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## **Computerised decision support systems to promote appropriate use of blood products (Protocol)**

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# Computerised decision support systems to promote appropriate use of blood products

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## ABSTRACT

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

To assess the effect of computerised decision support systems (DSSs) on transfusion practice.

## BACKGROUND

### Description of the condition

Blood transfusions have long been associated with significant short- and long-term risks in patients (Bolton-Maggs 2012; Bolton-Maggs 2014; Vamvakas 2009). One approach to minimise the use of blood involves applying a restrictive transfusion policy, whereby blood transfusions are given only when the potential benefits are deemed to outweigh the potential risks.

A Cochrane review compared restrictive versus liberal red blood cell (RBC) transfusion strategies and found reduced in-hospital mortality associated with a restrictive transfusion policy (Carson 2012a). Recent systematic reviews and meta-analyses have also shown reduced cardiac events, re-bleeding, bacterial infections

and mortality, and healthcare-associated infection, in individuals treated according to a restrictive compared with liberal transfusion strategy (Holst 2015; Rohde 2014; Salpeter 2014). A more liberal strategy is recommended for people with cardiovascular disease or acute coronary syndrome (Docherty 2016; NICE 2015).

Cochrane systematic reviews that compared a lower ( $10 \times 10^9/L$ ) versus a higher ( $20$  to  $30 \times 10^9/L$ ) platelet count threshold (Estcourt 2015a), or low dose versus high dose platelet transfusions (Estcourt 2015b), showed no evidence of a difference for bleeding outcomes and a significant reduction in platelet component usage for the more restrictive transfusion policies.

Current guidelines recommend these restrictive policies (Carson 2012b; Kaufman 2015; NICE 2015). However, national audits of blood use in the UK have consistently shown that around 20% of blood product usage is outside of guideline recommendations,

which results in risks to patients and unnecessary costs (Estcourt 2012; NCABT 2011; NCABT 2015).

## Description of the intervention

A decision support system (DSS) is defined as “any software designed to directly aid in clinical decision-making in which characteristics of individual patients are matched to a computerised knowledge base for the purpose of generating patient-specific assessments or recommendations that are then presented to clinicians for consideration” (Hunt 1998). Computerised DSSs have been introduced across a range of healthcare settings as an aid to both clinicians and patients in making healthcare decisions based on individualised patient characteristics (Cresswell 2012). Two large systematic reviews assessed the effect of DSSs across a range of clinical fields and demonstrated that the introduction of a DSS improved clinical practice in around two-thirds of included studies (Garg 2005; Kawamoto 2005).

A recent systematic review of DSS applied to transfusion practice found that implementation of a DSS improves RBC usage in many studies (Hibbs 2015). DSSs have been shown to be effective in intensive care unit (ICU) (Pentti 2003), cardiothoracic surgery (Razavi 2014), haematology settings (Butler 2015), and in paediatrics (Adams 2011; Baer 2011; McCrory 2014). DSSs can improve practice in recipients of red cells (Kassakian 2016), platelets (Butler 2015; Collins 2015; Pentti 2003; Lin 2010), and plasma (Pentti 2003). However, most of these studies were uncontrolled before-and-after studies that relied on historical controls as their comparator group, which led to potential bias in their conclusions (Hibbs 2015).

## How the intervention might work

Blood transfusion guidelines state that clinicians must take into account individual patient variables before implementing transfusion. One method of implementing a restrictive transfusion strategy is through the use of computerised DSSs, incorporating individual patient clinical characteristics and laboratory values, primarily data from blood counts, in order to promote appropriate use of blood transfusion and improve patient outcome.

DSSs can be used as a stand-alone resource (e.g. as a piece of computer software, internet resource, or smart phone application) or can be integrated into a computerised blood component request system. For example, a DSS could require the requester to choose the reason for the transfusion from a list of common transfusion indications. Based on the selected indication and the individual's most recent laboratory test results, the DSS could provide advice on whether the request is within the recommended guidelines and also provide an alert or recommendation for modifying the order if it is inappropriate.

## Why it is important to do this review

Unnecessary transfusions not only expose individuals to the risk of serious adverse transfusion reactions and transfusion-transmitted infections, but also reduce the availability of blood products for other people who need them (WHO 2015). The World Health Organization (WHO) recommends an integrated strategy for ensuring blood safety and availability. This includes the “rational use of blood and blood products to reduce unnecessary transfusions and minimize the risks associated with transfusion, the use of alternatives to transfusion, where possible, and safe and good clinical transfusion practices, including patient blood management” (WHO 2015).

Other systematic reviews have evaluated the effectiveness of interventions (such as educational initiatives, clinician feedback, and audits) intended to improve compliance with local transfusion guidelines and promote appropriate blood usage (Tinmouth 2005; Wilson 2002).

This Cochrane review will assess the use of DSSs to change the behaviour of clinical staff and reduce the number of unnecessary transfusions. Although most DSSs integrated into a computerised blood component request system are only likely to be relevant to high-income countries (Hibbs 2015), stand-alone DSSs on smart phones may be accessible to a much wider proportion of the world's population. In fact, smart phone ownership rates have risen dramatically in low- and middle-income countries from a median of 21% in 2013 to 37% in 2015 (Pew Research Center 2016).

## OBJECTIVES

To assess the effect of computerised decision support systems (DSSs) on transfusion practice.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

As a review of the effects of a health system strategy, we expect most studies to be non-randomised, or to have compared outcomes before and after the introduction of a DSS. We will therefore follow the suggestions of the Cochrane Effective Practice and Organisation of Care (EPOC) Group (Cochrane EPOC 2013a), and will include the following.

- Randomised controlled trials (RCTs)
- Non-randomised controlled trials (NRCTs)
- Controlled before-and-after (CBA) studies

- Interrupted time series (ITS) and repeated measures studies with a clearly defined time when the intervention occurred and at least three data points before and three after the intervention.

We will exclude uncontrolled studies, cross-sectional studies, and case-control studies.

We will exclude cluster-RCTs, non-randomised cluster trials, and CBAs with fewer than two intervention sites and two control sites. In studies with only one intervention or control site, the intervention (or comparison) is completely confounded by study site which makes it difficult to attribute any observed differences to the intervention rather than to other site-specific variables.

If there are sufficient data to answer this review's questions using only data from RCTs we will only report data from RCTs.

### Types of participants

We will include all people (adults and children) who are considered for transfusion of red blood cells (RBCs), platelets, plasma, cryoprecipitate, or granulocytes in any clinical setting.

We will exclude people who receive other blood products e.g. intravenous immunoglobulin, factor VIII.

### Types of interventions

Any electronic/computerised DSS that provides clinicians with recommendations on RBC, platelet, plasma, cryoprecipitate, or granulocyte ordering at the time the decision to order a transfusion is being made based on individual patient characteristics.

The comparator in the control group (for controlled studies) or prior to introduction of the intervention (for ITS studies) will be no DSS.

### Types of outcome measures

The primary and secondary outcomes of this review are outcomes of interest and we will not use them as inclusion criteria for the assessment of studies.

We will categorise all outcomes according to short-, medium-, and long-term outcomes. We will report the exact definition of these time frames over time periods that are common to as many studies as possible (e.g., up to three months, three to 12 months, and greater than 12 months from the start of the study). Included studies will typically involve a change in service for all people treated at a particular hospital with the aim of improving practice of the hospital as a whole; thus patient-reported quality of life outcomes are unlikely to be measured and we will not assess them in this review.

### Primary outcomes

- Proportion of participants who receive transfusions

- Amount of blood product used per participant (number of units in adults and volume in mL in infants and children)

- Serious adverse events
  - Transfusion-related (including transfusion-related acute lung injury (TRALI), transfusion-transmitted infection, transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD), acute transfusion reactions)
  - Bleeding (including World Health Organization (WHO) grade 3 or 4, or equivalent, or bleeding that requires an operation)
  - Infection
  - Arterial or venous thromboembolism (including deep vein thrombosis; pulmonary embolism; stroke; myocardial infarction)

### Secondary outcomes

- Number of transfusions compliant with institutional transfusion guidelines
- Blood count or coagulation parameter (e.g. haematocrit, haemoglobin, prothrombin time, partial thromboplastin time, or platelet count) preceding and after the transfusion
- Length of participant stay (in-hospital)
- Length of participant stay (intensive care unit (ICU))
- All-cause mortality
- Clinician workflow (additional time per intervention implemented)

### Search methods for identification of studies

The Systematic Review Initiative's Information Specialist (CD) will formulate the search strategies in collaboration with the Cochrane Haematological Malignancies Group.

### Electronic searches

We will search the following electronic databases for eligible studies from 1980 to present.

- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, current issue) ([www.cochranelibrary.com/](http://www.cochranelibrary.com/))
- MEDLINE (OvidSP, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE, 1946 onwards)
- PubMed (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, for recent records not yet added to MEDLINE) ([www.ncbi.nlm.nih.gov/sites/entrez](http://www.ncbi.nlm.nih.gov/sites/entrez))
- Embase (OvidSP, 1974 onwards)
- CINAHL (EBSCOHost, 1937 onwards)
- Proquest Dissertations and Thesis Global (ProQuest, 1861 onwards)

- Transfusion Evidence Library (1950 onwards) ([www.transfusionevidencelibrary.com](http://www.transfusionevidencelibrary.com))
- Web of Science Science & Social Sciences Conference Proceedings Indexes (CPSI-S & CPSSI, 1990 onwards)

We will search the following databases for ongoing trials.

- ClinicalTrials.gov ([clinicaltrials.gov/](http://clinicaltrials.gov/))
- WHO International Clinical Trials Registry Platform (ICTRP) ([apps.who.int/trialsearch/](http://apps.who.int/trialsearch/))

We will apply the Cochrane RCT search filters (Lefebvre 2011) and the SIGN systematic review and observational studies filters to the MEDLINE and Embase search strategies; and the SIGN RCT, systematic review and observational studies filters ([www.sign.ac.uk/methodology/filters.html](http://www.sign.ac.uk/methodology/filters.html)) to the searches in CINAHL. We will limit searches to 1980 onwards. We will not apply any restrictions on language or publication status. The search strategies can be found in [Appendix 1](#).

