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Larger versus smaller red blood cell volume per transfusion in hospitalized adults, children, and preterm neonates (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Larger versus smaller red blood cell volume per transfusion in hospitalized adults, children, and preterm neonates

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

The objective of this review is to compare the effectiveness and safety of larger versus smaller RBC volume per transfusion for anemia in hospitalized adults, children, and preterm neonates.

BACKGROUND

Description of the condition

Anemia in hospitalized patients is common and may be associated with multiple long-term morbidities. Anemia may be caused by congenital diseases (e.g. sickle cell disease, thalassemia) or acquired diseases (e.g. cancer, hemolysis, iron deficiency). In many hospitalized patients, anemia is caused by blood loss (bleeding, blood collection) and/or inflammatory-related anemia. Hospital management of anemia ranges from strategies to reduce phlebotomy, reduction of surgical and non-surgical bleeding, increasing production of red blood cells (RBCs) and RBC building blocks, and RBC transfusion. This approach is referred to as Patient Blood Management (PBM) by the World Health Organization (WHO), the pillars of which are detecting and managing anemia, minimizing blood loss, and optimizing the tolerance to anemia (WHO 2021). RBC transfusion has its own inherent risks including transfusion reactions, volume overload, and organ dysfunction (Bolton-Maggs 2013; Hébert 1999), therefore the risks must be weighed against the benefits. Furthermore, RBCs are a scarce and costly resource that must be managed sparingly (Amin 2004; Hofmann 2013; Lagerquist 2017; Shander 2007; Shander 2007; Shander 2010). Given these risks and limited resources, and no proven benefits of liberal transfusion practices, clinical practice has shifted toward more restrictive transfusion approaches.

Description of the intervention

There are currently no recommendations for a specific volume of RBC transfusion that is based on etiology. In their transfusion medicine practice recommendations, the 'Choosing Wisely' initiative recently made a recommendation for single-unit RBC transfusion in non-actively bleeding hospitalized anemic adult patients (Carson 2016). This recommendation is based on evidence of morbidity related to overall total amounts of blood received in studies of transfusion threshold and is supported by the Association for the Advancement of Blood and Biotherapies (AABB) (Callum 2014; Carson 2016). One of the most important morbidities related to RBC transfusion is transfusion-associated circulatory overload (TACO). TACO is characterized by respiratory deterioration due to volume overload and hydrostatic pulmonary edema, ensuing in the 12 hours after a transfusion (Wiersum-Osselton 2019). Hemovigilance reporting systems and a recently revised definition of TACO have increased detected cases and awareness of the condition; however, it may be difficult to distinguish TACO from other respiratory complications after transfusion (Piccin 2015; Wiersum-Osselton 2019). A restrictive volume of transfusion favors a resource-sparing strategy that may reduce unnecessary risks of transfusion reactions in the patient.

In children, there is a large variation in stated volume of RBC transfusion practice of clinicians for anemic non-bleeding hospitalized patients (Laverdiere 2002). The Australian Patient Blood Management guidelines recommend an RBC transfusion volume based on weight and desired target hemoglobin (National Blood Authority 2016). While there is little evidence on what the target hemoglobin should be in non-bleeding infants and children, a 4 mL/kg RBC volume leads to an approximate 10 g/L hemoglobin rise, making 15 mL/kg of RBC suitable for most stable children less than 20 kg (National Blood Authority 2016; New 2016). For children over 20 kg, a single unit is recommended for most patients (National Blood Authority 2016). These recommendations are largely based on expert opinion given the substantial lack of evidence (Muszynski 2018; New 2016; NICE 2015). However, with the transition to single-unit transfusions in adult patients, a 290 mL RBC volume in a 70 kg patient is equivalent to a dose of 4 mL/kg, leading to a divergent practice compared to the commonly recommended 10 to 20 mL/kg in pediatrics (New 2016). This may be placing pediatric patients at higher risk of avoidable transfusion reactions.

In this review, the intervention will be a larger volume of allogenic RBC transfusion for a given transfusion event of an anemic patient (example one versus two units in adults, and < 10 mL/kg and ≥ 10 mL/kg in children/neonates). We will define a transfusion event as a single transfusion within a six-hour period, or more than one transfusion in the case of immediate consecutive RBC transfusions (e.g. two consecutive RBC units). We will not include the volumes (or quantities) of RBC transfusions given multiple hours apart.

