

82. Joubert J, Joubert S, Raubenheimer J, et al. The long-term effects of training interventions on transfusion practice: A follow-up audit of red cell concentrate utilisation at Kimberley Hospital, South Africa. *Transfus Apher Sci* 2014;51(3):25-32. doi: http://dx.doi.org/10.1016/j.transci.2014.10.013

83. Leão SC, Gomes MAB, Aragão MCdA, et al. Practices for rational use of blood components in a universitary hospital. *Rev Assoc Med Bras* 2015;61(4):355-61.

84. Paone G, Brewer R, Likosky DS, et al. Transfusion rate as a quality metric: Is blood conservation a learnable skill? *Ann Thorac Surg* 2013;96(4):1279-84. doi: http://dx.doi.org/10.1016/j.athoracsur.2013.05.045

85. Valentine SL, Lightdale JR, Tran CM, et al. Assessment of hemoglobin threshold for packed RBC transfusion in a medical-surgical PICU. *Pediatr Crit Care Med* 2014;15(2):e89-94. doi: http://dx.doi.org/10.1097/PCC.0000000000000033

86. Yaffee DW, Smith IDE, Ursomanno PA, et al. Management of blood transfusion in aortic valve surgery: Impact of a blood conservation strategy. *Ann Thorac Surg* 2014;97(1):95-101. doi: http://dx.doi.org/10.1016/j.athoracsur.2013.09.057

87. Hoeg RT, Leinoe EB, Andersen P, et al. Measuring the impact of a restrictive transfusion guideline in patients with acute myeloid leukaemia. *Vox Sang* 2013;105(1):81-4. doi: http://dx.doi.org/10.1111/vox.12017

88. Horowitz PE, Lorenzen CM, Rhydderch RD. Limiting the usage of blood products in cardiovascular surgery. *Ann Saudi Med* 1991;11(2):213-7.

89. McSwiney M, O'Farrell D, Joshi G, et al. Blood transfusion in total hip arthroplasty: guidelines to eliminate overtransfusion. *Can J Anaesth* 1993;40(3):222-26.

90. Muller U, Exadaktylos A, Roeder C, et al. Effect of a flow chart on use of blood transfusions in primary total hip and knee replacement: prospective before and after study.[Erratum appears in BMJ. 2005 Feb;14(1):72], [Erratum appears in BMJ. 2004 Oct 9;329(7470):837]. *Bmj* 2004;328(7445):934-8.

91. Ciccocioppo A, Walker M, Taylor F, et al. Protocol management for patients presenting with lower GI haemorrhage saves costs and maintains outcomes. *ANZ J Surg* 2011;81(6):451-55. doi: http://dx.doi.org/10.1111/j.1445-2197.2010.05603.x

92. Lee Q-J, Mak W-P, Yeung S-T, et al. Blood management protocol for total knee arthroplasty to reduce blood wastage and unnecessary transfusion. *J Orthop Surg* 2015;23(1):66.

93. Rineau E, Chaudet A, Chassier C, et al. Implementing a blood management protocol during the entire perioperative period allows a reduction in transfusion rate in major orthopedic surgery: a before–after study. *Transfusion* 2016

94. Vrotsos E, Gonzalez B, Goldszer RC, et al. Improving blood transfusion practice by educational emphasis of the Blood Utilization Committee: experience of one hospital. *Transfus Clin Biol* 2015;22(1):1-4. doi: http://dx.doi.org/10.1016/j.tracli.2014.07.002

95. Whitney G, Daves S, Hughes A, et al. Implementation of a transfusion algorithm to reduce blood product utilization in pediatric cardiac surgery. *Paediatr Anaesth* 2013;23(7):639-46. doi: http://dx.doi.org/10.1111/pan.12126

96. Torella F, Haynes SL, Bennett J, et al. Can hospital transfusion committees change transfusion practice? *J R Soc Med* 2002;95(9):450-52.

97. Adams ES, Longhurst CA, Pageler N, et al. Computerized physician order entry with decision support decreases blood transfusions in children. *Pediatrics* 2011;127(5):e1112-e19.

98. Fernandez Perez ER, Winters JL, Gajic O. The addition of decision support into computerized physician order entry reduces red blood cell transfusion resource utilization in the intensive care unit. *Am J Hematol* 2007;82(7):631-3.

99. McWilliams B, Triulzi DJ, Waters JH, et al. Trends in RBC ordering and use after implementing adaptive alerts in the electronic computerized physician order entry system. *Am J Clin Pathol* 2014;141(4):534-41. doi: http://dx.doi.org/10.1309/AJCPEN6VHT0ECAFI

100. Pentti J, Syrjälä M, Pettilä V. Computerized quality assurance of decisions to transfuse blood components to critically ill patients. *Acta Anaesthesiol Scand* 2003;47(8):973-78.

101. Lewis CM, Monroe MM, Roberts DB, et al. An audit and feedback system for effective quality improvement in head and neck surgery: Can we become better surgeons? *Cancer* 2015;121(10):1581-7. doi: http://dx.doi.org/10.1002/cncr.29238

102. Tuckfield A, Haeusler MN, Grigg AP, et al. Reduction of inappropriate use of blood products by prospective monitoring of transfusion request forms. *Med J Aust* 1997;167(9):473-76.

103. Politsmakher A, Doddapaneni V, Seeratan R, et al. Effective reduction of blood product use in a community teaching hospital: when less is more. *Am J Med* 2013;126(10):894-902. doi: http://dx.doi.org/10.1016/j.amjmed.2013.06.013

104. Larson EAT, P. A. Anderson, Z. K. Anderson, K. A. Lupu, R. A. Tigner, V. Hoffman, W. W. Decreasing the critical value of hemoglobin required for physician notification reduces the rate of blood transfusions. *Int J Gen Med* 2016;9:133-6. doi: https://dx.doi.org/10.2147/IJGM.S96248

105. Meybohm P, Herrmann E, Steinbicker AU, et al. Patient Blood Management is Associated With a Substantial Reduction of Red Blood Cell Utilization and Safe for Patient's Outcome: A Prospective, Multicenter Cohort Study With a Noninferiority Design. *Ann Surg* 2016;264(2):203-11. doi: 10.1097/sla.0000000000001747 [published Online First: 2016/05/11]

106. Tseng ES, J. Cao, X. Callum, J. Lin, Y. An order set and checklist improve physician transfusion ordering practices to mitigate the risk of transfusion-associated circulatory overload. *Transfus Med* 2016;26(2):104-10. doi: https://dx.doi.org/10.1111/tme.12284

107. Eindhoven GB, Diercks RL, Richardson FJ, et al. Adjusted transfusion triggers improve transfusion practice in orthopaedic surgery. *Transfus Med* 2005;15(1):13-8.

108. Lam HT, Schweitzer SO, Petz L, et al. Effectiveness of a prospective physician self-audit transfusion-monitoring system. *Transfusion* 1997;37(6):577-84.

109. Joyce KM, Byrne D, O'Connor P, et al. An evaluation of the use of deliberate practice and simulation to train interns in requesting blood products. *Simul Healthc* 2015;10(2):92-97.

110. Hassan NE, Winters J, Winterhalter K, et al. Effects of blood conservation on the incidence of anemia and transfusions in pediatric parapneumonic effusion: a hospitalist perspective. *J Hosp Med* 2010;5(7):410-3. doi: http://dx.doi.org/10.1002/jhm.700

111. Lam H, Schweitzer S, Petz L, et al. Are retrospective peer-review transfusion monitoring systems effective in reducing red blood cell utilization? *Arch Pathol Lab Med* 1996;120:810-16.

112. Hébert PC, Wells G, Marshall J, et al. Transfusion requirements in critical care: a pilot study. *Jama* 1995;273(18):1439-44.

113. Tinmouth A. Reducing the amount of blood transfused by changing clinicians' transfusion practices. *Transfusion* 2007;47(s2):132S-36S.

114. Ivers N, Jamtvedt G, Flottorp S, et al. Audit and feedback: effects on professional practice and healthcare outcomes. *Cochrane Database Syst Rev* 2012(7)

115. Michie S, Johnston M, Abraham C, et al. Making psychological theory useful for implementing evidence based practice: a consensus approach. *Qual Saf Health Care* 2005;14(1):26-33.

116. Colquhoun HL, Squires JE, Kolehmainen N, et al. Methods for designing interventions to change healthcare professionals' behaviour: a systematic review. *Implement Sci* 2017;12(1):30.

117. Grimshaw JM, Thomas RE, MacLennan G, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health technology assessment (Winchester, England)* 2004;8(6):iii-iv, 1-72. [published Online First: 2004/02/13]

118. Fergusson D, Hebert P, Shapiro S. The before/after study design in transfusion medicine: methodologic considerations. *Transfus Med Rev* 2002;16(4):296-303.

119. Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. *Bmj* 2013;346:f2914.

120. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0; The Cochrane Collaboration March 2015 [cited 2016 November 25]. Available from: http://www.handbook.cochrane.org accessed November 25 2016.