Once we identify studies for inclusion, we will search MEDLINE (Ovid) for errata or retraction statements for the reports of these studies.

### Searching other resources

We will handsearch reference lists of included studies in order to identify further relevant studies. We will contact the lead authors of the included studies to identify any unpublished material, missing data, or information regarding ongoing studies.

## Data collection and analysis

### Selection of studies

We will select studies for inclusion according to Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). The Systematic Review Initiative's Information Specialist (CD) will initially screen all search hits for relevance against the eligibility criteria and discard all those that are clearly irrelevant. Thereafter, two review authors (SF, AD) will independently screen all the remaining references for relevance against the full eligibility criteria.

We will retrieve full-text papers of all references for which we cannot decide on eligibility based on the title and abstract alone. We will assess study design features against the inclusion criteria. We will request additional information from study authors, as necessary, to assess the eligibility for inclusion of individual studies. The two review authors will discuss the results of study selection and try to resolve any discrepancies between themselves. In the event that this is not possible, they will consult a third review author (LE). We will report the results of the study selection process using a PRISMA flow diagram (Moher 2009).

We will record the reasons for exclusion of studies after full-text assessment and will add those to the 'Characteristics of excluded studies' table.

We will collate multiple reports of one study so that the study, and not the report, is the unit of analysis.

### Data extraction and management

As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, two review authors (SF, AD) will independently extract data onto standardised forms and perform a cross-check (Higgins 2011a). We will pilot the data extraction form on two included studies (if available, one controlled study and one ITS study). The review authors will come to a consensus on the required changes. If they cannot reach an agreement, they will consult a third author (LE). The review authors will not be blinded to the names of authors, institutions, journals, or the study outcomes. We will extract the following information from each included study.

- Source: study ID; report ID; review author ID; date of extraction; ID of author checking extracted data; citation of paper; contact authors details
- General study information: publication type; study objectives; funding source; conflict of interest declared; other relevant study publication reviewed
- Study details: location; country; setting; number of centres; inclusion and exclusion criteria; total study duration; recruitment dates; defined primary and secondary outcomes; follow-up time points; power calculations
- Study methodology: design (RCT, NRCT, CBA, ITS), primary analysis (and definition); stopping rules; method of sequence generation and allocation concealment (controlled studies), blinding (of clinicians, participants, and outcome assessors) (controlled studies); any concerns regarding bias
- Characteristics of interventions: description of experimental arms with defined criteria for transfusion (e.g. laboratory values compared with institutional threshold, bleeding status of patient, presence of cardiac ischaemia or early septic shock); time of intervention (CBA and ITS studies); cost of intervention
- Characteristics of participants: age; gender; primary diagnosis etc.
- Participant flow: total number of participants screened for inclusion; total number recruited; total number excluded; total number allocated to each group (controlled studies); total number analysed (for review outcomes); number of allocated patients who received planned treatment; number of drop-outs with reasons (percentage in each arm); protocol violations; missing data
- Outcomes: proportion of patients receiving transfusions; amount of blood product used per participant; serious adverse events (transfusion-related, bleeding, infection, arterial, or venous thromboembolism); number of transfusions compliant

with institutional transfusion guidelines; mean blood count/coagulation parameter preceding transfusion; length of patient stay (in-hospital; ICU); number of deaths, and clinician workflow (additional time per intervention implemented)

- For interventional cohort and pre-post single arm or multiple arms studies we will also collect data if available on: confounding factors; the comparability of groups on confounding factors; methods used to control for confounding and on multiple effect estimates (both unadjusted and adjusted estimates) as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2011)

- For time series data reported graphically, we will extract crude data values for each time point from graphs by using PlotDigitizer (PlotDigitizer 2015).

## Assessment of risk of bias in included studies

### RCTs

We will assess the risk of bias for all included RCTs using the Cochrane 'Risk of bias' tool according to chapter eight of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). Two review authors (SF, AD) will independently assess each element of potential bias listed below as 'high', 'low', or 'unclear' risk of bias. We will provide a brief description of the judgement statements upon which the authors assess potential bias in the 'Characteristics of included studies' table. We will reach a consensus on the degree of risk of bias through comparison of the review authors statements and, where necessary, by consulting a third review author (LE). We will use the 'Risk of bias' assessment to explore statistical heterogeneity in each included study and to perform sensitivity analyses. We will use the Cochrane 'Risk of bias' assessment tool, which includes following domains.

### Selection bias

We will describe for each included study if and how the allocation sequence was generated and if allocation was adequately concealed prior to assignment. We will also describe the method used to conceal the allocation sequence in detail and determine if intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

### Performance bias

We will describe for each included study, where possible, if the study participants and personnel were adequately blinded from knowledge of which intervention a participant received. We will judge studies as low risk of bias if they were blinded, or if we judge that lack of blinding could not have affected the results.

### Detection bias

Was blinding of the outcome assessors effective in preventing systematic differences in the way in which the outcomes were determined?

### Attrition bias

We will describe for each included study the attrition bias due to amount, nature, or handling of incomplete outcome data. We will also try to evaluate whether intention-to-treat analysis has been performed or could be performed from published information.

### Reporting bias:

We will describe for each included study the possibility of selective outcome reporting bias.

### Other issues

Was the study apparently free of other problems that could put it at risk of bias?

We will summarise the risk of bias for each key outcome for each included study. We will judge studies with at least one domain of high risk to be at high risk of bias overall.

### Non-randomised studies

We will use ROBINS-I tool (formerly known as ACROBAT-NRSI) to rate the quality of non-randomised controlled trials (non-RCTs), CBAs, and ITS studies (Sterne 2014). This tool is based on the Cochrane 'Risk of bias' tool for rating the quality of RCTs (Higgins 2011c). The tool covers seven domains and the quality of evidence is rated as either low, moderate, serious, critical, or no information (see Appendix 2 for a copy of the tool), and uses signalling questions for the assessment of the following.

- Bias due to confounding
- Bias in the selection of participants
- Bias in measurement of interventions
- Bias due to departure from intended interventions
- Bias due to missing data
- Bias in measurement of outcomes
- Bias in the selection of the reported result

We will resolve disagreements on the assessment of quality of an included trial by discussion until we reach consensus or, failing that, we will consult a third review author (LE).

We have pre-specified the main potential confounding factors.

- Primary diagnosis of participant (e.g. liver disease; critical illness; pregnancy)
- Age: variability in the age of participants included, e.g. infant (zero to one year); paediatric (one year to 16 years) versus adult (greater than 16 years) versus older adult (greater than 60 years)



- Gender: male to female ratio
- Medications: use of anticoagulants or anti-platelet agents

## Measures of treatment effect

### RCTs

For continuous outcomes we will extract and report the mean or mean change from baseline, standard deviation (SD), and total number of participants in both the treatment and control groups. For dichotomous outcomes we will record the number of events and the total number of participants in both the treatment and control groups.

For continuous outcomes that use the same scale, we will perform analyses using the mean difference (MD) with 95% confidence intervals (CIs). If continuous outcomes are reported using different scales we will use standardised mean difference.

If available, we will extract and report hazard ratios (HRs) for time-to-event data (mortality or time in hospital) data. If HRs are not available, we will estimate as accurately as possible the HR by using the available data and a purpose built method based on the approaches of [Parmar 1998](#) and [Tierney 2007](#). If sufficient studies provide HRs, we will use HRs in favour of risk ratios (RRs) or MDs in a meta-analysis, but for completeness we will also perform a separate meta-analysis of data from studies providing only RRs or MDs for the same outcome.

For dichotomous outcomes we will extract and report the risk ratio (RR) with a 95% CI ([Deeks 2011](#)). Where the number of observed events is small (less than 5% of sample per group), and where trials have balanced treatment groups, we will report the Peto's Odds Ratio (OR) with 95% CI ([Deeks 2011](#)).

If data allow, we will undertake quantitative assessments using [Review Manager 5](#) (RevMan 5) ([Review Manager 5](#)).

### Non-randomised studies with a control group (including CBAs)

For continuous outcomes we will record the mean, SD, and total number of participants in both the treatment and control groups. For dichotomous outcomes we will record the number of events and the total number of participants in both the treatment and control groups.

For continuous variables we will extract and report the absolute change from a statistical analysis adjusting for baseline differences (such as regression models, mixed models, or hierarchical models) or the relative change adjusted for baseline differences in the outcome measures (i.e. the absolute post-intervention difference between the intervention and control groups, as well as the absolute pre-intervention difference between the intervention and control groups/the post-intervention level in the control group) ([Cochrane EPOC 2015](#)).

For dichotomous outcomes we will extract and report the RR with a 95% CI from statistical analyses adjusting for baseline differences (such as Poisson regressions or logistic regressions) or the ratio of RRs (i.e. the RR post-intervention/RR pre-intervention).

If data allow, we will undertake quantitative assessments using [RevMan 5](#) ([Review Manager 5](#)).

### ITS studies

For ITS studies, in order to obtain comparable effect size measures, we will re-analyse extracted data using segmented time-series regression analysis according to recommended methods for ITS designs as described ([Cochrane EPOC 2013b](#)), to obtain two standardised effect sizes for each study: i) change in level (the difference between the observed level at the first intervention time point and that predicted by the pre-intervention time trend) and ii) change in slope (the difference between post- and pre-intervention slopes) of the regression lines before and after the intervention ([Ramsay 2003](#)).

### All studies

Where appropriate, we will report the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH) with 95% CIs.

If we cannot report the available data in any of the formats described above, we will perform a narrative report and, if appropriate, we will present the data in tables.

### Unit of analysis issues

We do not expect to encounter unit of analysis issues as we are unlikely to include cluster-randomised trials, cross-over studies, and multiple observations for the same outcome in this Cochrane review. Should any studies of these designs arise, we will treat these in accordance with the advice given in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011c](#)).

### Dealing with missing data

Where we identify that data are missing or unclear in the published literature, we will contact the study authors directly. We will record the number of participants lost to follow-up for each included study. Where possible, we will analyse the data on an intention-to-treat (ITT) basis, but if insufficient data are available, we will present per protocol (PP) analyses ([Higgins 2011c](#)).