How the intervention might work

Allogenic blood transfusion treats anemia by increasing the quantity of circulating RBCs, thus improving the body's oxygen-carrying capacity. RBCs also increase the risk of immediate transfusion reactions, volume overload, and have been associated with poorer long-term outcomes in settings such as gastrointestinal bleeding, by mechanisms that are not well understood. There is no evidence-based consensus on the optimal amount of RBC needed to achieve clinical improvement in anemic patients, while reducing the associated risks of RBC transfusion (Carson 2016; Mueller 2019).

Why it is important to do this review

Multiple randomized trials have compared a restrictive to a liberal hemoglobin threshold for allogenic RBC transfusion in a variety of hospitalized patients, including critically ill adults (Hébert 1999), critically ill children (Lacroix 2007), traumatic brain injury patients, gastrointestinal bleeding (Villanueva 2013), coronary bypass (Bracey 1999), surgery and cancer, among others. A Cochrane review of randomized controlled trials (RCTs) compared a restrictive versus a liberal RBC transfusion strategy on 30-day mortality (Carson 2021). While many of these individual studies found that the liberal transfusion group received more RBC transfusions overall, the review found no difference in mortality or other clinical outcomes (cardiac events, stroke, thromboembolism) between the liberal and the restrictive group (Carson 2021). Importantly, none of the studies specifically evaluated the volume of RBCs per given transfusion event, but most recommended a first single RBC unit. Furthermore, including hospital length of stay and hospital-free days (composite of alive and not in hospital) are important outcomes for the hospitalized patient.

Four large RCTs evaluated the impact of the length of storage of RBC units on mortality of transfused hospitalized patients (Cooper 2017; Heddle 2016; Lacroix 2015; Steiner 2015). However, data on the volume per transfusion were not collected in any of the trials, but a 'one RBC unit per transfusion' policy was adopted in all four RCTs.

While substantial research has evaluated the safety, threshold, and storage for RBC transfusion, there is minimal literature on the impact of RBC transfusion volume per transfusion event in hospitalized patients. This review will evaluate the effect of the volume of RBC transfusion, administered when the decision has

been made to transfuse an anemic hospitalized patient, on hospital mortality.

Given significant transfusion practice variation in adults and children, and in order to reduce potential adverse events and morbidities associated with higher transfusion volumes (including transfusion-related acute lung injury (TRALI) and TACO) and spare limited donor resources, evidence is needed to guide clinicians in the practice of lower transfusion volume per transfusion event. The results of this systematic review will potentially support the 'Choosing Wisely' recommendation of a single unit per transfusion and provide guidance on the recommended volume of RBCs to transfuse in children and neonates.

OBJECTIVES

The objective of this review is to compare the effectiveness and safety of larger versus smaller RBC volume per transfusion for anemia in hospitalized adults, children, and preterm neonates.

METHODS

Criteria for considering studies for this review

Types of studies

We will include published RCTs and non-randomized studies of interventions (NRSI) in hospitalized adults, children, and preterm neonates with any etiology or cause of anemia. Randomized trials will include individual and cluster-RCTs. NRSI will include pre/post studies, interrupted time series, interventional cohorts, cross-sectional studies, case-control studies where two volumes of transfusion are being compared, and quasi-randomized studies. Quasi-randomized studies are experimental studies testing a causal hypothesis between manipulable causes between a control and intervention group; however, group assignment is not random but by means of self-selection or by administrator selection. The inclusion of NRSI in this review is based on the following.

1. Likely insufficient available evidence in randomized trials that address the study intervention (authors are unaware of any randomized trials comparing two RBC transfusion volumes in adults).
2. Recommendations for the current use of one-unit RBC per transfusion ('Choosing Wisely') makes undertaking studies randomizing patients to one versus two units of RBC ethically difficult (intervention is unlikely to be randomized).
3. Changes in transfusion policy recommendations over time make randomization of interventions impractical, suggesting that other study designs may be more appropriate.

The inclusion of NRSI therefore involves balancing the inclusion of lower-quality studies with lack of data on the intervention. We want to include the best available evidence rather than the highest-tier evidence for this high-priority question (involving patient risk reduction, utilization/management of blood, cost, donor involvement). NRSI inclusion increases the risk of systematic differences and confounders across studies, introducing bias. In addition, the inclusion of NRSI may lead to the demonstration of more extreme hard/benefit in one arm.

We will include full-text studies (not abstracts) and preprints published in English or French.