121. Ford I, Norrie J. Pragmatic trials. *New England Journal of Medicine* 2016;375(5):454-63.

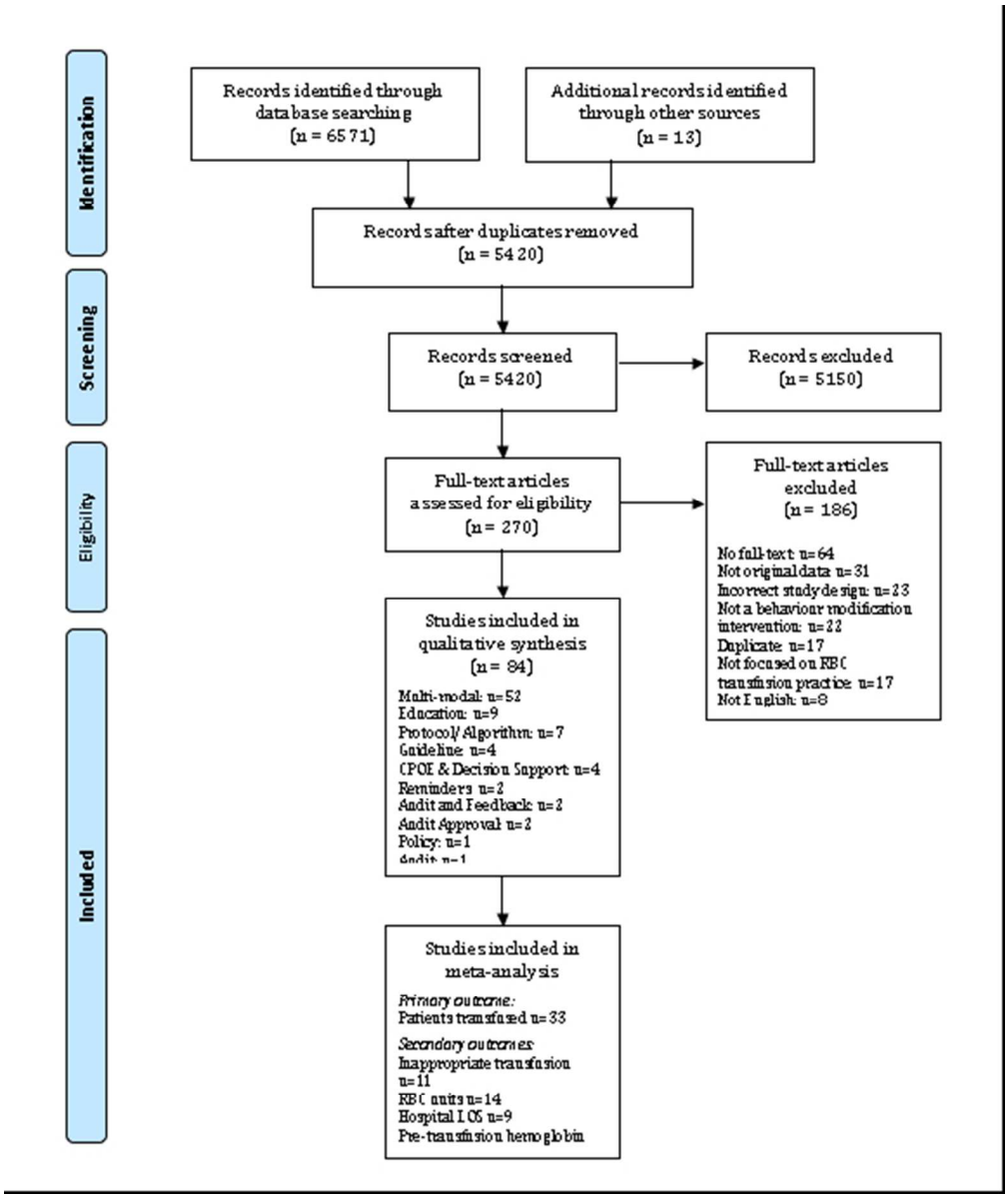
FIGURE LEGENDS

Figure 1. Preferred Reporting for Systematic Reviews and Meta-analyses (PRISMA) Flow Diagram of Included Studies.

Figure 2. Forest Plot of Odds of Patients Being Transfused, Stratified by Intervention.

Figure 3. Filled Funnel Plot with Pseudo 95% Confidence Limits.

The open circles represent the included studies and the squares with circles represent the imputed studies. The horizontal line represents the estimated measure of effect following the trim-and-fill method and the diagonal lines forming the triangle region represent the pseudo 95% confidence limits.



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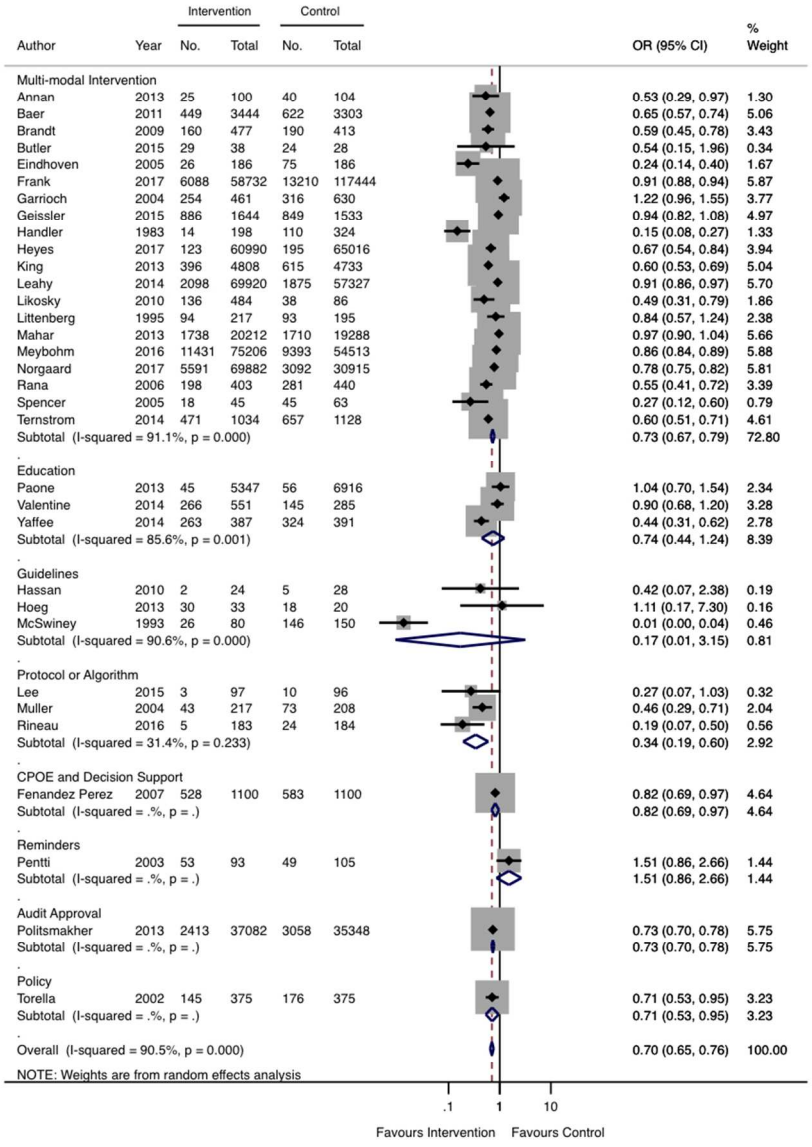

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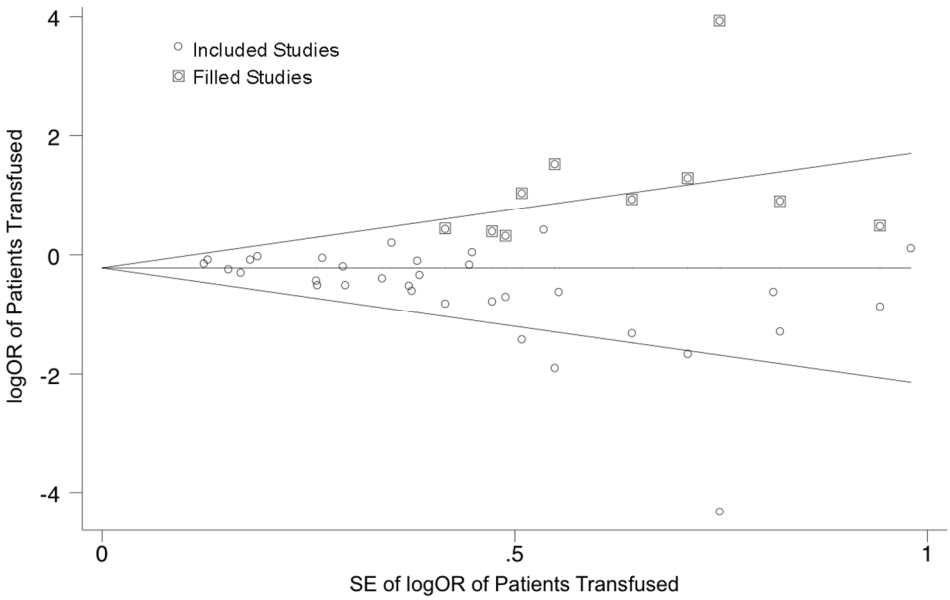

Figure 3. Filled Funnel Plot with Pseudo 95% Confidence Limits

Supplementary File 1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page # of Manuscript File (unless otherwise indicated)
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary File 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8, Supplementary File 4

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-10
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10-14, Supplementary File 5-6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	14-15, Supplementary Files 7-8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	15-18, Figure 2, Supplementary Files 9-15

Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	15-18, Figure 2, Supplementary Files 9-15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	18-19 Figure 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	18 Supplementary File 16
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-21, 22-24
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	25

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplementary File 2. Study Protocol

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

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Supplementary File 2. Study Protocol

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.

Supplementary File 2. Study Protocol

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)

Supplementary File 2. Study Protocol

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

Supplementary File 2. Study Protocol

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

Supplementary File 2. Study Protocol

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.

Supplementary File 2. Study Protocol

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.

Supplementary File 2. Study Protocol

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

Supplementary File 3. Sample Search Strategy

MEDLINE May 2016
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

Supplementary File 4. Inclusion and Exclusion Criteria for Review of Full-text Articles

Inclusion Criteria	Exclusion Criteria
Full-text articles	Articles not available in full-text (i.e. title or abstracts only)
Original data	Non-original data
Peer-reviewed articles	Grey literature
Physicians and other healthcare providers prescribing/ordering transfusions (any healthcare setting)	Animal studies
RCT or quasi-experimental studies	Case studies, commentaries, editorials, letters, opinions
Primary objective: efficacy/effectiveness of intervention to modify RBC transfusion practices	Not focused on primary objective
Interventions: behaviour modification intervention targeted at healthcare provider RBC transfusion practice (e.g. education, guidelines, audit and feedback, order entry systems, etc.)	Not a behaviour modification intervention
Comparator: any intervention including no intervention (i.e. standard of care, historical controls)	No comparator
Any outcomes (e.g. physician compliance or patient outcomes)	

Supplementary File 5. Characteristics of Included Studies

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
Multi-modal Interventions									
Abelow[33] (2017) Israel	Tertiary care centre	All physicians and nurses from transfusion service, medical, haematology –oncology, surgical and obstetric wards, and anaesthesia	RBC	Before and After	Historical Control	1 year	Hgb levels below 7 g/dL, or under 8 g/dL in the presence of active ischemia, active bleeding, or symptomatic anemia	NR	Education, Reminders
Alavi-Moghaddam[41] (2014) Iran	ED in one academic and general medical/surgical hospital	All ED staff and blood bank technicians	Blood	Before and After	Historical Control	3 months	NR	NR	Protocol, Education
Andreasen[42] (2012) Denmark	Cardiac surgeries in one academically -affiliated hospital	Anesthesiol-gists, surgeons, intensivists, and nurses	RBC, FFP, platelets	Before and After	Historical Control	24 months	NR	Defined over-transfusion as proportion of patients transfused with RBCs discharged with hemoglobin 7 mmol/L (11.3 g/dL)	Education, Guideline, Algorithm
Annan[43] (2013)	ICU in one academically	All ICU staff	RBC	Before and	Historical	1 month	NR	NR	"High-intensity ICU staffing

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Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
United States	-affiliated community hospital			After	Control				(HIS)", including: changes in Protocols, CPOE and Decision Support
Ansari[44] (2012) United States	One community hospital	All physicians ordering transfusions	RBC	Before and After	Historical Control	12 months	1) Acute bleeding (blood loss of >30%) with tachycardia and low blood pressure; 2) Hgb <9 g/dL in high-risk patients; 3) Hgb <7 g/dL in patients with symptomatic chronic anaemia; 4) Special circumstances (e.g. sickle cell crisis and other causes of poor oxygen delivery)	Transfusions that did not meet established criteria, including pre-transfusion hgb level greater than 9 g/dL	Guideline, Audit & Feedback
Baer[45] (2011) United States	Four neonatal ICUs in one healthcare system	All neonatal ICU staff	RBC	Before and After	Historical Control	12 months	Hematocrit falls below: • 40% for a patient on extracorporeal membrane oxygenation, • 35% for a patient on	N/A	Guideline, CPOE and Decision Support, and Audit