### Assessment of heterogeneity

If the clinical and methodological characteristics of individual studies are sufficiently homogeneous, we will combine the data to perform a meta-analysis. We will assess statistical heterogeneity



of treatment effects between studies using a  $\chi^2$  test with a significance level of  $P < 0.1$ . We will use the  $I^2$  statistic to quantify the degree of potential heterogeneity and classify it as moderate if the  $I^2$  statistic value is greater than 50% or considerable if the  $I^2$  statistic value is greater than 80%. We anticipate that we will identify at least moderate clinical and methodological heterogeneity within the included studies; therefore we will use a random-effects model. If we identify a cause for the heterogeneity, we will explore this with by sensitivity and subgroup analyses (Deeks 2011). If statistical heterogeneity is considerable and we cannot find a cause for the heterogeneity, we will not perform a meta-analysis but will comment on the results narratively and present the results from all studies in tables.

### Assessment of reporting biases

Where at least ten studies are identified for inclusion in a meta-analysis, we will explore potential publication bias (small trial bias) by generating a funnel plot and using a linear regression test. We will consider a  $P$  value of less than 0.1 as significant for this test (Lau 2006; Sterne 2011).

### Data synthesis

If studies are sufficiently homogenous in their study design, we will conduct a meta-analysis according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). For statistical analysis, we will enter data into the Cochrane statistical package RevMan 5 (Review Manager 5). One review author (SF) will enter the data into the software. A second review author (AD) will then check for accuracy. We will conduct separate analyses for each study design (RCTs, NRCTs, CBA studies, ITS studies). We will not conduct meta-analyses that include both RCTs and non-RCTs.

For RCTs where meta-analysis is feasible, we will use the random-effects model to pool data. For binary outcomes we will base the estimation of the between-study variance on the Mantel-Haenszel estimator. We will use the inverse-variance method for continuous outcomes, outcomes that include data from cluster-RCTs, or outcomes where HRs are available. If we find that the heterogeneity is above 80% and we identify a cause for the heterogeneity, we will explore this with subgroup analyses. If we cannot find a cause for the heterogeneity then we will not perform a meta-analysis, but we will comment on the results narratively and will present the results from all studies in tables.

If meta-analysis is feasible for non-RCTs or CBA studies, we will analyse these separately. We will only analyse outcomes with adjusted effect estimates if these are adjusted for the same factors using the inverse-variance method as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2011).

If meta-analysis is feasible for ITS studies, we will use the effect sizes if reported in the included studies or are obtained (as described

above) and pool them using the generic inverse variance method in RevMan 5 (Review Manager 5).

Where data do not allow quantitative assessment (either through insufficient studies of similar design or due to considerable heterogeneity), we will present outcome data individually per study and comment on any trends in the data.

We will document and summarise the reporting of clinician workflow but we will not perform any formal analysis of these outcomes.

### 'Summary of findings' table

We will use the GRADE system to build a 'Summary of findings' table using GRADEpro GDT 2014 software, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a; Schünemann 2011b). We have listed the outcomes that we will include when we compare DSS with no DSS.

- Proportion of participants who receive transfusions
- Total number of units of blood product used
- Mean dose of blood product received per transfused participant
- All-cause mortality
- Length of participant stay (in-hospital)
- Length of participant stay (ICU)

### Subgroup analysis and investigation of heterogeneity

If adequate data are available, we will perform subgroup analyses according to each of the following types of DSS.

- Mandatory or non-mandatory DSS
- Single laboratory value-based DSS or DSS incorporating patient clinical characteristics
  - DSS trigger with recommendation on amount to transfuse or DSS with trigger alone
  - DSS with ongoing additional interventions (e.g. education, training, other complex intervention) or DSS only

### Sensitivity analysis

We will assess the robustness of our findings by performing the following sensitivity analyses where appropriate.

- We will only include studies with a 'low risk of bias' (e.g. RCTs with methods assessed as low risk for random sequence generation and concealment of treatment allocation)
- We will only include studies with less than a 20% dropout rate

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\* Indicates the major publication for the study

## APPENDICES

### Appendix I. Search strategies

#### *CENTRAL (the Cochrane Library)*

- #1 MeSH descriptor: [Blood Transfusion] explode all trees
- #2 MeSH descriptor: [Transfusion Medicine] explode all trees
- #3 (transfus\* or pretransfus\* or posttransfus\* or retransfus\* or “red cell\*” or “red blood cell\*” or RBC\* or platelets or “fresh plasma” or “frozen plasma” or FFP or “platelet concentrate\*”):ti
- #4 (pretransfus\* or posttransfus\* or retransfus\* or “blood transfusion\*” or “red cell transfusion\*” or “red blood cell transfusion\*” or “RBC transfusion\*” or “platelet transfusion\*” or plasma transfusion\* or “fresh plasma” or “frozen plasma” or FFP or “platelet concentrate\*” or “blood management”):ab
- #5 (blood near/2 (use\* or usage\* or utiliz\* or utilis\* or requir\* or administ\* or need\* or management or replac\*)):ti
- #6 (“transfusion service\*” or “transfusion practice\*” or “transfusion medicine” or “transfusion trigger\*” or “transfusion threshold”)
- #7 (blood near/2 (product\* or component\*))
- #8 #1 or #2 or #3 or #4 or #5 or #6 or #7
- #9 MeSH descriptor: [Software] this term only
- #10 MeSH descriptor: [Computer Systems] explode all trees
- #11 MeSH descriptor: [Computer-Assisted Instruction] this term only
- #12 (computer\* or microcomputer\* or electronic\* or automat\* or web or internet or online or phone\* or iphone\* or android or cellphone\* or smartphone\* or mobile\* or telephone\* or tablet\* or iPad\*)
- #13 MeSH descriptor: [Cell Phones] explode all trees
- #14 MeSH descriptor: [Expert Systems] this term only
- #15 MeSH descriptor: [Neural Networks (Computer)] this term only
- #16 (expert system\* or neural network\* or artificial intellig\* or bayes\*)
- #17 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
- #18 MeSH descriptor: [Guidelines as Topic] explode all trees
- #19 MeSH descriptor: [Practice Guideline] this term only
- #20 MeSH descriptor: [Guideline Adherence] this term only
- #21 MeSH descriptor: [Physician's Practice Patterns] this term only
- #22 (remind\* or alert\* or request\* or notif\* or laborator\* or monitor\* or feedback or “order entry” or “order entries”)
- #23 (guideline\* near/2 (practice or adher\* or comply\* or complied or complian\*))
- #24 #18 or #19 or #20 or #21 or #22 or #23

#25 #17 and #24  
 #26 MeSH descriptor: [Medical Informatics] explode all trees  
 #27 MeSH descriptor: [Decision Making, Computer-Assisted] this term only  
 #28 MeSH descriptor: [Therapy, Computer-Assisted] this term only  
 #29 MeSH descriptor: [Decision Support Techniques] explode all trees  
 #30 MeSH descriptor: [Clinical Laboratory Information Systems] this term only  
 #31 MeSH descriptor: [Decision Support Systems, Clinical] this term only  
 #32 MeSH descriptor: [Health Information Systems] this term only  
 #33 MeSH descriptor: [Hospital Information Systems] this term only  
 #34 MeSH descriptor: [Medical Order Entry Systems] this term only  
 #35 MeSH descriptor: [Integrated Advanced Information Management Systems] this term only  
 #36 MeSH descriptor: [Decision Support Systems, Management] this term only  
 #37 MeSH descriptor: [Healthcare Common Procedure Coding System] this term only  
 #38 MeSH descriptor: [Operating Room Information Systems] this term only  
 #39 MeSH descriptor: [Medical Records Systems, Computerized] explode all trees  
 #40 MeSH descriptor: [Reminder Systems] this term only  
 #41 MeSH descriptor: [Medical Informatics Computing] this term only  
 #42 MeSH descriptor: [User-Computer Interface] this term only  
 #43 MeSH descriptor: [Point-of-Care Systems] this term only  
 #44 MeSH descriptor: [Medical Record Linkage] this term only  
 #45 MeSH descriptor: [Information Systems] this term only  
 #46 MeSH descriptor: [Management Information Systems] this term only  
 #47 MeSH descriptor: [Systems Integration] this term only  
 #48 MeSH descriptor: [Electronic Prescribing] this term only  
 #49 (order\* near/2 communicat\* near/2 system\*)  
 #50 (decision\* near/2 support\* near/2 (system\* or tool\* or aid\* or technique\*))  
 #51 ("decision support" or decision aid\* or reminder system\* or "point-of-care evidence")  
 #52 ((electronic\* or computer\* or web or internet or online or phone\* or iphone\* or android or cellphone\* or smartphone\* or mobile\* or telephone\* or tablet\* or iPad\*) near/5 (assist\* or decision\* or support\* or request\* or order\* or assess\* or generat\* or based or strateg\* or automat\* or guideline\* or treatment\* or intervention\* or "knowledge base" or suggestion\* or management or system\* or audit\*))  
 #53 (CDSS or OCS or CPOE or cerner or epic)  
 #54 MeSH descriptor: [Unnecessary Procedures] this term only  
 #55 #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54  
 #56 #8 and #55 [Publication Year from 1980 to 2016]

## MEDLINE (OvidSP)

1. exp Blood Transfusion/
2. "Transfusion Medicine"/
3. (transfus\* or pretransfus\* or posttransfus\* or retransfus\* or red cell\* or red blood cell\* or RBC\* or platelets or fresh plasma or frozen plasma or FFP or platelet concentrate\* or cryoprecipitate).ti,kf.
4. (pretransfus\* or posttransfus\* or retransfus\* or blood transfusion\* or red cell transfusion\* or RBC transfusion\* or red blood cell transfusion\* or platelet transfusion\* or plasma transfusion\* or fresh plasma or frozen plasma or FFP or platelet concentrate\* or blood management or cryoprecipitate).ab,kf.
5. (blood adj2 (use\* or usage\* or utiliz\* or utilis\* or requir\* or administ\* or need\* or management or replac\*)).ti,kf.
6. (transfusion adj (service\* or practice\* or medicine or trigger\* or threshold\*)).tw,kf.
7. (blood adj2 (product\* or component\*)).tw,kf.
8. or/1-7
9. Software/ or Computers/ or exp Microcomputers/ or Minicomputers/ or Computer-Assisted Instruction/ or User-Computer Interface/ or exp Cell Phones/
10. (computer\* or microcomputer\* or electronic\* or automat\* or web or internet or online or phone\* or iphone\* or android or cellphone\* or smartphone\* or mobile\* or telephone\* or tablet\* or iPad\*).tw,kf.