Types of participants

We will include studies of hospitalized adults and children, of any age (including preterm neonates), who received at least one allogenic RBC transfusion for anemia while in hospital. Hospitals will include centers that admit inpatients to medical/surgical/oncology wards, intensive care units (ICUs) or other units overnight.

We will include only hospitalized patients as they differ from outpatients requiring transfusions. The causes of anemia or transfusion requirements are different for hospitalized patients (severe illness, bleeding versus hematologic disease), and the baseline risks of the outcomes are higher in hospitalized patients. Our objective is therefore to generalize the findings of this review to the target population of hospitalized patients who have characteristics and baseline risk that cannot be generalized to the outpatient population.

While we are including a broad population of hospitalized patients, it is possible that only a subset of patients is eligible for the review within a study. Should this be the case, we will include the study in the descriptive reporting, but will only include the study in meta-analysis if the outcome of the given subset can be extracted from the total.

Types of interventions

We will include studies comparing two volumes of transfusion for a given RBC transfusion event. We will include studies comparing a larger volume of transfused RBC unit per transfusion (volume/kg/transfusion and/or volume/transfusion or number of transfusion units) to a smaller volume of RBC unit per transfusion and/or standard practice with respect to the volume of RBC unit per transfusion. We will define a transfusion event as a single transfusion, or more than one transfusion in the case of immediate consecutive RBC transfusions. We will not include multiple RBC transfusions given more than six hours apart (example during 'perioperative period' or within ICU or hospital stay) within the same transfusion event.

For the study intervention, participants should not be receiving autologous blood transfusion, whole blood or mixed blood components, massive transfusion (≥ 4 units per transfusion event) or blood prime for either cardiopulmonary bypass (CPB), extracorporeal membrane oxygenation (ECMO), or renal replacement therapy (RRT).

Intervention group: receive a larger volume of RBC unit per transfusion (volume/kg/transfusion or volume per transfusion or number of units/transfusion) than in the comparative group.

Comparative group(s): receive a smaller volume of RBC unit per transfusion (volume/kg and volume/transfusion) than in the intervention group. Examples include comparing ≤ 10 mL/kg and > 10 mL/kg per transfusion in children, or one unit versus two units per transfusion in adults.

Types of outcome measures

Measuring at least one of the primary or secondary outcome measures listed below is an inclusion criterion for the review. We will contact authors of studies that measure but do not report one of these outcomes.

Primary outcomes

1. Mortality. We will select hospital mortality first; if this is not available, we will use 28-day, 30-day, and other mortality post-first RBC transfusion (Higgins 2024).

Secondary outcomes

1. Length of hospital stay.
2. Hospital-free days (or 28-day hospital-free less length of hospital stay).
3. Transfusion reactions including 1) allergic, 2) non-hemolytic (including febrile non-hemolytic), 3) pulmonary complications (TACO (Bolton-Maggs 2013; Wiersum-Osselton 2019), transfusion-associated dyspnea (Badami 2015) and TRALI (Vlaar 2019)), 4) hemolytic and ABO incompatibility, 5) transfusion transmissible infections (TTI) (Haass 2019), and 6) delayed transfusion reactions (hemolysis and serologic reactions). We will abstract data as dichotomous per reaction; however, in the case of rare reporting or few included studies, these may be grouped to include 'any transfusion reaction.'
4. Organ dysfunction as defined by one of 1) Multiple Organ Dysfunction score or Sequential Organ Failure Assessment (SOFA) (Singer 2016) score; 2) circulatory shock requiring vasoactive agents (including vasoactive-free days) or myocardial infarction; 3) respiratory dysfunction or failure, defined as need for mechanical ventilation or as recent partial pressure of oxygen in arterial blood/fraction of inspired oxygen (FiO_2) of < 200 without prior patient history; 4) hematologic dysfunction, defined as a platelet count of < 100,000/µL, or prothrombin activity of < 50%, evidence of disseminated intravascular coagulation, or arterial or venous thrombosis (including deep vein thrombosis, stroke, and pulmonary embolism); 5) renal dysfunction, defined as a urine output of < 500 mL/day, a serum creatinine level of > 1.9 mg/dL, or dialysis for acute renal failure; and/or 6) hepatic dysfunction, defined as a serum bilirubin level of > 1.9 mg/dL.
   a. For preterm neonates only, organ dysfunction outcomes will include bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), interventricular hemorrhage (IVH), and retinopathy of prematurity (ROP).
5. Total number of individual allogenic RBC transfusions received during hospital stay.
6. Rebleeding, defined as a drop in hemoglobin by ≥ 2 g/dL within six hours of first transfusion, is an important outcome for hospitalized patients including surgical and trauma patients and those with endothelial dysfunction (sepsis, gastrointestinal bleeding, etc.).
   a. Rebleeding episodes will be measured per hospital stay.
7. Allogenic RBC donor exposure (number of allogenic RBC donors per patient per hospital stay) is an important hematologic outcome for patients requiring multiple and chronic transfusions, and all potential organ transplant or blood product recipients. Exposure to multiple transfusions from multiple donors increases transfusion-related allogenic antibodies. This may lead to increased risk of hemolytic transfusion reactions, difficulty finding donor compatibility, and pregnancy complications such as hemolytic disease of the fetus. Future organ recipients may have difficulty finding donor matches due to compatibility of alloantibodies as well.
   a. Allogenic donor exposure will be measured per hospital stay as specifically stated in the included studies. Assumptions that each RBC transfusion is a unique donor will not be made, given that infants/neonates often receive split RBC packs.