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
							mechanical ventilation 27% for a patient on supplemental oxygen or with signs of anemia but not on mechanical ventilation, • 20% in any neonatal ICU patient		
Beaty[46] (2013) United States	Cardiac surgical ICU in one academic hospital	Cardiac surgery attendings, cardiac residents, and ICU providers (intensivists, surgery residents, and mid-level providers)	RBC	Before and After	Historical Control	17 weeks	Hgb level of less than 8 g/dL	Transfusion trigger of hgb >8 g/dL	Protocol, Audit and Feedback
Brandis[47] (1994) Australia	One acute care hospital	All medical staff that order transfusions in anesthetics, surgery and	RBC	Before and After	Historical Control	6 months	Hgb level 7 g/dL	N/A	Education, Protocol, Policies

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
		ICU							
Brandt[48] (2009) United States	Surgical ICU in one hospital	Intensivists, fellows, and residents	RBC	Before and After	Historical Control	6 years	Hgb level 8 g/dL	NA	Protocol, Education (to residents)
Butler[49] (2015) United Kingdom	Inpatient hematology services in one academic hospital	Clinical hematolog-ists treating patients receiving intensive chemotherap y or hematopoie-tic stem cell transplants	RBC, platelets	Before and After	Historical Control	10 months	1) Massive bleeding with blood pressure instability; 2) Hgb 7 g/dL in a stable ICU patient; 3) Hgb 8.0 g/dL in a non-ICU patient with signs/symptoms of anemia; 4) Hgb 10 g/dL with acute cardiac ischemia; 5) Surgical blood loss anticipated	Above the recommended trigger of 8 g/dL	Education, CPOE and Decision Support, Audit and Feedback
Corwin[50] (2014) United States	One level 1 trauma centre	Clinical staff in all major clinical departments, high-volume transfusing services, and residents	RBC	Before and After	Historical Control	18 months	1) Acute hemorrhage or hemorrhagic shock; 2) Hgb <7–8 g/dL; 3) Acute MI, Hgb 8 g/dL; 4) Acute coronary syndrome Hgb 8 g/dL;	NA	Education, Guideline, CPOE and Decision Support

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
							Use of the hgb concentration alone as a trigger for RBC transfusion was recommended against; decision to order an RBC transfusion should also consider a patient's intravascular volume status, evidence of shock, duration and extent of anemia, and cardiopulmonary physiologic parameters as well as other symptomatology.		
Eindhoven[107] (2005) Netherlands	Two hospitals	All physicians and nurses treating patients undergoing elective, primary total hip replacement	RBC	Controlled Before and After	Standard of care in one hospital (i.e. patients transfused at a Hgb level below 10g/dL or haematocr-it level below 30%);	12 months	1) Presence of anaemia-related symptoms and signs; 2) Diminished oxygen uptake in the lungs due to respiratory disease; 3) Inability of the patient to	N/A	Education, Guideline (referred to as "6-8-10 Flexinorm")

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
					Historical Control		compensate for the effects of haemodilution; 4) Estimated blood loss and increased risk of re-bleeding; 5) Enhanced need for oxygen delivery (high body temperature, shivering and sepsis); and (6) Presence of symptoms or signs of atherosclerosis of heart, brain or renal vessels.		
Frank[34] (2017) United States	Two academic centers and three community hospitals	All medical staff ordering blood products	RBC, FFP, platelets	Before and After	Historical Controls	30 months	Hgb less than 7 g/dL	Hgb greater than or equal to 7 g/dL	"Patient Blood Management Program", including Education, Guidelines, CPOE and Decision Support, Audit and Feedback
Gallagher-Swann[51] (2011) Australia	Two hospitals: one tertiary maternity and	All medical staff in adult, neonatal, and	Blood	Before and After	Historical Control	28 months	NR	NR	Protocol, Education, Reminders

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
	gynaecological hospital; and one tertiary paediatric hospital	antenatal, and pediatric settings							
Gardner[52] (1993) United States	One tertiary hospital	All physicians and nurses ordering blood	Blood	Before and After	Historical Control	3 months	If ordering for anemia for packed cells: hgb < 10 g/dL or hematocrit below 30%	Defined over-transfusions as those that did not meet the transfusion criteria	CPOE and Decision Support, Audit and Feedback
Garrioch[53] (2004) United Kingdom (Scotland)	One academic hospital	All physicians	RBC	Before and After	Historical Control	3 months	NR	NR	Education, Guideline, Audit and Feedback, Reminders
Geissler[54] (2015) Germany	One trauma centre	All medical staff involved in cardiac surgeries (e.g. heart transplantation, aortic surgery, valve surgery)	RBC, FFP, platelets	Before and After	Historical Control	12 months	NR	NR	"Patient Blood Management (PBM) Initiative", including Education, Guidelines Audit and Feedback, and Policies
Goodnough[29 30] (2014a; 2014b) United States	One academic hospital	All physicians ordering transfusions	RBC	Before and After	Historical Control	36 months	Hgb level of 7 g/dL stable medical and surgical inpatients who were not bleeding, or 8	NR	Education, CPOE and Decision Support

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
							g/dL for patients with acute coronary syndromes		
Gutsche[55] (2013) United States	Surgical ICU in one academic hospital	Cardiologi-sts, cardiac surgeons, anesthesiolo-gists, and intensivists involved in the care of cardiac surgery patients	RBC	Before and After	Historical Control	6 months	Transfusion associated with a pre-transfusion hgb <7.0 g/dL	Transfusion associated with a hgb from 7 mg/dL to 7.9 mg/dL without evidence of organ ischemia, shock, pressor requirement, or hemorrhage	Education, Guideline, Audit and Feedback
Haldiman[56] (2014) United States	One tertiary-care, Level I trauma hospital	All physicians ordering transfusions	RBC, FFP, platelets, cryoprecipita te	Before and After	Historical Control	36 months	Hgb level of 8 g/dL or less and a hematocrit level of 24% or less as a trigger point	Transfusions not compliant with guideline	Guideline, Audit
Handler[32] (1983) United States	One community hospital	Surgeons	RBC	Between groups	Standard of care in four hospitals	12 months	NR	NR	Education, Audit and Feedback
Harrison[57] (2015) Australia	Regional healthcare system comprised of 232 public hospitals	Surgeons in five surgical groups: cardio-thoracic, colorectal, gynaecology and obstetrics, Orthopaedic,	RBC	Before and After	Historical Control	12 months	NR	When the Hgb min ≥ 100 g/dl post-operation; when Hgb min ≥ 70 g/l and ≤100 g/l and when no clinical indications are present; and when Hgb max levels	"Blood Watch Program" that involved 21 different system and behaviour modifying interventions, including Education, Audit and Feedback

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
		and general surgery						≤ 70 g/l when clinically indicated	
Heyes[35] (2017) United Kingdom	Eight general medical wards at one hospital	All physicians	RBC	Before and after	Historical Control	6 months	Hgb level 7 g/dl for non-bleeding patients	Hgb 10 g/dl	Education, Policy
Hicks[36] (2017) United States	Department of surgery in one academic hospital	Attending physicians, clinical fellows, residents, and mid-level providers	RBC, plasma, platelets	Before and After	Historical Control	9 months	Hgb level 7 g/dL for standard patients, 8 g/dL for cardiovascular disease	NR	Education, Audit and Feedback
King[58] (2013) United States	One community hospital	All physicians	RBC	Before and After	Historical Control	8 months	Hgb level 7 g/dL	NR	Education, Guideline, Audit and Feedback
Larson[104] (2016) United States	One community hospital	All physicians	RBC	Before and After	Historical Control	5 months	Hgb level 7 g/dL	Hgb greater than or equal to 7 g/dL	Education, Policy Audit approval
Leahy[59] (2014) Australia	One academic hospital	All physicians	RBC	Before and After	Historical Control	36 months	NR	NR	"Patient Blood Management Programme", including Protocol, Education, Guideline, Audit and Feedback, CPOE and decision support

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Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
Likosky[60] (2010) United States	Departments of medicine, surgery, anesthesia, and pathology, and disciplines from nursing, cardiothorac -ic surgery, anaesthesia, perfusion, quality improve- ment, transfusion medicine and epidemiolog y in one hospital	Surgeons treating non-emergent isolated coronary artery bypass graft surgery	RBC	Before and After	Historical Control	27 months	1) Intra-operative patients: when haematocrit falls below 19% on cardiopulmonary bypass 2) Post-operative patients <75 years: when haematocrit falls below 21% after the procedure until the patient was discharged from the hospital 3) Patients >75 years: when haematocrit falls below 24% after the procedure until the patient was discharged from the hospital	NR	Protocol, Education, Audit and Feedback
Littenberg[61] (1995) United States	ICU in one hospital	Intensivists	RBC	Before and After	Historical Control	3 months	During intervention period: Hgb < 8.6 g/dL or hematocrit < 26% During follow-up period: Hgb <= 7 g/dL or hematocrit <=21%	NR	Guideline, Order Form and Decision Support, Audit

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Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
Lucas[62] (1997) Australia	One hospital	All physicians	Blood	Before and After	Historical Control	3 months	Hgb level 80 g/L	NR	Education, Guideline
Mahar[63] (2013) Pakistan	One tertiary care, academic hospital	All physicians	RBC	Before and After	Historical Control	12 months	NR	NR	Protocol, Education
Marconi[64] (1996) Italy	One academic hospital	All physicians	RBC	Before and After	Historical Control	6 months	NR	Post-operative hematocrit above 36%	Protocol, Education, Guideline, CPOE and Decision Support
Markel[65] (2016) United States	Orthopedic services in two "peer" hospitals	Orthopaedic service line practitioners treating patients with primary total joint arthroplasty	RBC	Before and After	Historical Control	6 months	In post-operative patients: pre-transfusion hgb of 8 g/dL or less or for symptoms of chest pain, orthostatic hypotension, tachycardia unresponsive to fluid resuscitation, congestive heart failure	NR	Education, Guideline, Audit and Feedback
McCrory[66] (2014) United States	Pediatric ICU in one children's hospital	Pediatric ICU and pediatric hematology attending physicians	RBC	Before and After	Historical Control	24 months	NR	NR	Protocol, CPOE and Decision Support