11. exp Computer Communications Networks/ or Computer Systems/ or Electronics/ or Artificial Intelligence/ or "Neural Networks (Computer)"/ or Expert Systems/ or Automation/ or Automatic Data Processing/
12. (expert system\* or neural network\* or artificial intellig\* or bayes\*).tw,kf.
13. or/9-12
14. exp Guidelines as Topic/ or Practice Guidelines/
15. Guideline Adherence/
16. exp Physician's Practice Patterns/
17. (remind\* or alert\* or request\* or notif\* or laborator\* or monitor\* or feedback or (order adj entry)).tw.
18. (guideline\* adj2 (practice or adher\* or comply\* or complied or complian\*)).tw,kf.
19. or/14-18
20. 13 and 19
21. Medical Informatics/ or Medical Informatics Applications/ or Decision Making, Computer-Assisted/ or Therapy, Computer-Assisted/ or Decision Support Techniques/ or Clinical Laboratory Information Systems/ or Decision Support Systems, Clinical/ or Health Information Systems/ or Hospital Information Systems/ or Medical Order Entry Systems/ or Integrated Advanced Information Management Systems/ or Decision Support Systems, Management/ or Healthcare Common Procedure Coding System/ or Operating Room Information Systems/ or Medical Records Systems, Computerized/ or Reminder Systems/ or Medical Informatics Computing/ or Electronic Health Records/ or "User-Computer Interface"/ or Point-of-Care Systems/
22. Medical Record Linkage/
23. Information Systems/ or Management Information Systems/
24. Systems Integration/
25. Electronic Prescribing/
26. (order\* adj2 communicat\* adj2 system\*).tw,kf.
27. (decision\* adj2 support\* adj2 (system\* or tool\* or aid\* or technique\*)).tw,kf.
28. (decision support or decision aid\* or reminder system\* or point-of-care evidence).tw,kf.
29. ((electronic\* or computer\* or web or internet or online or phone\* or iphone\* or android or smartphone\* or cellphone\* or mobile\* or telephone\* or tablet\* or iPad\*) adj5 (assist\* or decision\* or support\* or request\* or order\* or assess\* or generat\* or based or strateg\* or automat\* or guideline\* or treatment\* or intervention\* or knowledge base or suggestion\* or management or system\* or audit\*)).tw,kf.
30. (CDSS or OCS or CPOE or cerner or epic).tw.
31. Unnecessary Procedures/
32. or/20-31
33. 8 and 32
34. animals/ not humans/
35. 33 not 34
36. RANDOMIZED CONTROLLED TRIAL.pt.
37. CONTROLLED CLINICAL TRIAL.pt.
38. (randomi\* or trial\*).tw,kf.
39. (placebo\* or randomly or groups).ab.
40. CLINICAL TRIALS AS TOPIC.sh.
41. or/36-40
42. exp COHORT STUDIES/
43. (cohort\* or controlled trial\* or controlled stud\* or comparative trial\* or comparative stud\* or comparison group\* or comparator group\* or control group\*).tw,kf.
44. ((follow up or observational) adj (study or studies)).tw,kf.
45. (longitudinal\* or retrospective\* or prospective\* or cross sectional\*).mp.
46. CROSS-SECTIONAL STUDIES/
47. CONTROLLED BEFORE-AFTER STUDIES/
48. OBSERVATIONAL STUDY/
49. HISTORICALLY CONTROLLED STUDY/
50. INTERRUPTED TIME SERIES ANALYSIS/
51. (nonrandom\* or non random\*).tw,kf.
52. ((before adj15 (after or during)) or "before-after" or time series or time point\* or repeated measur\*).tw,kf.
53. (pre-post or pre-test\* or pretest\* or posttest\* or post-test\* or (pre adj5 post)).tw,kf.
54. or/42-53



55. Meta-Analysis.pt.  
 56. (meta analy\* or metaanaly\*).ab.  
 57. META-ANALYSIS/  
 58. or/55-57  
 59. (studies or trials).ab.  
 60. 58 and 59  
 61. (meta analy\* or metaanaly\*).ti.  
 62. (systematic\* adj2 (review\* or overview\*)).tw,kf.  
 63. (cochrane or medline or pubmed or embase or cinahl or cinhal or lilacs or "web of science" or science citation index or search terms or published articles or search strateg\* or reference list\* or bibliograph\* or handsearch\* or hand search\* or manual\* search\*).ab.  
 64. (additional adj (papers or articles or sources)).ab.  
 65. (electronic adj (sources or resources or databases)).ab.  
 66. (relevant adj (journals or articles)).ab.  
 67. "REVIEW LITERATURE AS TOPIC"/  
 68. META-ANALYSIS AS TOPIC/  
 69. or/60-68  
 70. Review.pt.  
 71. exp CLINICAL TRIALS AS TOPIC/  
 72. selection criteria.ab. or critical appraisal.ti.  
 73. (data adj (extraction or analys\*)).ab.  
 74. RANDOMIZED CONTROLLED TRIALS/  
 75. OBSERVATIONAL STUDY/  
 76. ((cohort\* or observational or retrospective\*) adj1 (trial\* or stud\*)).tw,kf.  
 77. or/71-75  
 78. 70 and 77  
 79. 69 or 78  
 80. (Comment or Letter or Editorial).pt.  
 81. 79 not 80  
 82. 41 or 54 or 81  
 83. ((before adj15 (after or during)) or "before-after" or time series or time point\* or repeated measur\* or ((study or time) adj5 periods)).tw,kf.  
 84. (pre-post or pre-test\* or pretest\* or posttest\* or post-test\* or (pre adj15 post)).tw,kf.  
 85. 82 or 83 or 84  
 86. exp animals/ not humans/  
 87. 85 not 86  
 88. 35 and 87  
 89. limit 88 to yr="1980 -Current"

### PubMed (epublications only)

#1 (pretransfus\* OR posttransfus\* OR retransfus\* OR blood transfusion\* OR RBC transfusion\* OR RBCs OR red cell transfusion\* OR red blood cell transfusion\* OR platelet transfusion\* OR plasma transfusion\* OR fresh plasma OR frozen plasma OR FFP OR platelet concentrate\* OR platelets[TI] OR cryoprecipitate OR blood product\* OR blood component\* OR transfusion service\* OR transfusion practice\* OR transfusion medicine OR blood management OR transfusion trigger\* OR transfusion threshold\* OR transfus\*[TI])  
 #2 (blood[TI] AND (use\*[TI] OR usage\*[TI] OR utiliz\*[TI] OR utilis\*[TI] OR requir\*[TI] OR administ\*[TI] OR need\*[TI] OR management[TI] OR replac\*[TI]))  
 #3 #1 OR #2  
 #4 (computer\* OR microcomputer\* OR electronic\* OR automat\* OR web OR internet OR online OR phone\* OR iphone\* OR android OR cellphone\* OR smartphone\* OR telephone\* OR tablet\* OR iPad\* OR expert system\* OR neural network\* OR artificial intellig\* OR bayes\*)  
 #5 (guideline\* AND (practice OR adher\* OR comply\* OR complied OR compliant OR compliance))  
 #6 #4 AND #5  
 #7 (order\* AND communicat\* AND (system OR systems))

#8 (decision\* AND support\* AND (system OR systems OR tool\* OR aid\* OR technique\*))

#9 ("decision support" OR "decision aid" OR "decision aids" OR "reminder system" OR "reminder systems" OR "point-of-care evidence")

#10 ((electronic\*[TI] OR computer\*[TI] OR web[TI] OR internet[TI] OR online[TI] OR phone\*[TI] OR iphone[TI] OR android[TI] OR cellphone\*[TI] OR smartphone\*[TI] OR telephone\*[TI] OR tablet\*[TI] OR iPad\*[TI]) AND (assist\*[TI] OR decision\*[TI] OR support\*[TI] OR request\*[TI] OR order\*[TI] OR assess\*[TI] OR generat\*[TI] OR based[TI] OR strateg\*[TI] OR automat\*[TI] OR guideline\*[TI] OR treatment\*[TI] OR intervention\*[TI] OR "knowledge base"[TI] OR suggestion\*[TI] OR management[TI] OR system[TI] OR systems[TI] OR audit\*[TI]))

#11 (CDSS OR OCS OR CPOE OR cerner OR epic)

#12 #6 OR #7 OR #8 OR #9 OR #10 OR #11

#13 #3 AND #12

#14 (random\* OR blind\* OR "control group" OR placebo\* OR controlled OR groups OR trial\* OR "systematic review" OR "meta-analysis" OR metaanalysis OR "literature search" OR medline OR pubmed OR cochrane OR embase OR case control\* OR case series OR cohort\* OR comparative OR comparison OR comparator OR follow-up study OR follow-up studies OR observational\* OR retrospective\* OR non-random\* OR cross-sectional\* OR longitudinal\* OR prospective\* OR (before AND after) OR (before AND during) OR time series OR time point\* OR repeated measure\* OR (study AND period\*) OR pre-post OR pre-test\* OR posttest\* OR post-test\* OR (pre AND post)) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])

