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Non-erythropoiesis stimulating agent, non-iron therapies for the management of anaemia: a protocol for a systematic scoping review

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This protocol has been registered prospectively on the Open Science Framework Registry (https://osf.io/registries?view_only=).

ABSTRACT

Introduction

Pre-operative anaemia is associated with poor postoperative outcomes and is the strongest predictor of allogenic blood transfusion, which contribute further to patient morbidity. As such, emphasis has been placed on correcting anaemia prior to surgery to mitigate these outcomes. Conflicting evidence exists regarding the benefit of currently recommended interventions. With greater understanding of the mechanisms behind iron haemostasis and erythropoiesis, new targeted therapies have been identified. These novel agents are at varying stages of development with some demonstrating promising results in patients with chronic kidney disease. However, it is not known how these agents have been studied outside this population, particularly in the peri-operative context. To address this knowledge gap, we will conduct a scoping review of the published literature to systematically chart the evidence.

Methods and Analysis

The scoping review will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews framework. We will refine our search strategy with the expertise and guidance of research librarians. The electronic database search will span several databases. This review will have three objectives; (1) describe the mechanisms of action for novel agents; (2) describe the level of evidence and stage of development of novel agents in a perioperative setting; and (3) determine the potential agents suitable for prospective controlled trials in a pre- or postoperative patient cohort and aiming to improve patient centred outcomes. The review process will involve two reviewers screening abstracts and reading full text articles with a third reviewer resolving disagreements. Data will be extracted and organised with subsequent analysis in an iterative process.

Ethics and Dissemination

This scoping review does not require research ethics approval. The results will be published in a peer-reviewed journal and inform the development of future prospective trials based on established evidence from potential therapeutic agents.

ARTICLE SUMMARY

Strengths and limitations of this study

- The results of this scoping review will directly inform the design of prospective trials focused on improving patient-centred outcome measures.
- The exclusion of papers published prior to 2010 will focus the study on contemporary evidence specific to our research aims; namely, the stage of development of novel drugs.
- This scoping review will identify the evidence pertaining to a broad range of outcome measures relevant to the peri-operative patient, allowing further characterisation of evidence gaps and direction of future studies.
- Exclusion of studies related to patients with chronic kidney disease will limit indirectness in assessing the evidence outside this population.
- The exclusion of the chronic kidney disease population from our search may in turn limit the results yielded and thus the applicability of our results. However, were this to occur it would not reflect failure, and instead reflect the extent of such gaps in the literature.

INTRODUCTION

Rationale

While the global prevalence of anaemia is decreasing, the global burden of disease remains high. Approximately 25% of the general population have anaemia (1), which has been associated with worse outcomes and greater health care costs across a range of specific patient populations.(1-7) There is an independent association between pre-operative anaemia and worse postoperative outcomes.(5, 8-10) Pre-operative anaemia is also the strongest predictor of allogeneic red cell transfusion, which is also associated with worse postoperative outcomes, including risk of delirium, wound complications, sepsis, acute kidney injury and increased length of hospital stay.(11, 12) Absolute or functional iron deficiency (and by extension the 'anaemia of inflammation' [AOI]) is the underlying cause of anaemia in most hospitalised patients.(13) AOI occurs due to disruption of the hepcidin-ferroportin axis resulting in iron restricted erythropoiesis, functional iron deficiency and anaemia despite 'sufficient' iron stores .(11, 14) AOI confers a poorer prognosis and worsens quality of life.(14, 15)

Renal medicine has treated anaemia previously as a modifiable risk factor that can be targeted to improve patient outcomes. Indeed, intravenous iron and erythropoietin stimulating agents (ESAs) are now standard of care when haemoglobin concentration falls below 100 g/L in this cohort.(9, 16) Intravenous iron has since been shown to improve biochemical and patient centred outcome measures in patients with anaemia without renal disease; however, these results are yet to be translated consistently to the surgical setting.(17-24) As an example, a 2019 Cochrane review and meta-analysis by Ng *et al.* concluded there was no difference in transfusion rates between those who did and those who did not receive iron prior to surgery .(25) These results differ to previous studies in specific surgical populations investigating the same intervention.(26-28) Furthermore, this conclusion contradicts a meta-analysis performed