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
Meybohm[105] (2016) Germany	Four academic hospitals	All staff	RBC	Before and After	Historical Control	21 months	Hgb < 6 g/dL independent of any compensation possibility; Hgb 6-8 g/dL clinical symptoms of anemix hypoxia, limited compensation, existing risk factors	NR	"Patient Blood Management program", including Education, Guidelines, Checklist
Morrison[67] (1993) United States	Department of Obstetrics and Gynecology in one academic hospital	All staff physicians and residents	RBC, FFP, platelets	Before and After	Historical Control	10 months	NR	NR	Education, Guideline, Audit and Feedback, Paper Order Form
Murphy[68] (2016) United States	Seven ICUs in an academic healthcare system	Intensivists, advanced practice providers (APPs) (i.e. nurse practitioners and physician assistants), and physicians in training	RBC	Before and After	Historical Control	12 months	NR	NR	Education, Audit and Feedback, and Unit-based Provider Financial Incentives
Norgaard[38] (2017)	One tertiary care hospital	All physicians	RBC	Before and After	Historical Control	12 months	Hgb 7.3 g/dL for stable non-	Hgb > 9.7 g/dL	"Patient Blood Management

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
Denmark		and nurses					bleeding patients		Intervention", including Education, Guidelines, Audit and Feedback
Oliver[69] (2014) United States	One academic hospital	All physicians	RBC, FFP, platelets	Before and After	Historical Control	6 months	Hgb 7 g/dL or less in non-bleeding patients (as per TRICC trial) • Transfuse 1 unit and reassess unless ongoing blood loss (1500 - 2000ml) or hemodynamic instability • Exceptions: active coronary ischemia, ongoing blood loss, severe sepsis/septic shock	Not	Education, Guideline, Audit and Feedback
Rana[70] (2006) United States	Multidisciplinary ICU (medical, surgical, and mixed) in one tertiary academic	All ICU physicians and nurses	RBC	Before and After	Historical Control	3 months	Hgb level 7g/dL	Pre-transfusion hgb >7 g/dL in the absence of active bleeding, early septic shock, or ischemia	Education, CPOE and Decision Support, Algorithm

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
	hospital								
Rehm[71] (1998) United States	One Veteran Affairs hospital	All staff and residents in medical and surgical specialties from two local university programmes	RBC	Before and After	Historical Control	12 months	Hgb level <7 g/dL	Hgb level >10 g/dL	Paper order form and Decision Support, Audit and Feedback, Audit Approval, Reminders
Rosen[72] (1993) United States	One private tertiary care hospital	All staff	RBC, FFP, platelets, cryoprecipit-ate	Before and After	Historical Control	36 months	Hgb level <8g/dL	Transfusions not meeting transfusion criteria	Education, Guideline, CPOE and Decision Support, Audit and Feedback
Rothschild[31] (2007) United States	One academic hospital	All staff	RBC, FFP, platelets	Before and After	Historical Control	3 months	Hematocrit <21%	Transfusions not meeting transfusion criteria	Education, Guideline
Spencer[73] (2005) United States	One hospital	All anesthetic and surgical staff treating patients undergoing hip and knee arthroplasty	RBC	Before and After	Historical Control	12 months	Signs of cardiovascular instability from excessive intra-operative blood loss, was symptomatically anaemic postoperatively, or the hgb level fell below 8 g/dL	Transfusions not meeting transfusion criteria	Guideline, Paper Order Form and Decision Support, Audit and Feedback, Reminders
Tavares[74] (2014)	One academic	All staff	RBC	Before and After	Historical Control	9 years	Hgb level between 8-9 g/dL	Hgb level >9g/dL recommended for	Education, Audit Approval

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
United States	tertiary care hospital							cancellation	
Ternstrom[75] (2014) Sweden	Cardiac surgery services in one academic hospital	All staff particularly surgeons, anaesthetis-ts, residents, OR-, ICU- and ward nurses, nurse helpers, physiothera-pists and perfusionists	RBC, plasma, platelets	Before and after	Historical Control	24 months	Hgb level <6 g/dL	NR	"Blood Conservation Programme" consisting of Education, Guidelines, and Self-Audit
Tseng[106] (2016) Canada	One academic hospital	Residents or attending physicians	RBC	Before and After	Historical Control	3 months	Bleeding patients: hgb < 8 g/dL Non-bleeding patients: hgb < 6 g/dL	NR	Checklist, Order Set
Vos[76] (1994) Tanzania	Eight hospitals: four government hospitals and three missions hospitals	All physicians	All blood components	Before and After	Historical Control	24 months	1) Operated patients: hgb >10 g/dL; 2) Pregnancy: hgb >7 g/dL when >36 weeks, hgb >6 g/dL when <36 weeks; 3) children: hgb >4 g/dL; other: hgb >5 g/dL	NR	Education, Guideline
Yeh[77] (2015) United States	Surgical ICU in one tertiary care	Residents, fellows, attending	RBC	Before and After	Historical Control	6 months	Hgb level <8 g/dL	Hgb level >8 g/dL	Education, Audit and Feedback

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
	hospital	physicians of both ICU and surgical teams							
Yerrabothala[78] (2014) United States	One academic tertiary care hospital	All staff	RBC	Before and After	Historical Control	6 months	Hgb level < 7g/dL	Transfusions not meeting transfusion criteria	CPOE and Decision Support, Policy
Zelinka[79] (2010) United States	Cardiac surgery services in one community hospital	All medical staff involved in cardiac surgeries	RBC	Before and After	Historical Control	4 years	NR	NR	
Single Interventions									
Boral[80] (2015) United States	One tertiary care hospital	All medical, surgical, nursing and blood bank staff	RBC	Before and After	Historical Control	36 months	Hgb level of 7 g/dL or Hct of 21%	NR	Education
Hillman[81] (1979) United States	Twenty-two area hospitals	All physicians	RBC, whole blood	Before and After	Historical Control	6 months	NR	NR	Education
Joubert[82] (2014) South Africa	Departments of internal medicine, intensive care, obstetrics & gynaecology and general surgery in	All physicians	RBC	Before and After	Historical Control	2 weeks	Usually appropriate when Hgb ≤ 6.9 g/dL; When Hb 7.0–9.9 g/dL depends on clinical picture	NR required when Hgb level >10g/dL	Education

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Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
	one hospital								
Joyce[109] (2015) Ireland	One academic hospital	Interns	All blood components	Between Groups	Standard of Care	3 months	NR	NR	Education
Leão[83] (2015) Brazil	One academic hospital	All physicians, nurses, and nursing technicians	RBC	Before and After	Historical Control	6 months	NR	NR	Education
Paone[84] (2013) United States	Thirty-three hospitals in one state	Cardiac surgeons	RBC, FFP, platelets	Before and After	Historical Control	4 years	NR	NR	Education
Soumerai[40] (1993) United States	Surgical and medical services from two academic and two community hospitals	Surgeons in orthopedic, vascular, and general surgery and general medicine attending physicians	RBC	Cluster RCT (service-level)	Standard of Care	6 months	1) Hematocrit <24%, a fall in hematocrit of 6 percentage points or more within 24 hours, or 2) A pre-transfusion hematocrit between 24% and 30% in the presence of one of the following: angina within 24 hours prior to transfusion, myocardial infarction within 6 weeks prior to transfusion, an	Transfusions not meeting transfusion criteria	Education

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
							electrocardiogram indicating acute ischemia or acute infarction, or 3) Blood loss of 1000 mL or greater prior to transfusion		
Valentine[85] (2014) United States	Medical-surgical pediatric ICU in one children's hospital	Pediatric intensivists	RBC, whole blood	Before and After	Historical Control	24 months	Hgb level <7 g/dL	NR	Education
Yaffee[86] (2014) United States	Cardiac surgery services in one hospital	Surgeons, surgical residents, anesthesiol-ogists, perfusionis-ts, and recovery room and intensive care unit nurses, operating on aortic valve replacement patients	RBC	Before and After	Historical Control	24 months	Hgb level <8 g/dL	NR	Education
Hassan[110] (2010) United States	One children's hospital	General pediatricians and	Blood	Between Groups	Standard of Care	36 months	NR	NR	Guideline

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
		hospitalists							
Hoeg[87] (2013) Denmark	Hematology department in one university hospital	All medical staff treating patients with acute myeloid leukemia	RBC	Before and After	Historical Control	36 months	Hgb level between 7.3 and 9.7 g/dL and only in the presence of symptomatic anaemia, coronary artery disease, ongoing blood loss or sepsis	NR	Guideline
Horowitz[88] (1991) Saudi Arabia	One hospital	All physicians treating cardiac surgery patients	RBC, FFP, platelets, cryoprecipitate	Before and After	Historical Control	6 months	NR	Transfusions not justified by the results of hgb levels (not specified) and coagulation tests	Guideline
McSwiney[89] (1993) Ireland	Anesthesia department in one hospital	All physicians treating patients undergoing total hip arthroplasty	Blood	Before and After	Historical Control	NR	Hematocrit less than 30 in men and 27 in women	Discharge hematocrit exceeding 36%	Guideline
Ciccocioppo[91] (2011) Australia	One hospital	All medical staff treating patients with lower GI bleed	RBC	Before and After	Historical Control	30 months	NR	NR	Protocol
Despotis[39] (1994) United States	One hospital	Anesthesiol-ogy and surgery staff physicians treating	RBC, FFP, platelets	RCT (individual-level)	Standard of Care	NR	NR	NR	Algorithm

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
		cardiac surgery patients							
Lee[92] (2015) China	One hospital	Physicians treating patients for total knee replacement	Blood	Before and After	Historical Control	4 months	NR	NR	Protocol
Muller[90] (2004) Switzerland	Orthopedic unit and intensive care unit in tertiary care hospital	Nurses and physicians in orthopaedic, anaesthesio-logy, and intensive care treating patients underoing total joint replacement	RBC	Before and After	Historical Control	NR	Multi-criteria based on implemented guideline	NR	Algorithm
Rineau[93] (2016) France	Orthopaedic surgery service in one academic hospital	All physicians treating patients undergoing total hip arthroplasty or total knee arthroplasty	Blood	Before and After	Historical Control	6 months	Hgb level <7 or 8 g/dL depending on cormobidities	NR	Protocol
Vrotsos[94] (2015) United States	Cardiac unit in one hospital	All physicians	Blood	Before and After	Historical Control	6 months	NR	NR	Protocol
Whitney[95] (2013)	Pediatric operating	All physicians	RBC, plasma,	Before and After	Historical Control	12 months	NR	NR	Protocol

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
United States	rooms and ICU in one tertiary care children's hospital	treating pediatric cardiac surgery patients	platelets, cryoprecipitate						
Torella[96] (2002) United Kingdom	One academic hospital	All physicians treating patients undergoing coronary artery bypass graft surgery, total hip replacement, colectomy, and transurethral prostatect-omy.	RBC	Before and After	Historical Control	6 months	Hgb level <8g/dL in the absence of symptoms	NR	Policy
Adams[97] (2011) United States	Acute care and Pediatric ICU wards in one children's hospital	Pediatricians and pediatric intensivists	RBC	Before and After	Historical Control	12 months	NR	NR	CPOE and Decision Support
Fernandez Perez[98] (2007) United States	Three multi-disciplinary ICUs in one hospital	Intensivists	RBC	Before and After	Historical Control	12 months	Hgb level >7 g/dL in the presence of active bleeding, ischemia or early septic shock	NR	CPOE and Decision Support