#15 #13 AND #14

## Embase (OvidSP)

1. exp Blood Transfusion/
2. "Transfusion Medicine"/
3. (transfus\* or pretransfus\* or posttransfus\* or retransfus\* or red cell\* or red blood cell\* or RBC\* or platelets or fresh plasma or frozen plasma or FFP or platelet concentrate\* or cryoprecipitate).ti,kw.
4. (pretransfus\* or posttransfus\* or retransfus\* or blood transfusion or red cell transfusion\* or red blood cell transfusion\* or RBC transfusion\* or platelet transfusion\* or plasma transfusion\* or fresh plasma or frozen plasma or FFP or platelet concentrate\* or blood management or cryoprecipitate).ab,kw.
5. (blood adj2 (use\* or usage\* or utiliz\* or utilis\* or requir\* or administ\* or need\* or management or replac\*)).ti.
6. (transfusion adj (service\* or practice\* or medicine or trigger\* or threshold\*)).tw,kw.
7. (blood adj2 (product\* or component\*)).tw,kw.
8. or/1-7
9. exp computer/ or exp computer program/
10. exp automation/
11. exp mobile phone/
12. (computer\* or microcomputer\* or electronic\* or automat\* or web or internet or online or phone\* or iphone\* or android or cellphone\* or smartphone\* or mobile\* or telephone\* or tablet\* or iPad\*).ti,kw.
13. (expert system\* or neural network\* or artificial intellig\* or bayes\*).tw,kw.
14. 9 or 10 or 11 or 12 or 13
15. exp practice guideline/
16. clinical practice/
17. decision making/
18. (remind\* or alert\* or request\* or notif\* or laborator\* or monitor\* or feedback or (order adj entry)).ti,kw.
19. (guideline\* adj2 (practice or adher\* or comply\* or complied or complian\*)).mp.
20. 15 or 16 or 17 or 18 or 19
21. 14 and 20
22. data processing/ or exp communication protocol/ or computer assisted diagnosis/ or exp computer assisted therapy/
23. exp electronic medical record/ or computer interface/ or computer system/ or "decision tree"/ or dental informatics/ or electronic data interchange/ or human computer interaction/ or medical informatics/ or nursing informatics/
24. exp information system/ or information technology/ or internet/
25. (order\* adj2 communicat\* adj2 system\*).tw,kw.
26. (decision\* adj2 support\* adj2 (system\* or tool\* or aid\* or technique\*)).tw,kw.
27. (decision support or decision aid\* or reminder system\* or point-of-care evidence).mp.

28. ((electronic\* or computer\* or web or internet or online or phone\* or iphone\* or android or cellphone\* or smartphone\* or mobile\* or telephone\* or tablet\* or iPad\*) adj5 (assist\* or decision\* or support\* or request\* or order\* or assess\* or generat\* or based or strateg\* or automat\* or guideline\* or treatment\* or intervention\* or knowledge base or suggestion\* or management or system\* or audit\*)).mp.
29. (CDSS or OCS or CPOE or cerner or epic).tw,kw.
30. Unnecessary Procedures/
31. or/21-30
32. 8 and 31
33. animals/ not humans/
34. 32 not 33
35. exp Controlled Study/
36. Longitudinal Study/
37. Retrospective Study/
38. Observational Study/
39. Intervention Study/
40. Prospective Study/
41. Cohort Analysis/
42. Comparative Study/
43. Comparative Effectiveness/
44. (cohort\* or controlled trial\* or controlled stud\* or comparative trial\* or comparative stud\* or comparison group\* or comparator group\* or control group\*).tw.
45. ((follow up or observational or longitudinal\* or retrospective\* or prospective\* or cross sectional\*) adj (study or studies)).tw.
46. (nonrandom\* or non random\*).tw.
47. ((before adj15 (after or during)) or “before-after” or time series or time point\* or repeated measur\* or ((study or time) adj5 periods)).mp.
48. (pre-post or pre-test\* or pretest\* or posttest\* or post-test\* or (pre adj15 post)).mp.
49. or/35-48
50. Meta Analysis/
51. Systematic Review/
52. (meta analy\$ or metaanalys\$).tw.
53. ((systematic or literature) adj2 (review\$ or overview\$ or search\$)).tw.
54. (cochrane or embase or cinahl or cinhal or lilacs or BIDS or science citation index or psyclit or psychlit or psycinfo or psychinfo or cancerlit).ti,ab.
55. (electronic\$ adj (sources or resources or databases)).ab.
56. (bibliograph\$ or handsearch\$ or hand search\$ or (manual\$ adj1 search\$) or reference lists).ab.
57. (additional adj (papers or articles or sources)).ab.
58. (relevant adj (journals or articles)).ab.
59. (search term\$ or published articles or search strateg\$).ab.
60. or/50-59
61. review.pt. and (data extraction or selection criteria).ab.
62. editorial.pt.
63. 61 not 62
64. 60 or 63
65. Randomized Controlled trial/ or Single-Blind Procedure/ or Crossover-Procedure/ or Double-Blind Procedure/
66. (random\* or factorial\* or crossover\* or cross over\* or cross-over\* or placebo\* or doubl\* blind\* or singl\* blind\* or assign\* or allocat\* or volunteer\*).mp.
67. 65 or 66
68. 49 or 64 or 67
69. 34 and 68
70. limit 69 to yr=“1980-Current”

## **CINAHL (EBSCOHost)**

S1 (MH “Blood Transfusion+”)

S2 (MH "Transfusion Medicine")

S3 TI (transfus\* or pretransfus\* or posttransfus\* or retransfus\* or RBC\* or red cell\* or red blood cell\* or platelets or fresh plasma or frozen plasma or FFP or platelet concentrate\*)

S4 AB (pretransfus\* or posttransfus\* or retransfus\* or blood transfusion\* or RBC transfusion\* or red cell transfusion\* or red blood cell transfusion\* or platelet transfusion\* or plasma transfusion\* or fresh plasma or frozen plasma or FFP or platelet concentrate\* or blood management)

S5 TI (blood N2 (use\* or usage\* or utiliz\* or utilis\* or requir\* or administ\* or need\* or management or replac\*)) OR TX (blood N2 (product\* or component\*))

S6 TI (transfusion N1 (service\* or practice\* or medicine or trigger\* or threshold\*))

S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6

S8 (MH "Software")

S9 (MH "Computers and Computerization+")

S10 (MH "User-Computer Interface")

S11 (MH "Cellular Phone+")

S12 TI ( (computer\* or microcomputer\* or electronic\* or automat\* or web or internet or online or phone\* or iphone\* or android or cellphone\* or smartphone\* or mobile\* or telephone\* or tablet\* or iPad\*) ) OR AB ( (computer\* or microcomputer\* or electronic\* or automat\* or web or internet or online or phone\* or iphone\* or android or cellphone\* or smartphone\* or mobile\* or telephone\* or tablet\* or iPad\*) )

S13 (MH "Artificial Intelligence+")

S14 TI ( (expert system\* or neural network\* or artificial intellig\* or bayes\*) ) OR AB ( (expert system\* or neural network\* or artificial intellig\* or bayes\*) )

S15 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14

S16 (MH "Guideline Adherence") OR (MH "Practice Guidelines")

S17 TI ( (remind\* or alert\* or request\* or notif\* or laborator\* or monitor\* or feedback or order entr\*) ) OR AB ( (remind\* or alert\* or request\* or notif\* or laborator\* or monitor\* or feedback or order entr\*) )

S18 TI ( (guideline\* N2 (practice or adher\* or comply\* or complied or complian\*)) ) OR AB ( (guideline\* N2 (practice or adher\* or comply\* or complied or complian\*)) )

S19 S16 OR S17 OR S18

S20 S15 AND S19

S21 (MH "Decision Making, Computer Assisted") OR (MH "Therapy, Computer Assisted+") OR (MH "Remote Access to Information")

S22 (MH "Decision Support Techniques+")

S23 (MH "Clinical Laboratory Information Systems")

S24 (MH "Access to Information+")

S25 (MH "Reminder Systems")

S26 (MH "Health Informatics+")

S27 (MH "Information Seeking Behavior")

S28 (MH "Information Technology+")

S29 (MH "Systems Development+")

S30 (MH "Health Information Systems+")

S31 (MH "Decision Support Systems, Management")

S32 TI (order\* N2 communicat\* N2 system\*) OR AB (order\* N2 communicat\* N2 system\*)

S33 TX (decision\* N2 support\* N2 (system\* or tool\*))

S34 TX (decision support or decision aid\* or reminder system\* or point-of-care evidence)

S35 TX (CDSS or OCS or CPOE or cerner or epic)

S36 (MH "Unnecessary Procedures")

S37 TI ( ((electronic\* or computer\* or web or internet or online or phone\* or iphone\* or android or cellphone\* or smartphone\* or mobile\* or telephone\* or tablet\* or iPad\*)) N5 (assist\* or decision\* or support\* or request\* or order\* or assess\* or generat\* or based or strateg\* or automat\* or guideline\* or treatment\* or intervention\* or knowledge base or suggestion\* or management or system\* or audit\*)) ) OR AB ( ((electronic\* or computer\* or web or internet or online or phone\* or iphone\* or android or cellphone\* or smartphone\* or mobile\* or telephone\* or tablet\* or iPad\*)) N5 (assist\* or decision\* or support\* or request\* or order\* or assess\* or generat\* or based or strateg\* or automat\* or guideline\* or treatment\* or intervention\* or knowledge base or suggestion\* or management or system\* or audit\*)) )

S38 S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34  
 OR S35 OR S36 OR S37  
 S39 S7 AND S38  
 S40 (MH "Animals+")  
 S41 (MH "Human")  
 S42 S40 NOT S41  
 S43 S39 NOT S42  
 S44 Limiters - Published Date: 19800101-20160831  
 S45 S43 AND S44

## Transfusion Evidence Library

#1 title:(decision support OR decision aid OR computer OR computers OR web OR internet OR online OR phone OR iphone OR android OR cellphone OR smartphone OR telephone OR tablet OR iPad OR electronic OR automated OR CDSS OR OCS OR CPOE OR cerner OR epic) OR keywords:(decision support OR decision aid OR computer OR computers OR web OR internet OR online OR phone OR iphone OR android OR cellphone OR smartphone OR telephone OR tablet OR iPad OR electronic OR automated OR CDSS OR OCS OR CPOE OR cerner OR epic)  
 #2 title: (reminder OR request OR feedback OR guideline OR notification OR expert OR alert OR order OR ordering OR orders OR hospital OR information) AND title: (system OR systems)  
 #3 keywords: (reminder OR request OR feedback OR guideline OR notification OR expert OR alert OR order OR orders OR ordering OR hospital OR information) AND keywords: (system OR systems)  
 #4 #1 OR #2 OR #3 [LIMIT TO 1980 TO PRESENT]