Search methods for identification of studies

Electronic searches

We will search the following databases from inception to search date.

1. MEDLINE Ovid (1946 to current)
2. Embase Ovid (1974 to current)
3. Web of Science
4. EBM Reviews (this includes the Cochrane Central Register of Controlled Trials (CENTRAL))
5. LILACS (Latin American and Caribbean Health Science Information database; 1982 to current)
6. Transfusion Evidence Library

The search strategy will be restricted to full texts published in English and French only. A primary search will be performed by a librarian of CHU Sainte-Justine (PD) who is familiar with the methodology of systematic reviews (Lefebvre 2020). An example of this search strategy is provided in Appendix 1.

Searching other resources

We will conduct a manual bibliographic search of references for all included studies and relevant systematic reviews found in the primary search.

Data collection and analysis

Selection of studies

We will upload the results of the study search into EndNote. One review author (GS) will independently assess the titles and abstracts of records retrieved by the search, with two-person screening (GS, NR) for 10% to 15% of studies. We will obtain the full texts of studies deemed potentially relevant, and two review authors (GS, NR) will independently assess the full texts for inclusion in the review. Lists of included studies will be compared and any disagreements resolved by discussion or consultation with a third review author (JL).

We will categorize studies excluded at the full-text stage according to the reason for exclusion, including wrong study design, setting, population, intervention, or outcomes. The unit of selection is the study. Should multiple full-text articles report on the same study, these will be grouped into a single reference.

Study selection will follow PRISMA guidelines. We will generate a PRISMA flow diagram (Liberati 2009; Page 2021).

Data extraction and management

Two review authors (GS, NR) will independently and in duplicate extract data from the included studies using a specified previously piloted data abstraction form in Microsoft Excel. Any disagreements will be solved by discussion or consultation with a third review author (JL). We will abstract data according to the guidelines proposed by Cochrane (Higgins 2020).

We will extract the following data from each study.

1. Study data: first author, year of publication, country

2. Study design: RCT or NRSI, hospital setting, number of sites
3. Study population: age range, diagnostic group, number included, number randomized, number transfused, inclusion and exclusion criteria
4. Intervention(s): larger volume per RBC transfusion event
5. Comparison: smaller volume per RBC transfusion event
6. Outcomes: median or average number of allogenic RBC transfusions in each group, numbers of deaths in each group, secondary outcome types and definitions with numbers for each group; co-intervention(s) (co-maneuvers)
7. Information related to risk of bias: missing data, imputation
8. Sources of funding and conflicts of interest stated by study authors

We will contact study authors for clarification or additional information where necessary. One review author (NR) will enter the data into RevMan software (RevMan 2024), and a second review author will check the data entry (JL).

The rate of agreement (concordance) between review authors for the full-text inclusion of studies will be expressed in percentage (%), and the statistical significance of this concordance will be calculated using the Kappa score (Kramer 1981).

All study data will be synthesized in a 'Characteristics of included studies' table and included in a narrative review. Studies will be tabulated by study design (RCT and NRSI), as well as by patient age group (adults versus children/neonates), given that the volume of transfusion in adults is typically in units, whereas in pediatrics it is in mL/kg.