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
McWilliams[99] (2014) United States	Eleven hospitals in a regional healthcare system, including level 1 trauma centers, a cancer treatment hospital, and one centre specializing in women's health	All physicians	RBC	Before and After	Historical Control	10 months	1) Hgb level of 8.0 g/dL or lower in a non–ICU patient with signs and symptoms of anemia 2) Hgb level of 7.5 g/dL or lower in a stable ICU patient 3) Hgb level of 10 g/dL or lower with acute cardiac ischemia 4) Surgical blood loss anticipated 5) Acute bleeding with blood pressure (BP) instability	NR	CPOE and Decision Support
Rothschild[31] (2007) United States	One academic hospital	All staff	RBC, FFP, platelets	RCT (individual -level)	Standard of Care	4 months	Hematocrit <21%	Transfusions not meeting transfusion criteria	CPOE and Decision Support
Lam[108] (1997) United States	Two "peer" non-academic hospitals	All physicians	RBC, FFP, platelets	Controlled Before and After	Standard of Care; Historical Control	4 months	NR	NR	Reminders (through self-audit)
Pentti[100] (2003) Finland	Medical-surgical ICU in one academic	All physicians	RBC, FFP, platelets	Before and After	Historical Control	3 months	Hgb level <80 g/L	Transfusions above the recommended transfusion	Reminders (through electronic audit)

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
	hospital							criteria	
Lam[111] (1996) United States	Five hospitals including three academic and two non-academic	All physicians	RBC	Between Groups	Standard of Care	34 months	Hgb level >= 90g/L	NR	Audit and Feedback
Lewis[101] (2015) United States	Cancer centre in one academic hospital	All physicians treating patients with head and neck cancer	RBC	Before and After	Historical Control	24 months	NR	NR	Audit and Feedback
Tuckfield[102] (1997) Australia	One hospital	All medical staff	RBC, FFP, platelets	Before and After	Historical Control	3 months	1) Hgb <7 g/dL for severe anemia; 2) Hgb between 7-10 g/dL for anemia, bone marrow failure, anemia and sepsis, continuing blood loss, and abnormal bleeding during an operation; 3) Hgb <8 g/dL for perioperative period	Transfusions not meeting transfusion criteria	Audit Approval
Politsmakher[103] (2013) United States	Departments of medicine, surgery, obstetrics/	All physicians	RBC, FFP, platelets, cryo-	Before and After	Historical Control	24 months	1) Symptomatic anemia Hgb <7 g/dL; 2) Active	Transfusions not meeting transfusion	Audit Approval

Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
	gynecology, pediatrics, and emergency medicine in one community-based academic hospital		precipitate				bleeding, blood loss 15% of blood volume; 3) Chronic transfusion in sickle cell/ thalassemia patients; 4) Before major elective procedure Hgb <8 g/dL 5) Red cell exchange in sickle cell patients to attain Hgb ¼ 10g/dL and Hgb S <30%	criteria	
Madrigal[37] (2017) United States	Two tertiary hospitals, one trauma centre	All physicians	RBC	Interrupted Time Series	Historical Control	3.5 years	Symptomatic anemia with Hgb less than 7 g/dL; or acute bleed with shock; or symptomatic anemia with Hgb less than 8 g/dL for patients on chemotherapy or with MDS diagnosis; or anemia with Hgb less than 9 with cardiac symptoms, angina, ischemic	NR	Prospective Audit

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Author (Year) Country	Healthcare Setting	Target Clinician Group	Blood Component	Study Design	Type of Control	Length of Follow-up	RBC Transfusion Criteria	Definition of Inappropriate Transfusion	Types of Interventions
							EKG changes		

ED: emergency department; CPOE: computerized physician order entry; FFP: fresh frozen plasma; GI: gastrointestinal; Hgb: hemoglobin; ICU: intensive care unit; NR: not reported; RBC: red blood cell; RCT: randomized controlled trial;

Supplementary File 6. Composition of Multi-modal Interventions

Study	Interventions												
	Education	Guideline	Audit and Feedback	CPOE & Decision Support	Protocol/ Algorithm	Paper Order Form	Reminder	Policy	Audit Approval	Financial Incentive	Order Sets	Checklists	
Abelow (2017) [33]	✓						✓						
Alavi-Moghaddam (2014) [41]	✓				✓								
Andreasen (2012) [42]	✓	✓			✓								
Annan (2013) [43]				✓	✓								
Ansari (2012) [44]		✓	✓										
Baer (2011) [45]		✓		✓									
Beaty (2013) [46]			✓		✓								
Brandis (1994) [47]	✓				✓			✓					
Brandt (2009) [48]	✓				✓								
Butler (2015) [49]	✓		✓	✓									
Corwin (2014) [50]	✓	✓		✓									
Eindhoven (2005) [107]	✓	✓											
Frank (2017) [34]	✓	✓	✓	✓									
Gallagher-Swann (2011) [51]	✓				✓		✓						
Gardner (1993) [52]			✓	✓									
Garrioch (2004) [53]	✓	✓	✓				✓						
Geissler (2015) [54]	✓	✓	✓					✓					
Goodnough (2014a; 2014b) [29 30]	✓			✓									
Gutsche (2013) [55]	✓	✓	✓										

Study	Interventions												
	Education	Guideline	Audit and Feedback	CPOE & Decision Support	Protocol/ Algorithm	Paper Order Form	Reminder	Policy	Audit Approval	Financial Incentive	Order Sets	Checklists
Haldiman (2014) [56]		✓										
Handler (1983) [32]	✓		✓									
Harrison (2015) [57]	✓		✓									
Heyes (2016) [35]	✓							✓				
Hicks (2017) [36]	✓		✓									
King (2013) [58]	✓	✓	✓									
Larson (2016) [104]	✓							✓	✓			
Leahy (2014) [59]	✓	✓	✓	✓	✓							
Likosky (2010) [122]	✓		✓		✓							
Littenberg (1995) [61]		✓				✓						
Lucas (1997) [62]	✓	✓										
Mahar (2013)[63]	✓				✓							
Marconi (1996) [64]	✓	✓		✓	✓							
Markel (2016) [65]	✓	✓	✓									
McCrory (2014) [66]				✓	✓							
Meybohm (2016) [105]	✓	✓										✓
Morrison (1993) [67]	✓	✓	✓			✓						
Murphy (2016) [68]	✓		✓							✓		
Noorgard (2017) [38]	✓	✓	✓									
Oliver (2014) [69]	✓	✓	✓									
Rana (2006) [70]	✓			✓	✓							

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Study	Interventions												
	Education	Guideline	Audit and Feedback	CPOE & Decision Support	Protocol/ Algorithm	Paper Order Form	Reminder	Policy	Audit Approval	Auto	Financial Incentive	Order Sets	Checklists
Rehm (1998) [71]			✓			✓	✓		✓				
Rosen (1993) [72]	✓	✓	✓	✓									
Rothschild (2007) [31]	✓	✓											
Spencer (2005) [73]		✓	✓			✓	✓						
Tavares (2014) [74]	✓								✓				
Ternstrom (2014) [75]	✓	✓								✓			
Tseng (2016) [106]												✓	✓
Vos (1994) [76]	✓	✓											
Yeh (2015) [77]	✓		✓										
Yerrabothala (2014) [78]				✓				✓					
Zelinka (2010) [79]					✓					✓			
TOTAL	**31**	**22**	**20**	**12**	**14**	**4**	**4**	**3**	**2**	**6**	**1**	**1**	**2**

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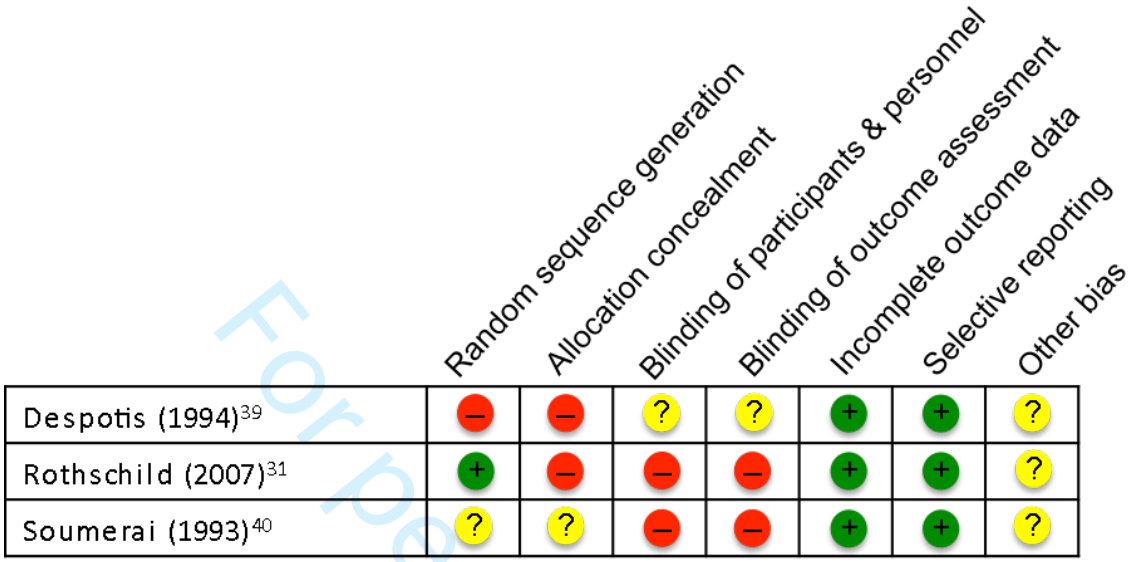
Supplementary File 7. Risk of Bias in RCTs Assessed with Cochrane Risk of Bias Tool



Supplementary File 8. Quality Assessment of Quasi-Experimental Studies Using Adapted Downs and Black Checklist