## ProQuest Dissertations & Theses Global

S1 all((pretransfus\* OR posttransfus\* OR retransfus\* OR blood transfusion\* OR RBC transfusion\* OR RBCs OR red cell transfusion\* OR red blood cell transfusion\* OR platelet transfusion\* OR plasma transfusion\* OR fresh plasma OR frozen plasma OR FFP OR platelet concentrate\* OR cryoprecipitate OR blood product\* OR blood component\* OR transfusion service\* OR transfusion practice\* OR transfusion medicine OR blood management OR transfusion trigger\* OR transfusion threshold\*)) OR ti(((platelets OR transfus\*) OR (blood AND (use\* OR usage\* OR utiliz\* OR utilis\* OR requir\* OR administ\* OR need\* OR management OR replac\*)) ))  
 S2 all((computer\* OR microcomputer\* OR electronic\* OR automat\* OR web OR internet OR online OR phone\* OR iphone\* OR android OR cellphone\* OR smartphone\* OR telephone\* OR tablet\* OR iPad\* OR expert system\* OR neural network\* OR artificial intellig\* OR bayes\*))  
 S3 all(guideline\* AND (practice OR adher\* OR comply\* OR complied OR compliant OR compliance))  
 S4 S2 AND S3  
 S5 all((order\* AND communicat\* AND (system OR systems)) ) OR all(((decision\* AND support\* AND (system OR systems OR tool\* OR aid\* OR technique\*)) OR ("decision support" OR "decision aid" OR "reminder system" OR "point-of-care evidence" OR CDSS OR OCS OR CPOE OR cerner OR epic)))  
 S6 ti((electronic\* OR computer\* OR web OR internet OR online OR phone\* OR iphone\* OR android OR cellphone\* OR smartphone\* OR telephone\* OR tablet\* OR iPad\*) AND (assist\* OR decision\* OR support\* OR request\* OR order\* OR assess\* OR generat\* OR based OR strateg\* OR automat\* OR guideline\* OR treatment\* OR intervention\* OR "knowledge base" OR suggestion\* OR management OR system OR systems OR audit\*))  
 S7 S4 OR S5 OR S6  
 S8 S1 AND S7  
 S9 all((random\* OR blind\* OR "control group" OR placebo\* OR controlled OR groups OR trial\* OR "systematic review" OR "meta-analysis" OR metaanalysis OR "literature search" OR medline OR pubmed OR cochrane OR embase OR case control\* OR case series OR cohort\* OR comparative OR comparison OR comparator OR follow-up study OR follow-up studies OR observational\* OR retrospective\* OR non-random\* OR cross-sectional\* OR longitudinal\* OR prospective\* OR time series OR time point\* OR repeated measure\* OR study period\* OR pre-post OR pre-test\* OR posttest\* OR post-test\*))  
 S10 all(before AND after)  
 S11 all((before AND during))  
 S12 S9 OR S10 OR S11  
 S13 S8 AND S12

## Web of Science CPCI-S

#1 TS=(pretransfus\* OR posttransfus\* OR retransfus\* OR blood transfusion\* OR RBC transfusion\* OR RBCs OR red cell transfusion\* OR red blood cell transfusion\* OR platelet transfusion\* OR plasma transfusion\* OR fresh plasma OR frozen plasma OR FFP OR platelet concentrate\* OR cryoprecipitate OR blood product\* OR blood component\* OR transfusion service\* OR transfusion practice\* OR transfusion medicine OR blood management OR transfusion trigger\* OR transfusion threshold\*)

#2 TI=(platelets OR transfus\*)

#3 TI=(blood AND (use\* OR usage\* OR utiliz\* OR utilis\* OR requir\* OR administ\* OR need\* OR management OR replac\*))

#4 #1 OR #2 OR #3

#5 TS=(computer\* OR microcomputer\* OR electronic\* OR automat\* OR web OR internet OR online OR phone\* OR iphone\* OR android OR cellphone\* OR smartphone\* OR telephone\* OR tablet\* OR iPad\* OR expert system\* OR neural network\* OR artificial intellig\* OR bayes\*)

#6 TS=(guideline\* AND (practice OR adher\* OR comply\* OR complied OR compliant OR compliance))

#7 #5 AND #6

#8 TS=(order\* AND communicat\* AND (system OR systems))

#9 TS=(decision\* AND support\* AND (system OR systems OR tool\* OR aid\* OR technique\*))

#10 TS=("decision support" OR "decision aid" OR "reminder system" OR "point-of-care evidence" OR CDSS OR OCS OR CPOE OR cerner OR epic)

#11 TI=((electronic\* OR computer\* OR web OR internet OR online OR phone\* OR cellphone\* OR smartphone\* OR iphone\* OR android OR telephone\* OR tablet\* OR iPad\*) AND (assist\* OR decision\* OR support\* OR request\* OR order\* OR assess\* OR generat\* OR based OR strateg\* OR automat\* OR guideline\* OR treatment\* OR intervention\* OR "knowledge base" OR suggestion\* OR management OR system OR systems OR audit\*))

#12 #7 OR #8 OR #9 OR #10 OR #11

#13 #4 AND #12

#14=(random\* OR blind\* OR "control group" OR placebo\* OR controlled OR groups OR trial\* OR "systematic review" OR "meta-analysis" OR metaanalysis OR "literature search" OR medline OR pubmed OR cochrane OR embase OR case control\* OR case series OR cohort\* OR comparative OR comparison OR comparator OR follow-up study OR follow-up studies OR observational\* OR retrospective\* OR non-random\* OR cross-sectional\* OR longitudinal\* OR prospective\* OR (before AND after) OR (before AND during) OR time series OR time point\* OR repeated measure\* OR (study AND period\*) OR pre-post OR pre-test\* OR posttest\* OR post-test\* OR (pre AND post))

#15 #13 AND #14

## ClinicalTrials.gov

Search Terms: (transfusion OR "red cells" OR "red blood cells" OR "blood product" OR "blood component" OR RBCs OR platelet OR platelets OR cryoprecipitate OR plasma OR FFP)

AND

Interventions: (decision OR reminder OR alert OR electronic OR "point-of-care evidence" OR computer OR computerized OR "ordering system" OR internet OR online OR web OR phone OR smartphone OR iPhone OR android OR iPad)

## WHO ICTRP

Title/Intervention: transfusion OR red cells OR red blood cells OR blood product OR blood component OR RBC OR platelet OR platelets OR cryoprecipitate OR plasma OR FFP

AND

Title/Intervention: decision OR reminder OR alert OR electronic OR point of care evidence OR computer OR computerized OR ordering system OR internet OR online OR web OR phone OR smartphone OR iPhone OR android OR iPad

AND

Recruitment Status: All

## Appendix 2. ROBINS-I tool (Risk Of Bias in Non-Randomized Studies - of Interventions)

### ROBINS-I tool (Stage I)

Specify the review question

<b>Participants</b>	We will include all people (adults and children) who are considered for transfusion of red blood cells (RBCs), platelets, plasma, cryoprecipitate, or granulocytes in any clinical setting We will exclude people who are receiving other blood products e.g. intravenous immunoglobulin, factor VIII
<b>Experimental intervention</b>	Any electronic/computerised decision support system (DSS) that provides clinicians with recommendations on RBC, platelet, plasma, cryoprecipitate or granulocyte ordering at the time the decision to order a transfusion is being made based on individual patient characteristics
<b>Control intervention</b>	The comparator in the control group (controlled studies) or prior to introduction of the intervention (ITS) will be no DSS
<b>Outcomes</b>	Primary outcomes <ul style="list-style-type: none"><li>• Proportion of participants receiving transfusions</li><li>• Amount of blood product used per participant (number of units in adults and volume in mL in infants and children)</li></ul> Secondary outcomes <ul style="list-style-type: none"><li>• Number of transfusions compliant with institutional transfusion guidelines</li><li>• Blood count or coagulation parameter (e.g. haematocrit, haemoglobin, prothrombin time, partial thromboplastin time or platelet count) preceding and after the transfusion</li><li>• Length of participant stay (in-hospital)</li><li>• Length of participant stay (intensive care unit)</li><li>• All-cause mortality</li><li>• Clinician workflow (additional time per intervention implemented)</li></ul>

#### List the confounding areas relevant to all or most studies

We have pre-specified the main potential confounding factors.

1. Primary diagnosis of participant (e.g. liver disease; critical illness; pregnancy)
2. Age: variability in the age of participants included, e.g. infant (zero to one year); paediatric (one to 16 years) versus adult (greater than 16 years) versus older adult (greater than 60 years)
3. Gender: male to female ratio

#### List the possible co-interventions that could differ between intervention groups and could impact on outcomes

We have pre-specified the possible co-interventions that could differ between intervention groups and could impact on outcomes.

### The ROBINS-I tool (Stage II): for each study

Specify a target trial specific to the study



<b>Design</b>	Individually randomised/cluster randomised/matched
<b>Participants</b>	
<b>Experimental intervention</b>	
<b>Control intervention</b>	

#### Is your aim for this study...?

- ☐ To assess the effect of initiating intervention (as in an intention-to-treat analysis)
- ☐ To assess the effect of initiating and adhering to intervention (as in a per-protocol analysis)

#### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the 'Summary of findings' table). Specify whether this is a proposed benefit or harm of intervention.

#### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. risk ratio (RR) = 1.52 (95% confidence interval (CI) 0.83 to 2.77) or a reference (e.g. to a table, figure or paragraph) or both that uniquely defines the result being assessed.

#### Preliminary consideration of confounders

Complete a row for each important confounding area:

1. listed in the review protocol; and
2. relevant to the setting of this particular study, or which the study authors identified as potentially important. "Important" confounding areas are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the area, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

1. Confounding areas listed in the review protocol				
Confounding area	Measured Variable (s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding area measured validly and reliably by this variable (or these variables)?	Optional: is adjusting for this variable (alone) expected to favour the experimental or the control group?
			Yes/No/No information	Favour intervention/Favour control / No information

(Continued)


2. Additional confounding areas relevant to the setting of this particular study, or that the study authors identified as important				
Confounding area	Measured variable(s)	Is there evidence that controlling for this variable was unnecessary? <sup>1</sup>	Is the confounding area measured validly and reliably by this variable (or these variables)?	Optional: is adjusting for this variable (alone) expected to favour the experimental or the control group?
			Yes/no/no information	Favour intervention/ favour control/no information

<sup>1</sup>In the context of a particular study, variables can be demonstrated not to be confounders and so excluded from the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

### Preliminary consideration of co-interventions

Complete a row for each important co-intervention:

1. listed in the review protocol; and
2. relevant to the setting of this particular study, or which the study authors identified as important.