Assessment of risk of bias in included studies

Two review authors (GS, NR) will independently assess risk of bias in the included studies using the Cochrane RoB 2 tool for RCTs (Risk of Bias 2 (RoB 2) tool) and the Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I) tool for non-randomized studies (Sterne 2016). We will assess risk of bias for the primary outcome of mortality and the secondary outcomes of length of stay, hospital-free days, transfusion reactions, organ dysfunction, and number of transfusions. We will measure mortality, transfusion reactions, and organ dysfunction as dichotomous outcomes, and length of stay, hospital-free days, and number of transfusions as continuous outcomes, each measured at 28 days unless otherwise specified. We will include no specific confounders or co-interventions. We will summarize the risk of bias by domain across studies for each outcome, with the overall risk of bias being the least favorable assessment across domains.

We will evaluate intervention assignment in RCTs in each group at baseline (as per intention-to-treat (ITT)).

The RoB 2 tool includes the following domains:

1. bias arising from the randomization process;
2. bias due to deviations from intended interventions;
3. bias due to missing outcome data;
4. bias in measurement of the outcome;
5. bias in selection of the reported results.

We will then estimate an overall risk of bias for each outcome in each study as follows (Sterne 2019).

1. 'Low risk of bias': the study is at low risk of bias for all domains for this result.
2. 'Some concerns': the study raised some concerns in at least one domain for this result, but is not at high risk of bias for any domain.
3. 'High risk of bias': the study is at high risk of bias in at least one domain for the result, or there are some concerns for multiple domains such that our confidence in the results is substantially lowered.

For cluster- and cross-over RCTs, we will use the dedicated versions of the RoB 2 tool, adjusting the bias assessment based on type of study (this includes adjusting for identification/recruitment bias, intervention allocation, washout periods, carry-on and period effects).

For NRSI, we will employ an analogue of ITT by using 'start of intervention' in experimental and control groups (RBC transfusion started). Bias domains of the tool will be adjusted based on the type of NRSI (i.e. controlled or uncontrolled). The ROBINS-I domains for risk of bias in NRSI include:

1. confounding;
2. selection bias;
3. bias in measurement classification of intervention;
4. bias due to deviation from intended interventions;
5. bias due to missing data;
6. bias due to measurement of outcomes;
7. bias in selection of the reported result.

The levels of judgment for the risk of bias are:

1. low risk of bias;
2. moderate risk of bias;
3. serious risk of bias;
4. critical risk of bias;
5. no information.

The overall risk of bias for outcomes will be based upon the levels of judgment in each domain (the most serious risk of bias) and how often this arises in multiple domains. A level of bias in any of the domains implies that the overall risk of bias for the outcome is at least this severe, and outcomes may be downgraded if all domains show this level of bias. We will exclude studies with critical risk of bias from the pooled meta-analysis.

The risk of bias assessments will be piloted for a few studies (RCT and NRSI) to ensure agreement, and we will use Excel template sheets provided by RoB 2 and ROBINS-I. Any disagreements will be resolved through discussion or consultation with a third review author (JL) if needed. We will use the risk of bias assessment to determine study quality. Where possible, we will conduct a sensitivity analysis of studies with low risk of bias.

We will illustrate the risk of bias for both study design types (RCT and NRSI) using 'traffic light' plots. The risk of bias assessment will inform the GRADE assessment and summary of findings table (Schünemann 2024a).

Measures of treatment effect

We will conduct a meta-analysis, illustrated by a forest plot, if studies are homogeneous with regard to clinical characteristics (population, clinical intervention, outcome), and methods (study design) in either adults or children. We will analyze adults and children separately given the difference in population practice, intervention volumes, and baseline risk of outcomes. We will analyze dichotomous data using risk ratio (RR) with 95% confidence interval (CI), and continuous data as mean difference (MD) with 95% CI. We will enter data as a scale with a consistent direction of effect.

For categorical (dichotomous) outcomes (mortality, transfusion-related events, organ dysfunction), we will combine data to estimate a total RR and its 95% CI across the studies using a random-effects model. A correction factor of 0.5 will be attributed to all cells of a given contingency table if it contains one or more zero cells. For continuous outcomes (number of transfusions, length of stay), we will combine data with the same units of measure using MD according to Section 15.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2024b). If studies report time-to event data for the primary outcome (mortality), we will pool hazard ratios (HRs) (with log hazard ratio and standard error log hazard ratio) using the inverse variance methods.

For studies with rare events, or studies with zero values in one or both arms, we will perform summary estimates using continuity correction factors and consult a statistician.

Unit of analysis issues

Given the clinical nature of the review, the unit of analysis will be the participant for all included studies. For any included cluster-, cross-over, or multi-arm randomized trials, we will reanalyze the results according to the guidance provided in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020).