Study	REPORTING										EXTERNAL VALIDITY			INTERNAL VALIDITY – BIAS AND CONFOUNDING								Total /22
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q16	Q17	Q18	Q19	Q20	Q21	Q22	Q25	Q26	
Abelow [33]	1	1	0	1	0	1	0	0	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	13
Adams [97]	1	0	1	1	0	1	1	0	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Alavi-Moghaddam [41]	1	1	0	0	0	1	1	0	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	13
Andreasen [42]	1	0	0	1	0	1	0	0	0	0	1	UTD	1	1	0	0	1	1	1	n/a	UTD	UTD	9
Annan [43]	1	1	1	1	0	1	0	0	0	0	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	12
Ansari [44]	1	0	0	1	0	1	0	1	0	0	1	UTD	1	UTD	0	1	1	0	1	n/a	UTD	UTD	9
Baer [45]	0	0	1	1	0	1	1	1	0	1	1	UTD	1	1	1	0	1	1	1	n/a	UTD	UTD	13
Beaty [46]	1	1	1	1	0	1	0	1	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	14
Boral [80]	1	0	0	1	0	1	1	1	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	13
Brandis [47]	0	0	0	1	0	1	0	1	0	0	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	10
Brandt [48]	1	0	0	1	0	1	0	1	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	12
Butler [49]	0	1	0	0	1	1	0	1	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	12
Ciccocioppo [91]	0	1	0	1	0	1	1	1	0	0	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	12
Corwin [50]	0	1	0	1	0	1	1	1	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	13
Eindhoven [107]	1	0	0	1	0	1	1	1	0	1	1	UTD	1	0	1	1	UTD	1	0	UTD	UTD	UTD	11/23
Fernandez Perez [98]	1	1	0	0	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Frank [34]	1	1	1	1	0	1	0	0	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14

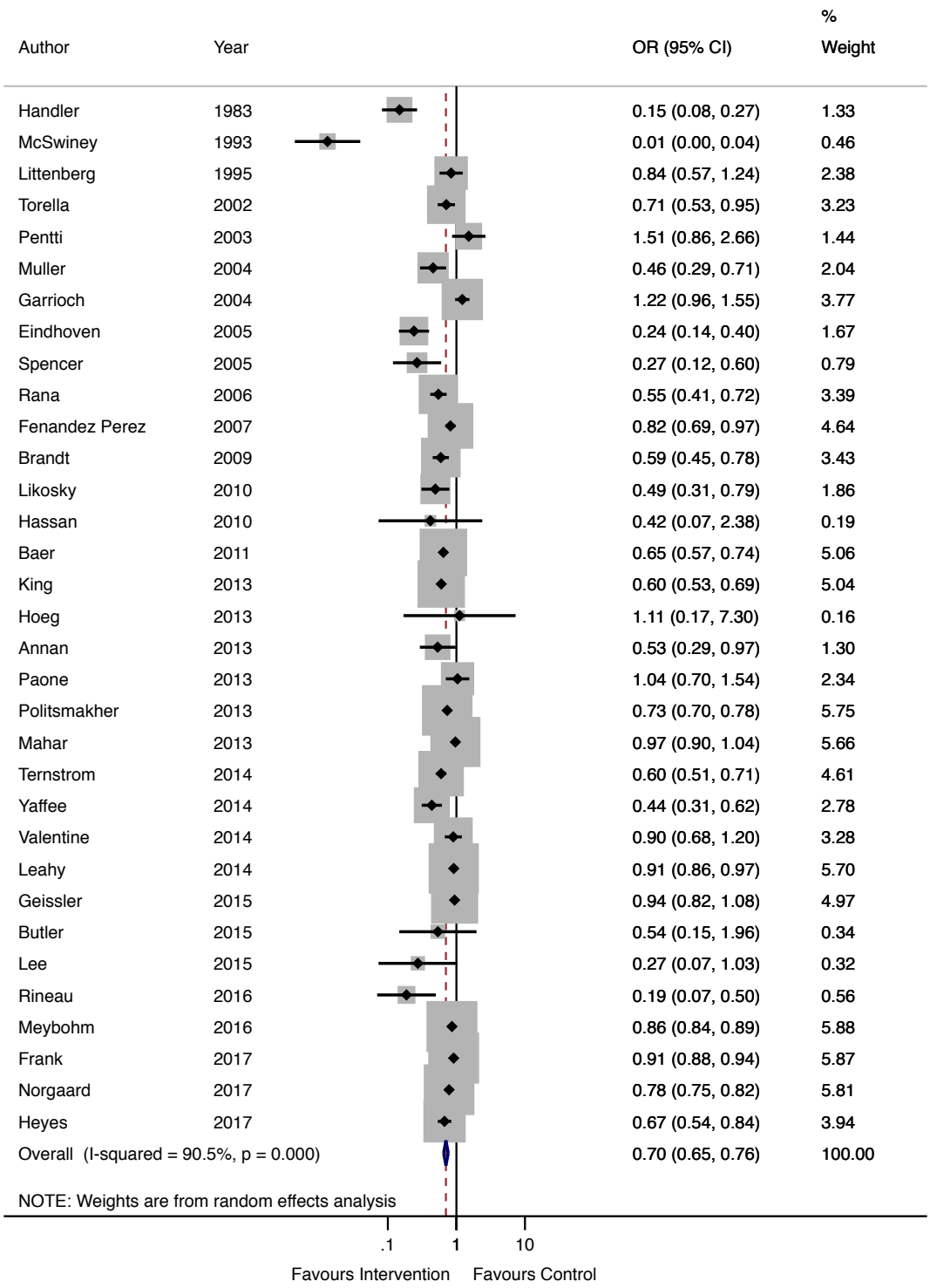
Study	REPORTING										EXTERNAL VALIDITY			INTERNAL VALIDITY – BIAS AND CONFOUNDING								Total /22
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q16	Q17	Q18	Q19	Q20	Q21	Q22	Q25	Q26	
Gallagher-Swann [51]	1	0	1	1	0	1	0	0	0	n/a	UTD	UTD	1	UTD	1	n/a	1	1	1	n/a	UTD	UTD	9
Gardner [52]	1	1	0	1	0	1	0	1	0	0	1	UTD	1	UTD	0	1	1	1	1	n/a	UTD	UTD	11
Garrioch [53]	1	1	0	1	0	1	1	1	0	0	1	UTD	1	UTD	0	1	1	1	1	n/a	UTD	UTD	12
Geissler [54]	1	0	0	1	0	1	1	1	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	13
Goodnough [30]	1	1	0	1	0	1	0	1	0	1	1	UTD	1	0	0	1	1	1	1	n/a	UTD	UTD	12
Goodnough [29]	1	1	0	1	0	1	0	1	0	0	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	12
Gutsche [55]	1	0	0	1	0	1	1	1	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	13
Haldiman [56]	1	1	0	1	0	1	0	0	0	n/a	1	UTD	1	UTD	1	n/a	1	1	1	n/a	UTD	UTD	10
Handler [32]	0	1	0	1	0	0	0	0	0	n/a	1	UTD	1	1	1	n/a	UTD	1	0	1	UTD	UTD	8/23
Harrison [57]	1	1	0	1	0	1	0	1	0	0	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	12
Hassan [110]	1	1	0	0	0	1	1	1	0	1	1	UTD	1	1	1	0	1	1	0	1	UTD	UTD	13/23
Heyes [35]	1	1	0	1	0	1	0	0	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	12
Hicks [36]	1	1	0	1	0	1	0	0	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	13
Hillman [81]	1	0	0	0	0	1	1	0	0	0	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	10
Hoeg [87]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	UTD	1	1	1	1	1	n/a	UTD	UTD	14
Horowitz [88]	1	0	0	1	0	1	0	0	0	0	1	UTD	1	1	1	1	1	UTD	1	n/a	UTD	UTD	10
Joubert [82]	1	1	0	1	0	1	0	0	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	13
Joyce [109]	1	0	0	1	0	1	1	0	1	0	UTD	UTD	1	1	1	1	UTD	1	1	UTD	UTD	UTD	11/23

Study	REPORTING										EXTERNAL VALIDITY			INTERNAL VALIDITY – BIAS AND CONFOUNDING								Total /22
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q16	Q17	Q18	Q19	Q20	Q21	Q22	Q25	Q26	
King [58]	1	1	0	1	0	1	0	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	13
Lam [108]	1	1	1	0	0	1	0	0	0	1	1	UTD	1	1	1	0	1	1	0	1	UTD	UTD	13/23
Lam [111]	1	1	0	1	0	1	0	0	0	1	1	UTD	1	1	UTD	1	UTD	1	1	1	UTD	UTD	12/23
Larson [104]	1	1	0	1	0	1	0	0	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	13
Leahy [59]	0	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Leão [83]	1	1	0	1	0	1	0	0	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	13
Lee [92]	0	1	0	1	0	1	0	0	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	11
Lewis [101]	0	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Likosky [60]	1	1	0	1	0	1	0	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Littenberg [61]	1	1	0	1	0	1	0	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Lucas [62]	0	1	0	1	0	1	0	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	12
Madrigal [37]	1	1	0	1	0	1	1	0	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Mahar [63]	1	1	0	1	0	1	0	0	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	12
Markel [65]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
Meybohm [105]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	14
McCrory [66]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
McSwiney [89]	1	1	0	1	0	1	1	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
McWilliams [99]	1	0	0	1	0	1	0	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	13