“Important” co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.

1. Co-interventions listed in the review protocol		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental or the control group
		Favour experimental/favour comparator/ no information

(Continued)

		Favour experimental/favour comparator/ no information
		Favour experimental/favour comparator/ no information

## 2. Additional co-interventions relevant to the setting of this particular study, or that the study authors identified as important

Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental or the control group
		Favour experimental/favour comparator/ no information
		Favour experimental/favour comparator/ no information
		Favour experimental/favour comparator/ no information

## 'Risk of bias' assessment (cohort-type studies)

Bias domain	Signalling questions	Elaboration	Response options
Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study? If N or PN to 1.1: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	In rare situations, such as when studying harms that are very unlikely to be related to factors that influence treatment decisions, no confounding is expected and the study can be considered to be at low risk of bias due to confounding, equivalent to a fully randomised trial There is no NI (no information) option for this signalling question	Y/PY/PN/N
	If Y or PY to 1.1: determine whether there is a need to assess time-varying confounding		
	1.2. Was the analysis based on splitting participants' follow-up	If participants could switch between intervention groups then	NA/Y/PY/PN/N/NI

(Continued)

	time according to intervention received? If N or PN, answer questions relating to baseline confounding (1.4 to 1.6) If Y or PY, proceed to question 1.3.	associations between intervention and outcome may be biased by time-varying confounding. This occurs when prognostic factors influence switches between intended interventions	
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? If N or PN, answer questions relating to baseline confounding (1.4 to 1.6) If Y or PY, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)	If intervention switches are unrelated to the outcome, e.g. when the outcome is an unexpected harm, then time-varying confounding will not be present and only control for baseline confounding is required	NA/Y/PY/PN/N/NI
	<b>Questions relating to baseline confounding only</b>		
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding areas?	Appropriate methods to control for measured confounders include stratification, regression, matching, standardization, and inverse probability weighting. They may control for individual variables or for the estimated propensity score. Inverse probability weighting is based on a function of the propensity score. Each method depends on the assumption that there is no unmeasured or residual confounding	NA/Y/PY/PN/N/NI
	1.5. If Y or PY to 1.4: were confounding areas that were controlled for measured validly and reliably by the variables available in this study?	Appropriate control of confounding requires that the variables adjusted for are valid and reliable measures of the confounding domains. For some topics, a list of valid and reliable measures of confounding domains will be specified in the review protocol but for others such a list may not be available. Study authors may cite references to support the use	NA/Y/PY/PN/N/NI

(Continued)

		of a particular measure. If authors control for confounding variables with no indication of their validity or reliability pay attention to the subjectivity of the measure. Subjective measures (e.g. based on self-report) may have lower validity and reliability than objective measures such as lab findings	
	1.6. Did the authors control for any post-intervention variables?	Controlling for post-intervention variables is not appropriate. Controlling for mediating variables estimates the direct effect of intervention and may introduce confounding. Controlling for common effects of intervention and outcome causes bias	NA/Y/PY/PN/N/NI
	<b>Questions relating to baseline and time-varying confounding</b>		
	1.7. Did the authors use an appropriate analysis method that adjusted for all the important confounding areas and for time-varying confounding?	Adjustment for time-varying confounding is necessary to estimate per-protocol effects in both randomised trials and NRSI. Appropriate methods include those based on inverse-probability weighting. Standard regression models that include time-updated confounders may be problematic if time-varying confounding is present	NA/Y/PY/PN/N/NI
	1.8. If Y or PY to 1.7: were confounding areas that were adjusted for measured validly and reliably by the variables available in this study?	See 1.5 above.	NA/Y/PY/PN/N/NI
	'Risk of bias' judgement	Low : no confounding expected.	Low/moderate/serious/critical/NI
		Moderate: confounding expected, all known important confounding domains appropriately measured and controlled for; and	

(Continued)

		reliability and validity of measurement of important domains were sufficient, such that we do not expect serious residual confounding	
		Serious: at least one known important domain was not appropriately measured, or not controlled for; or reliability or validity of measurement of a important domain was low enough that we expect serious residual confounding	
		<b>Critical</b> - Confounding inherently not controllable, or the use of negative controls strongly suggests unmeasured confounding	
	Optional: what is the predicted direction of bias due to confounding?	Can the true effect estimate be predicted to be greater or less than the estimated effect in the study because one or more of the important confounding domains was not controlled for? Answering this question will be based on expert knowledge and results in other studies and therefore can only be completed after all of the studies in the body of evidence have been reviewed. Consider the potential effect of each of the unmeasured domains and whether all important confounding domains not controlled for in the analysis would be likely to change the estimate in the same direction, or if one important confounding domain that was not controlled for in the analysis is likely to have a dominant impact	Favours experimental/favours comparator/unpredictable
<b>Bias in selection of participants into the study</b>	2.1. Was selection of participants into the study (or into the analysis) based on partici-	This domain is concerned only with selection into the study based on participant character-	Y/PY/PN/N/NI

(Continued)

	pant characteristics observed after the start of intervention?	istics observed after the start of intervention. Selection based on characteristics observed before the start of intervention can be addressed by controlling for imbalances between intervention and control groups in baseline characteristics that are prognostic for the outcome (baseline confounding)	
<b>If N or PN to 2.1: go to 2.4</b>			
	2.2. If Y or PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention	Selection bias occurs when selection is related to an effect of either intervention or a cause of the outcome. Therefore, the result is at risk of selection bias if selection into the study is related to both the intervention and the outcome	NA/Y/PY/PN/N/NI
	2.3 If Y or PY to 2.2: were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?		NA/Y/PY/PN/N/NI
	2.4. Do start of follow-up and start of intervention coincide for most participants?	If participants are not followed from the start of the intervention then a period of follow-up has been excluded, and individuals who experienced the outcome soon after intervention will be missing from analyses. This problem may occur when prevalent, rather than new (incident), users of the intervention are included in analyses	Y/PY/PN/N/NI
	2.5. If Y or PY to 2.2 and 2.3, or N or PN to 2.4: were adjustment techniques used that are likely to correct for the presence of selection biases?	It is in principle possible to correct for selection biases, e. g. by using inverse probability weights to create a pseudo-population in which the selection bias has been removed, or by modelling the distributions	NA/Y/PY/PN/N/NI



(Continued)

		of the missing participants or follow-up times and outcome events and including them using missing data methodology. However such methods are rarely used and the answer to this question will usually be “No”	
	'Risk of bias' judgement	<p>Low: all participants who would have been eligible for the target trial were included in the study and start of follow-up and start of intervention coincide for all subjects</p> <hr/> <p>Moderate: selection into the study may have been related to intervention and outcome, but the authors used appropriate methods to adjust for the selection bias; or start of follow-up and start of intervention do not coincide for all participants, but:</p> <ol style="list-style-type: none"> <li>1. the proportion of participants for which this was the case was too low to induce important bias;</li> <li>2. the authors used appropriate methods to adjust for the selection bias; or</li> <li>3. the review authors are confident that the rate (hazard) ratio for the effect of intervention remains constant over time.</li> </ol> <hr/> <p>Serious: selection into the study was related to intervention and outcome; or start of follow-up and start of intervention do not coincide, and a potentially important amount of follow-up time is missing from analyses, and the rate ratio is not constant over time</p>	Low/moderate/serious/critical/NI

(Continued)

		Critical: selection into the study was strongly related to intervention and outcome; or a substantial amount of follow-up time is likely to be missing from analyses, and the rate ratio is not constant over time	
	Optional: what is the predicted direction of bias due to selection of participants into the study?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental/favours comparator/towards null/away from null/unpredictable
<b>Bias in classification of interventions</b>	3.1 Were intervention groups clearly defined?	A pre-requisite for an appropriate comparison of interventions is that the interventions are well defined. Ambiguity in the definition may lead to bias in the classification of participants. For individual-level interventions, criteria for considering individuals to have received each intervention should be clear and explicit, covering issues such as type, setting, dose, frequency, intensity and timing of intervention. For population-level interventions (e.g. measures to control air pollution), the question relates to whether the population is clearly defined, and the answer is likely to be 'Yes'	Y/PY/PN/N/NI
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	In general, if information about interventions received is available from sources that could not have been affected by subsequent outcomes, then differential misclassification of intervention status is unlikely. Collection of the information at the time of the intervention makes it easier to avoid such misclassification. For population-level interventions (e.g. measures to	Y/PY/PN/N/NI

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		control air pollution), the answer to this question is likely to be 'Yes'	
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Collection of the information at the time of the intervention may not be sufficient to avoid bias. The way in which the data are collected for the purposes of the NRSI should also avoid misclassification	Y/PY/PN/N/NI
	'Risk of bias' judgement	<p>Low: intervention status is well defined and based solely on information collected at the time of intervention</p> <p>Moderate: intervention status is well defined but some aspects of the assignments of intervention status were determined retrospectively</p> <p>Serious: intervention status is not well defined, or major aspects of the assignments of intervention status were determined in a way that could have been affected by knowledge of the outcome</p> <p>Critical: (unusual) an extremely high amount of misclassification of intervention status, e.g. because of unusually strong recall biases</p>	Low/moderate/serious/critical/NI
	Optional: what is the predicted direction of bias due to measurement of outcomes or interventions?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental/favours comparator/towards null/away from null/unpredictable
<b>Bias due to departures from intended interventions</b>	4.1. Was the intervention implemented successfully for most participants?	Consider the success of implementation of the intervention in the context of its complexity. Was recommended practice followed by those administer-	Y/PY/PN/N/NI