If the data cannot be reanalyzed such that a single participant is the unit of analysis, we will contact the study authors for help with data completion where appropriate. If we cannot complete the data collection, we will report the unit of analysis as the cluster and report this separately.

We will only include cross-over studies in the analysis if the outcome at 28 days can be measured after the first randomized period, and before the cross-over. This approach will avoid unit of analysis errors, errors in the CIs, and use of paired T-test in the meta-analysis.

If multi-arm transfusion studies are included, we will combine arms where possible, into large- and small-volume transfusion groups, with the participant as the unit of analysis.

Dealing with missing data

We will contact study authors to obtain or clarify any missing data. If we are unable to obtain the missing data, we will report the data as missing (Higgins 2020). If a measure remains incompletely reported despite author contact, we will attempt to impute the missing data where possible. If different effect measures are reported, we will attempt to transform to the same effect measure where possible. We will conduct a sensitivity analysis to assess whether the assumptions made for missing data are reasonable.

Assessment of heterogeneity

Given the inclusion of a clinically diverse population of different age groups and of hospitalized patients, there will be statistical heterogeneity in the results. We will examine studies for heterogeneity by evaluating the overlap in the CIs of the treatment effect, and by conducting a Chi^2 test across studies. A high Chi^2 statistic and low P value provides evidence of heterogeneity across intervention effect. We will use the I^2 statistic to estimate the proportion of the variation in the effect measures that is due to heterogeneity rather than sampling error, where $I^2 > 75\%$ will be interpreted as considerable (Deeks 2020).

Assessment of reporting biases

We will use a funnel plot to estimate the possibility of a non-reporting publication bias if at least 10 studies are included in the meta-analysis (Page 2020). The statistical significance of the symmetry or asymmetry of the funnel plot will be estimated using Egger's test (Egger 1997)

Data synthesis

Meta-analysis of numerical data

Studies will be analyzed by study design (RCT and NRSI) according to their different risk of bias ratings. We will report meta-analyses using forest plots for each outcome and each design (McKenzie 2023 2023). Given the high likelihood of heterogeneity, we will use a random-effects model. This choice is supported by the fact that the intervention effect may vary between heterogeneous hospitalized patient populations (patients with different diagnoses), and between adults, children, and preterm infants (Deeks 2020).

Synthesis using other methods

If there are too few studies (≤ 2) to perform a meta-analysis, or there is significant bias in the evidence (missing studies and missing data), we will conduct a narrative synthesis according to Synthesis Without Meta-analysis (SWiM), as described in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2024). This will include presenting results in a table and a forest plot without combined effect measures, as described in Table 12.1.a of the *Cochrane Handbook for Systematic Reviews of Interventions* (McKenzie 2023).

Subgroup analysis and investigation of heterogeneity

We will analyze adults and children separately given the difference in intervention RBC volumes and baseline risk of outcomes. While older children may often resemble adults in clinical practice and transfusion volume (> 20 kg), most studies of children involve a majority of infants, therefore we will conduct a subgroup population analysis of children and preterm neonates in the case of sufficient included studies (at least two per category for RCT and NRSI). The planned subgroups for children will include:

1. children (term to < 18 years of age); and
2. preterm neonates (< 37 weeks gestation).

Preterm neonates have different baseline risk of mortality (especially the < 28 weeks' group), and interventions for blood drawing and transfusions vary between preterm infants and children.

Planned subgroups within the adult population will include (Carson 2021):

1. critically ill patients;
2. trauma patients;
3. cardiac and vascular surgery;
4. surgical patients (general surgical, orthopedic and other non-cardiac/vascular);
5. myocardial infarction patients;
6. postpartum patients; and
7. cancer and hematologic patients.

Results of the subgroup analyses should be interpreted with caution and will be observational in nature. Given that we expect to find few studies within each subgroup, we will not compare subgroups to each other, but will simply evaluate the magnitude of effect, if any, in each subgroup. Should there be sufficient high-quality studies within subgroups, we will consult a statistician to help with the analysis across subgroups (rather than across individuals) using formal statistical tests.

There will likely be insufficient studies to consider most of the above subgroups, but these will be evaluated based on the findings.

Sensitivity analysis

We will conduct a sensitivity analysis of studies at low risk of bias in the case of sufficient included studies.