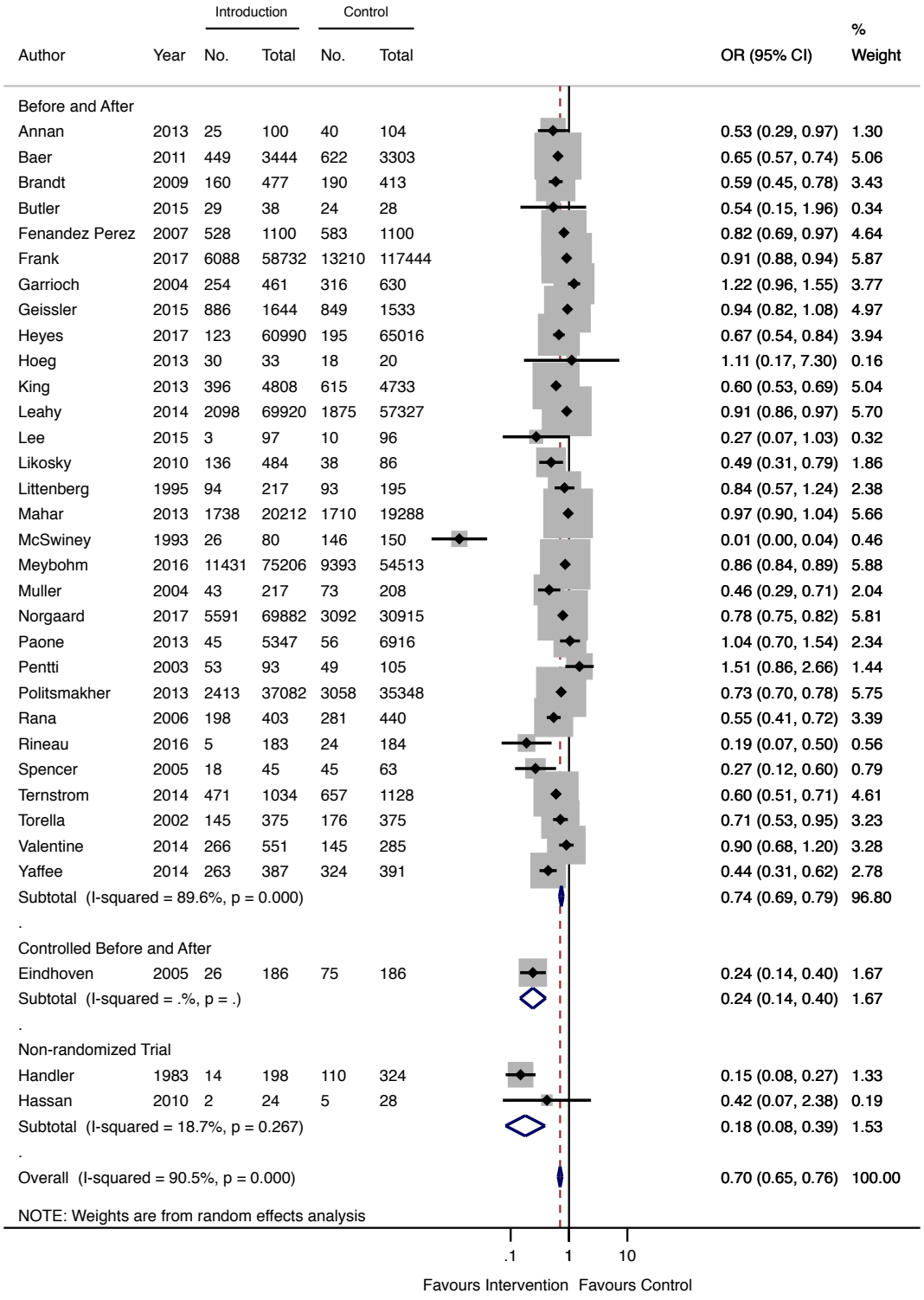
Study	REPORTING										EXTERNAL VALIDITY			INTERNAL VALIDITY – BIAS AND CONFOUNDING								Total /22
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q16	Q17	Q18	Q19	Q20	Q21	Q22	Q25	Q26	
Morrison [67]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
Muller [90]	1	1	0	1	0	1	1	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Murphy [68]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
Norgaard [38]	1	1	0	1	0	1	1	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Oliver [69]	1	1	0	1	0	1	0	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Paone [84]	1	1	0	1	0	1	0	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Pentti [100]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
Politsmakher [103]	0	1	0	1	0	1	0	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	12
Rana [70]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
Rehm [71]	0	1	0	1	0	1	0	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	12
Rineau [93]	1	1	0	1	0	1	0	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Rothschild [31]	1	1	1	1	0	1	1	1	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	15
Rosen [72]	1	0	0	1	0	1	0	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	12
Spencer [73]	1	1	0	1	0	1	0	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	13
Tavares [74]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
Ternstrom [75]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
Torella [96]	0	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Tseng [106]	1	1	0	1	0	1	0	0	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	13

Study	REPORTING										EXTERNAL VALIDITY			INTERNAL VALIDITY – BIAS AND CONFOUNDING								Total /22
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q16	Q17	Q18	Q19	Q20	Q21	Q22	Q25	Q26	
Tuckfield [102]	1	1	0	1	0	1	0	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	14
Valentine [85]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	UTD	1	1	1	1	1	n/a	UTD	UTD	14
Vos [76]	1	1	0	1	0	1	0	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	13
Vrotsos [94]	0	1	0	1	0	1	0	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	12
Whitney [95]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
Yaffee [86]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	0	1	1	1	1	n/a	UTD	UTD	14
Yeh [77]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
Yerrabothala [78]	1	1	0	1	0	1	1	1	0	1	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	15
Zelinka [79]	0	1	0	1	0	1	0	1	0	0	1	UTD	1	1	1	1	1	1	1	n/a	UTD	UTD	12

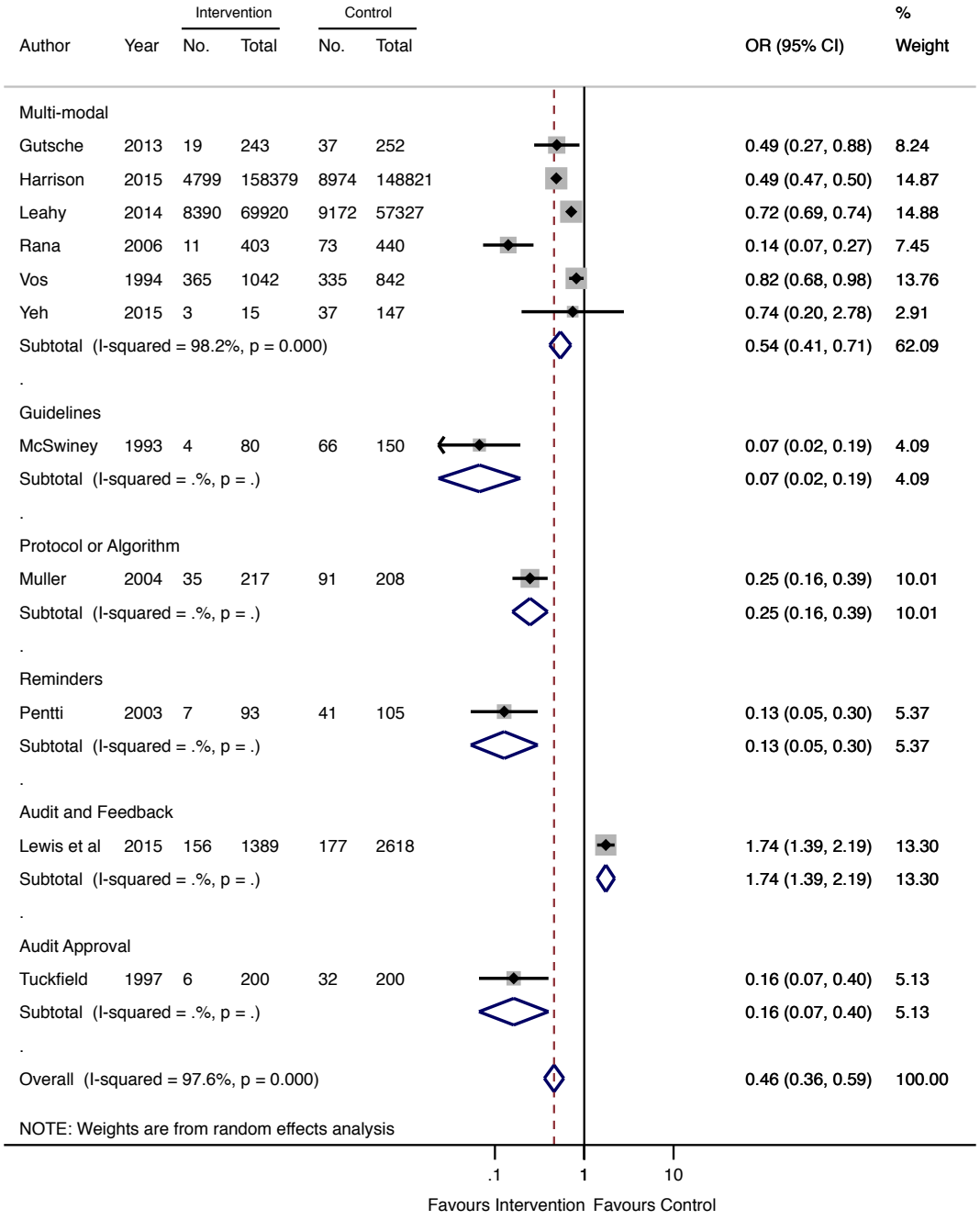
Supplementary File 9. Forest Plot for Odds of Patients Being Transfused Sorted by Year of Publication



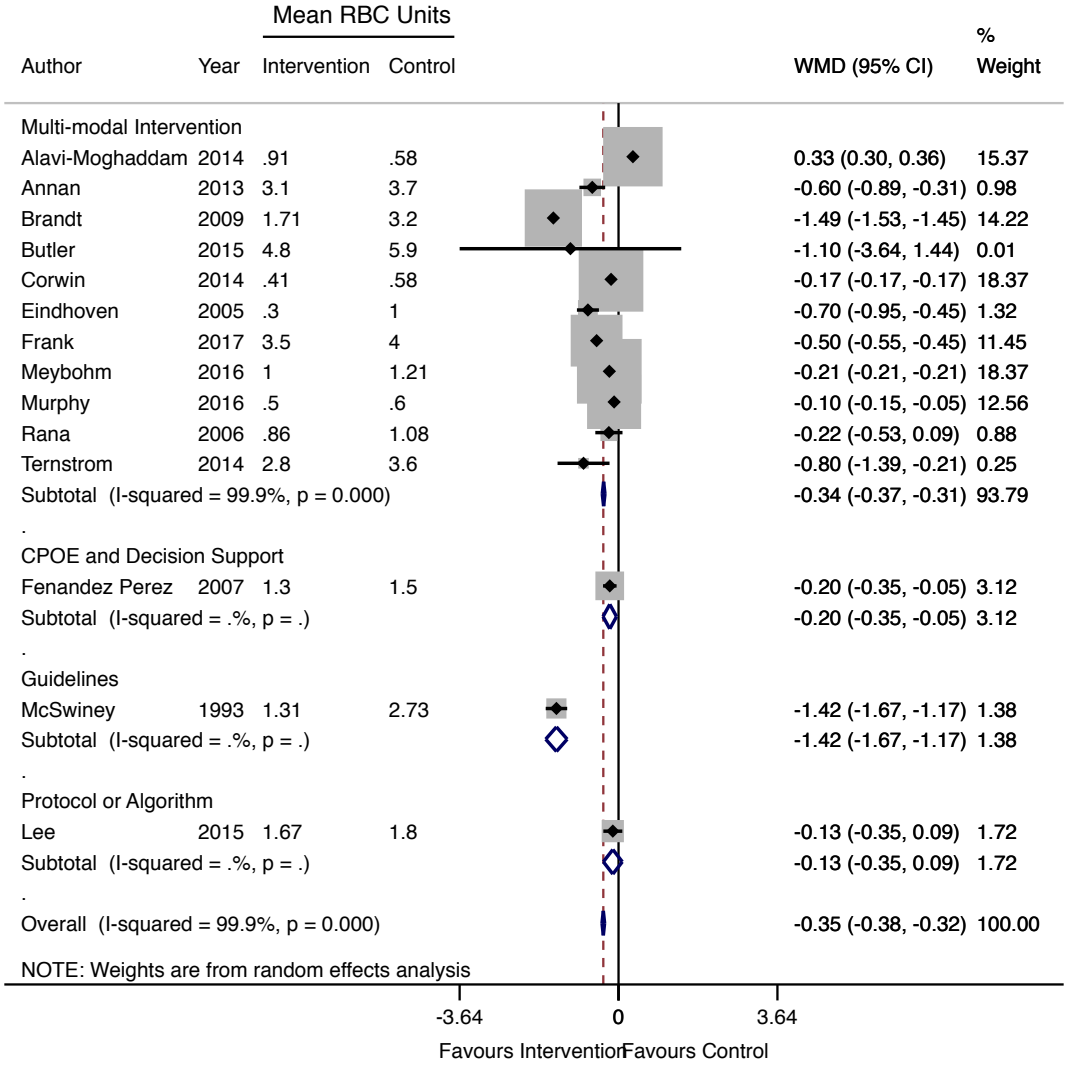
Supplementary File 10. Forest Plot of Odds of Patients Being Transfused, Stratified by Study Design