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	ing the intervention?	
<b>If your aim for this study is to assess the effect of initiating and adhering to intervention (as in a per-protocol analysis), answer questions 4.2 to 4.4</b>		
4.2. Did study participants adhere to the assigned intervention regimen?	<p>Lack of adherence to assigned intervention includes cessation of intervention, crossovers to the comparator intervention and switches to another active intervention. We distinguish between analyses where:</p> <ol style="list-style-type: none"> <li>1. intervention switches led to follow-up time being assigned to the new intervention; and</li> <li>2. intervention switches (including cessation of intervention) where follow-up time remained allocated to the original intervention;</li> <li>3. is addressed under time-varying confounding, and should not be considered further here.</li> </ol> <p>Consider available information on the proportion of study participants who continued with their assigned intervention throughout follow-up. Was lack of adherence sufficient to impact the intervention effect estimate?</p>	NA/Y/PY/PN/N/NI
4.3. Were important co-interventions balanced across intervention groups?	Consider the co-interventions that are likely to affect the outcome and to have been administered in the context of this study, based on the preliminary consideration of co-interventions and available literature. Consider whether these co-interventions are balanced between intervention groups	NA/Y/PY/PN/N/NI
4.4. If N or PN to 4.1, 4.2 or 4.3: were adjustment techniques used that are likely to correct for these issues?	Such adjustment techniques include inverse-probability weighting to adjust for	NA/Y/PY/PN/N/NI

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		censoring at deviation from intended intervention, or inverse probability weighting of marginal structural models to adjust for time-varying confounding. Specialist advice may be needed to assess studies that used these approaches	
	'Risk of bias' judgement	Low: no bias due to deviation from the intended intervention is expected, e.g. if both the intervention and comparator are implemented over a short time period, and subsequent interventions are part of routine medical care, or if the specified comparison relates to initiation of intervention regardless of whether it is continued	Low/moderate/serious/critical/ NI
		Moderate: bias due to deviation from the intended intervention is expected, and switches, co-interventions, and some problems with intervention fidelity are appropriately measured and adjusted for in the analyses. Alternatively, most (but not all) deviations from intended intervention reflect the natural course of events after initiation of intervention	
		Serious: switches in treatment, co-interventions, or problems with implementation fidelity are apparent and are not adjusted for in the analyses	
		Critical: substantial deviations from the intended intervention are present and are not adjusted for in the analysis	
	Optional: what is the predicted direction of bias due to departures from the intended interventions?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being	Favours experimental/favours comparator/towards null/away from null/unpredictable

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		towards (or away from) the null, or as being in favour of one of the interventions	
<b>Bias due to missing data</b>	5.1 Were there missing outcome data?	This aims to elicit whether the proportion of missing observations is likely to result in missing information that could substantially impact our ability to answer the question being addressed. Guidance will be needed on what is meant by 'reasonably complete'. One aspect of this is that review authors would ideally try and locate an analysis plan for the study	Y/PY/PN/N/NI
	5.2 Were participants excluded due to missing data on intervention status?	Missing intervention status may be a problem. This requires that the intended study sample is clear, which it may not be in practice	Y/PY/PN/N/NI
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	This question relates particularly to participants excluded from the analysis because of missing information on confounders that were controlled for in the analysis	Y/PY/PN/N/NI
	5.4 If Y or PY to 5.1, 5.2 or 5.3: are the proportion of participants and reasons for missing data similar across interventions?	This aims to elicit whether either (i) differential proportion of missing observations or (ii) differences in reasons for missing observations could substantially impact on our ability to answer the question being addressed	NA/Y/PY/PN/N/NI
	5.5 If Y or PY to 5.1, 5.2 or 5.3: were appropriate statistical methods used to account for missing data?	It is important to assess whether assumptions employed in analyses are clear and plausible. Both content knowledge and statistical expertise will often be required for this. For instance, use of a statistical method such as multiple imputation does not guarantee an appropriate an-	NA/Y/PY/PN/N/NI

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		<p>swer. Review authors should seek naïve (complete-case) analyses for comparison, and clear differences between complete-case and multiple imputation-based findings should lead to careful assessment of the validity of the methods used</p>	
	'Risk of bias' judgement	<p>Low: data were reasonably complete; or Proportions of and reasons for missing participants were similar across intervention groups; or Analyses that addressed missing data are likely to have removed any risk of bias</p> <p>Moderate: proportions of missing participants differ across interventions; or Reasons for missingness differ minimally across interventions; and Missing data were not addressed in the analysis</p> <p>Serious: proportions of missing participants differ substantially across interventions; or Reasons for missingness differ substantially across interventions; and Missing data were addressed inappropriately in the analysis; or The nature of the missing data means that the risk of bias cannot be removed through appropriate analysis</p> <p>Critical: (unusual) there were critical differences between interventions in participants with missing data that were not, or could not, be addressed through appropriate analysis</p>	Low/moderate/serious/critical/NI
	Optional: what is the predicted direction of bias due to missing data?	<p>If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null,</p>	Favours experimental/favours comparator/towards null/away from null/unpredictable



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		or as being in favour of one of the interventions	
<b>Bias in measurement of outcomes</b>	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Some outcome measures involve negligible assessor judgment, e.g. all-cause mortality or non-repeatable automated laboratory assessments. Risk of bias due to measurement of these outcomes would be expected to be low	Y/PY/PN/N/NI
	6.2 Were outcome assessors aware of the intervention received by study participants?	If outcome assessors were blinded to intervention status, the answer to this question would be 'No'. In other situations, outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators; the answer to this question would then also be 'No'. In studies where participants report their outcomes themselves, e.g. in a questionnaire, the outcome assessor is the study participant. In an observational study, the answer to this question will usually be 'Yes' when the participants report their outcomes themselves	Y/PY/PN/N/NI
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Comparable assessment methods (i.e. data collection) would involve the same outcome detection methods and thresholds, same time point, same definition, and same measurements	Y/PY/PN/N/NI
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	This question refers to differential misclassification of outcomes. Systematic errors in measuring the outcome, if present, could cause bias if they are related to intervention or to a confounder of the intervention-outcome relationship.	Y/PY/PN/N/NI

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		This will usually be due either to outcome assessors being aware of the intervention received or to non-comparability of outcome assessment methods, but there are examples of differential misclassification arising despite these controls being in place	
	'Risk of bias' judgement	<p>Low: the methods of outcome assessment were comparable across intervention groups; and the outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants (i.e. is objective) or the outcome assessors were unaware of the intervention received by study participants; and any error in measuring the outcome is unrelated to intervention status</p> <p>Moderate: the methods of outcome assessment were comparable across intervention groups; and the outcome measure is only minimally influenced by knowledge of the intervention received by study participants; and any error in measuring the outcome is only minimally related to intervention status</p> <p>Serious: the methods of outcome assessment were not comparable across intervention groups; or the outcome measure was subjective (i.e. likely to be influenced by knowledge of the intervention received by study participants) and was assessed by outcome assessors aware of the intervention received by study participants; or there was an error in measuring the outcome was related to intervention status</p>	Low/moderate/serious/critical/ NI

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		Critical: the methods of outcome assessment were so different that they cannot reasonably be compared across intervention groups	
	Optional: What is the predicted direction of bias due to measurement of outcomes?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental/favours comparator/towards null/away from null/unpredictable
<b>Bias in selection of the reported result</b>	Is the reported effect estimate unlikely to be selected, on the basis of the results, from:		
	7.1 Multiple outcome measurements within the outcome domain?	For a specified outcome domain, it is possible to generate multiple effect estimates for different measurements. If multiple measurements were made, but only one or a subset is reported, there is a risk of selective reporting on the basis of results	Y/PY/PN/N/NI
	7.2 Multiple analyses of the intervention-outcome relationship?	Because of the limitations of using data from non-randomised studies for analyses of effectiveness (need to control confounding, substantial missing data, etc), analysts may implement different analytic methods to address these limitations. Examples include unadjusted and adjusted models; use of final value vs change from baseline vs analysis of covariance; different transformations of variables; a continuously scaled outcome converted to categorical data with different cut-points; different sets of co-variables used for adjustment; and different analytic strategies for dealing with missing data. Application of such methods generates multiple effect estimates for a specific	Y/PY/PN/N/NI

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		outcome metric. If the analyst does not pre-specify the methods to be applied, and multiple estimates are generated but only one or a subset is reported, there is a risk of selective reporting on the basis of results	
	7.3 Different subgroups?	Particularly with large cohorts often available from routine data sources, it is possible to generate multiple effect estimates for different subgroups or simply to omit varying proportions of the original cohort. If multiple estimates are generated but only one or a subset is reported, there is a risk of selective reporting on the basis of results	Y/PY/PN/N/NI
	'Risk of bias' judgement	<p>Low: there is clear evidence (usually through examination of a pre-registered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses and sub-cohorts</p> <hr/> <p>Moderate: the outcome measurements and analyses are consistent with an a priori plan, or are clearly defined and both internally and externally consistent; and there is no indication of selection of the reported analysis from among multiple analyses; and there is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results</p> <hr/> <p>Serious: outcome measurements or analyses are internally or externally inconsistent; or There is a high risk of selective reporting from among multiple analyses; or The cohort or subgroup</p>	Low/moderate/serious/critical/NI

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		is selected from a larger study for analysis and appears to be reported on the basis of the results	
		Critical: there is evidence or strong suspicion of selective reporting of results, and the unreported results are likely to be substantially different from the reported results	
	Optional: what is the predicted direction of bias due to selection of the reported result?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental/favours comparator/towards null/away from null/unpredictable
<b>Overall bias</b>	'Risk of bias' judgement	Low: the study is judged to be at low risk of bias for all domains	Low/moderate/serious/critical/NI
		Moderate: the study is judged to be at low or moderate risk of bias for all domains	
		Serious: the study is judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain	
		Critical: the study is judged to be at critical risk of bias in at least one domain	
		No information (NI): there is no clear indication that the study is at serious or critical risk of bias and there is a lack of information in one or more key domains of bias (a judgement is required for this)	
	Optional: what is the overall predicted direction of bias for this outcome?		Favours experimental/favours comparator/towards null/away from null/unpredictable

Abbreviations:

ITS: Interrupted time series

N: No  
NI: no information  
PN: Probably No  
PY: Probably yes  
Y: Yes

## CONTRIBUTIONS OF AUTHORS

Sheila Fisher developed the protocol and is a methodological expert.

Lise Estcourt developed the protocol and is a content expert.

Annemarie Docherty developed the protocol and is a content expert.

Carolyn Doree developed the protocol.

Stephen Hibbs developed the protocol and is a content expert.

Michael Murphy developed the protocol, and is a content expert.

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