Summary of findings and assessment of the certainty of the evidence

We will create a summary of findings table, using GRADEpro GDT in RevMan software, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (GRADEpro GDT; Schünemann 2024a). We will use GRADE to assess the certainty of the body of evidence according to the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) (Guyatt 2008). The overall risk of bias judgment assessed using RoB 2 and ROBINS-I will inform the GRADE assessment. We will downgrade the certainty of the evidence if there are concerns in any of the above domains. For NRSI, the certainty of evidence can be upgraded in the following rare cases: large effect sizes, dose-effect response, and plausible confounding.

We will assess the GRADE certainty of evidence as follows.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Two review authors (GS, NR) will independently perform the GRADE assessment, with any disagreements resolved by a third review author (JL).

We will use plain language to summarize these findings and make practice recommendations.

The summary of findings table will include the primary outcome (mortality) and the first five secondary outcomes (length of stay, hospital-free days, transfusion reactions, organ dysfunction, and total number of individual allogenic RBC transfusions), measured at 28 days when specified.

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Editorial and peer reviewer contributions

Cochrane Central Editorial Service supported the authors in the development of this review protocol.

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Zoe McQuilten, Monash University, Australia;
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Sue Marcus, Cochrane Central Editorial Service;
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments, and supported the editorial team): Jacob Hester, Cochrane Central Editorial Service;
- Copy Editor (copy editing and production): Lisa Winer, Cochrane Central Production Service;
- Peer reviewers (provided comments and recommended an editorial decision): Tetsuya Yumoto, MD, PhD, Department of Emergency, Critical Care, and Disaster Medicine, Faculty of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama University (clinical/content review); Mark T Friedman, NYU Langone Health, NYU Grossman Long Island School of Medicine (clinical/content review); Radheshyam Meher, MD, All India Institute of Medical Sciences, New Delhi, India (consumer review); Jo-Ana Chase, Cochrane Evidence Production and Methods Directorate (methods review); Jo Platt, Central Editorial Information Specialist (search review).

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APPENDICES

Appendix 1. Preliminary MEDLINE (Ovid) search strategy

Example Search strategy (medline, EBM Embase)

Ovid Medline(R) All

1	Transfusion red blood cells	Exp Erythrocyte Transfusion/ OR (((Transfus* OR exchange OR infusion* OR retransfus*) adj3 (Red cell* OR red blood cell* OR RBC OR RBCs OR Erythrocyte* OR Normocyte*)) OR Erythroexchange* OR Erythro-exchange*).ti,ab,kw,kf
2	Hospitalised	Exp Hospitals/ OR exp Hospital Units/ OR exp Hospital Medicine/ OR exp Emergency Service, Hospital/ OR exp Hospitalization/ OR exp Critical Care/ OR Surgical Procedures, Operative/ OR Postoperative Complications/ OR intraoperative complications/ OR exp blood loss, surgical/ OR Surgery.fs OR exp Specialties, Surgical/ OR exp Emergencies/ OR exp Emergency Medicine/ OR exp Inpatients/ OR child, hospitalized/ OR adolescent, hospitalized/ OR (Hospital* OR Operating room* OR Emergenc* OR Intensive care OR Critical care OR Acute care OR critically ill OR ICU OR ICUs OR NICU* OR PICU* OR Surger* OR Surgical* OR Operation OR Operations OR Operative* OR Postoperative* OR intraoperative* OR Inpatient*).ti,ab,kw,kf
3	Volume	Exp Erythrocyte Count/ OR exp Erythrocyte Volume/ OR (Volume* OR Quantit* OR Unit OR Units OR Size OR Amount* OR "mL kg" OR "cc kg" OR "mL per kg" OR "cc per kg" OR count OR counts OR mass OR masses OR (number* NOT Registration Number)).ti,ab,kw,kf
4	Not	(exp Animals/ NOT exp humans/) OR comment/ or editorial/ or letter/ or Cross-Sectional Studies/ or case reports/ OR (Murine OR Rat OR Rats OR Mice OR

(Continued)

		Mouse* OR Cat OR Cats OR feline* OR Dog OR Dogs OR canine* OR Cattle OR Cow OR Cows OR Pig OR Pigs OR Sow OR Sows OR swine* OR rabbit*).ti,ab,kw,kf
5	Combination	((1 AND 2 AND 3) NOT 4) AND (english OR French).lg 5305 résultats