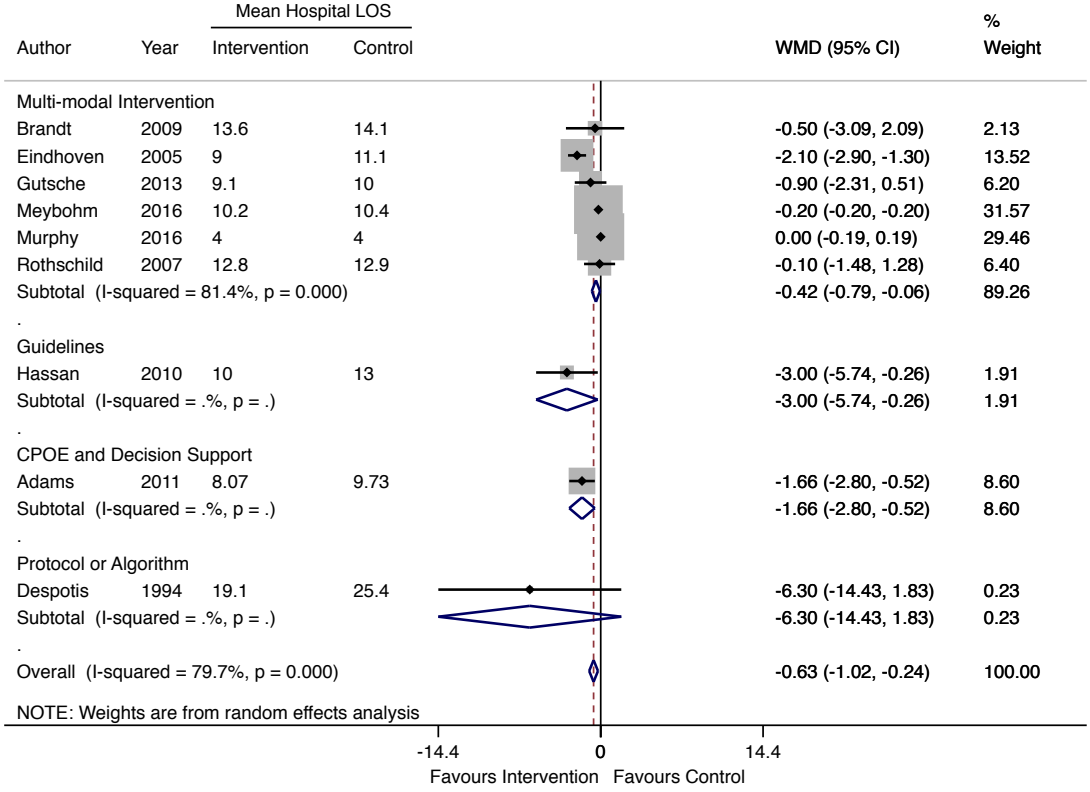
Supplementary File 11. Forest Plot for the Odds of Patients Being Inappropriately Transfused



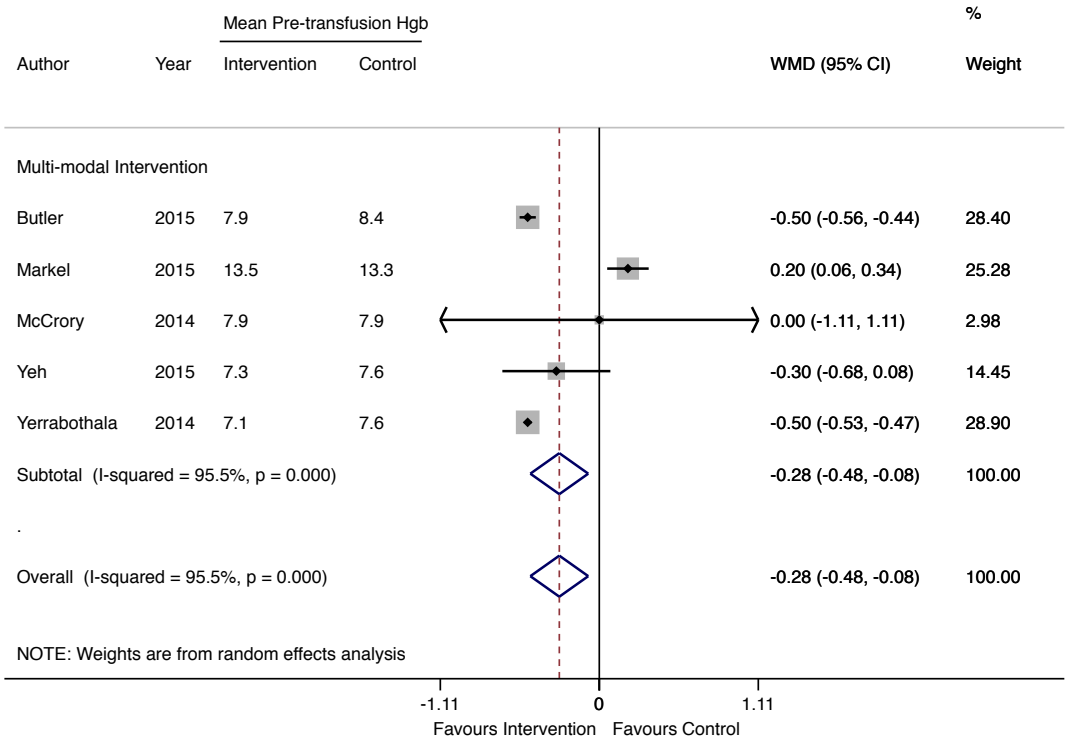
Supplementary File 12. Forest Plot for the Mean Number of RBC Units Transfused Per Patient



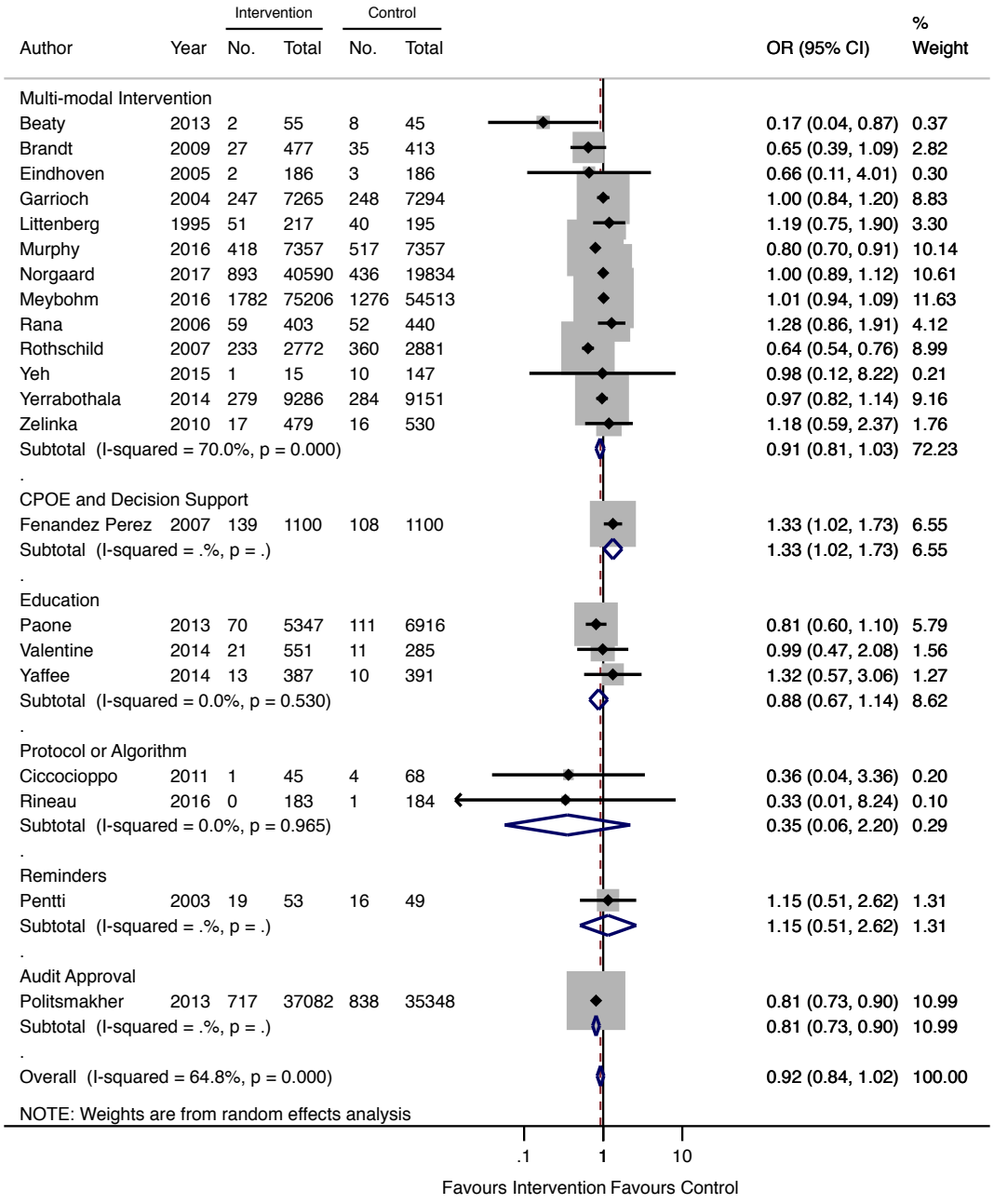
Supplementary File 13. Forest Plot for the Mean Hospital Length of Stay (days)



Supplementary File 14. Forest Plot for the Mean Pre-transfusions Hemoglobin Level (g/dL)



Supplementary File 15. Forest Plot for the Odds of In-hospitality Mortality



Supplementary File 16. Results of Meta-Regression Analysis

Covariate	Patients Transfused	
	Coefficient of logOR (SE)	*p* value
Year of Publication	0.002 (0.014)	0.915
Number of Interventions	0.052 (0.062)	0.406
Multi-Modal Intervention	-0.011 (0.163)	0.948
Setting in Single Unit/ Clinical Service	-0.108 (0.163)	-0.660
Follow-up ≥ 1 year	0.008 (0.165)	0.960
Education	0.111 (0.160)	0.491
Guideline	0.010 (0.153)	0.949
Audit and Feedback	0.163 (0.158)	0.311
CPOE and Decision Support	0.075 (0.175)	0.670
Protocol/ Algorithm	-0.150 (0.175)	0.398
Reminder	0.361 (0.263)	0.181
Policy	0.135 (0.230)	0.561
Audit Approval	0.074 (0.366)	0.842
Audit	0.064 (0.225)	0.777
Paper Order Entry	-0.205 (0.342)	0.554