Ovid All EBM Reviews

1	Transfusion red blood cells	Exp Erythrocyte Transfusion/ OR (((Transfus* OR exchange OR infusion* OR retransfus*) adj3 (Red cell* OR red blood cell* OR RBC OR RBCs OR Erythrocyte* OR Normocyte*)) OR Erythroexchange* OR Erythro-exchange*).ti,ab,kw,kf
2	Hospitalised	Exp Hospitals/ OR exp Hospital Units/ OR exp Hospital Medicine/ OR exp Emergency Service, Hospital/ OR exp Hospitalization/ OR exp Critical Care/ OR Surgical Procedures, Operative/ OR Postoperative Complications/ OR intraoperative complications/ OR exp blood loss, surgical/ OR Surgery.fs OR exp Specialties, Surgical/ OR exp Emergencies/ OR exp Emergency Medicine/ OR exp Inpatients/ OR child, hospitalized/ OR adolescent, hospitalized/ OR (Hospital* OR Operating room* OR Emergenc* OR Intensive care OR Critical care OR Acute care OR critically ill OR ICU OR ICUs OR NICU* OR PICU* OR Surger* OR Surgical* OR Operation OR Operations OR Operative* OR Postoperative* OR intraoperative* OR Inpatient*).ti,ab,kw,kf
3	Volume	Exp Erythrocyte Count/ OR exp Erythrocyte Volume/ OR (Volume* OR Quantit* OR Unit OR Units OR Size OR Amount* OR "mL kg" OR "cc kg" OR "mL per kg" OR "cc per kg" OR count OR counts OR mass OR masses OR (number* NOT Registration Number)).ti,ab,kw,kf
4	Not	(exp Animals/ NOT exp humans/) OR comment/ or editorial/ or letter/ or Cross-Sectional Studies/ or case reports/ OR (Murine OR Rat OR Rats OR Mice OR Mouse* OR Cat OR Cats OR feline* OR Dog OR Dogs OR canine* OR Cattle OR Cow OR Cows OR Pig OR Pigs OR Sow OR Sows OR swine* OR rabbit*).ti,ab,kw,kf
5	Combination	((1 AND 2 AND 3) NOT 4) AND (english OR French).lg 1504 résultats

Ovid Embase

1	Transfusion red blood cells	Exp Erythrocyte Transfusion/ OR (((Transfus* OR exchange OR infusion* OR retransfus*) adj3 (Red cell* OR red blood cell* OR RBC OR RBCs OR Erythrocyte* OR Normocyte*)) OR Erythroexchange* OR Erythro-exchange*).ti,ab,kw
2	Hospitalised	Exp Hospital/ OR Hospital Medicine/ OR exp hospital emergency service/ OR Hospitalization/ OR exp hospital care/ OR surgery/ OR Postoperative Complication/ OR peroperative complication/ OR operative blood loss/ OR Su.fs OR Emergency/ OR exp Emergency Medicine/ OR exp hospital patient/ OR (Hospital* OR Operating room* OR Emergenc* OR Intensive care OR Critical care OR Acute care OR critically ill OR ICU OR ICUs OR NICU* OR PICU* OR Surger* OR

(Continued)

		Surgical* OR Operation OR Operations OR Operative* OR Postoperative* OR intraoperative* OR Inpatient*).ti,ab,kw
3	Volume	Erythrocyte Count/ OR Erythrocyte Volume/ OR (Volume* OR Quantit* OR Unit OR Units OR Size OR Amount* OR "mL kg" OR "cc kg" OR "mL per kg" OR "cc per kg" OR count OR counts OR mass OR masses OR (number* NOT Registration Number)).ti,ab,kw
4	Not	(exp Animal/ NOT exp human/) OR Cross-Sectional Study/ or case study/ or case report/ OR (Letter or Conference Abstract or Conference Paper or Short Survey or Conference Review or Editorial).pt OR (Murine OR Rat OR Rats OR Mice OR Mouse* OR Cat OR Cats OR feline* OR Dog OR Dogs OR canine* OR Cattle OR Cow OR Cows OR Pig OR Pigs OR Sow OR Sows OR swine* OR rabbit*).ti,ab,kw
5	Combination	((1 AND 2 AND 3) NOT 4) AND (english OR French).lg 6902 résultats

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Nadia Roumeliotis wrote the protocol, reviewed inclusion of population, outcomes, and study design based on literature review.

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DECLARATIONS OF INTEREST

NR has no declarations of interest.

GS has no declarations of interest.

PD has no declarations of interest.

GDT has no declarations of interest.

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MT has no declarations of interest.

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