in 2013 which – while having a higher sample size – was not restricted to the peri-operative setting.(29) More recently, the PREVENTT trial reported similar results in a larger sample.(30) Like Ng *et al*., the PREVENTT investigators concluded that pre-operative intravenous iron was not superior to placebo in reducing the need for blood transfusion or death in patients with anaemia prior to open, major, elective abdominal surgery. This evidence suggests that intravenous iron in isolation is an inadequate management option for the anaemia of inflammation commonly seen in the surgical setting. ESAs similarly improve biochemical outcomes outside the renal population; however, implementation as part of wider patient blood management programs has been limited in recent years due to the perceived increased risks of thrombosis, stroke, and mortality and – particularly in Australia – the lack of a government pharmaceutical subsidy for this indication.(31) Kei *et al*. addressed some of these concerns with a meta-analysis conducted in 2019 that reviewed the relative efficacy and safety of ESA and iron (as recommended in guidelines) *vs* iron alone.(31) While limited by significant heterogeneity and potential confounding from the inclusion of studies with non-anaemic patients, their results suggest a reduced risk of allogenic red cell transfusion in the intervention group. Importantly their analysis noted no difference regarding safety.

Given the heterogeneous results of trials examining intravenous iron as an intervention for anaemia in surgical patients and the lack of uptake of ESAs as part of standard practice, attention has shifted to novel agents that purport to treat the causes of anaemia (particularly the anaemia of inflammation) more directly. These agents have varied mechanisms of action that attempt to balance the multifactorial nature of anaemia in a multimorbid patients.(32-37) Trials of one such class of agents, the hypoxia inducible factor – prolyl hydroxylase inhibitors (HIF-PHIs) have suggested that these agents improve haemoglobin concentration reliably in the chronic kidney disease (CKD) population.(38-41) However, a recent meta-analysis concluded

that while HIF-PHIs demonstrate biochemical efficacy and safety, they lack evidence of benefit for patient-centred outcome measures.(42) Furthermore, it is unclear what studies have been conducted in a population outside of patients with CKD. As such, a scoping review of the literature is necessary to chart the available evidence for novel therapeutics (that is, non-ESA, non-iron therapies) in the management of anaemia in non-CKD patient cohorts.

Objectives

The objectives of this scoping review will be to identify, appraise and map the existing evidence for any available non-ESA, non-iron agents that can be utilised in patients with pre-operative anaemia to improve outcomes, guide future research and determine the need for a full systematic review and meta-analysis. The proposed review will therefore answer the following questions:

1. What are the described mechanism of action for non-ESA, non-iron therapies to increase haemoglobin?
2. What is the level of evidence and stage of development for non-ESA, non-iron novel anaemia therapies in a peri-operative setting?
3. Which potential agents are suitable for prospective controlled trials in a pre- or postoperative patient cohort with aims to improve peri-operative patient centred outcomes (including patient-centred outcome measures)?

METHODS

This protocol draws from the Preferred Reporting Items for Systematic Review and Meta-Analysis – Protocols 2015 (PRISMA-P) checklist (43) and is refined in context to the application of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR).(44) Where aspects of the PRISMA-P checklist are not applicable, a brief discussion and rational for exclusion will be given.

Eligibility Criteria

We have used a PICO format to develop our eligibility criteria and outline our outcome measures:

Population

We will include studies examining adults ≥ 18 years of age with anaemia. Given the varied definition of anaemia used in reporting and to ensure we capture all relevant literature we will define anaemia as any haemoglobin concentration < 130 g/L regardless of sex.(45, 46) Studies in which anaemia is caused by primary renal dysfunction, infection (i.e., malaria) or haemolysis will be excluded. Studies will be excluded if the patient population is restricted to a specific haematological disorder such as sickle cell disease; thalassaemia subgroups; sideroblastic anaemia; haematological malignancy and primary disease of the bone marrow such as myelodysplasia. Any study not performed in humans will be excluded.

Intervention

All studies in which anaemia is treated using a non-ESA or iron-based therapy will be reviewed. Primarily, novel agents (those that are neither marketed nor utilised for another primary indication) will be sought. Examples of such interventions and their mechanisms of action are shown in Table 1. Publications will be restricted to those published since 2010. Studies that utilise a novel agent in addition to standard or routine care will be included.

Comparison

Comparisons will be made to iron preparations (oral or intravenous), ESAs, routine care (i.e., no intervention in addition to standard management) or placebo. We will include studies that do not have a defined comparator for appraisal and charting as appropriate in line with the scoping review methodology

Outcome

We recognise the recent development of standardised outcome measures defined by the COMPAC-StEP group as the current standard for research in peri-operative medicine; however, as the development of these measures is relatively recent, it is unlikely that many studies will have been performed utilising these endpoints.(47) As such, biochemical surrogates will be used to determine efficacy, and the potential for further study of identified agents in a peri-operative context. Where available, patient-related outcomes will be included in the evidence mapping. Similarly, where possible, the total duration of follow-up, as well as the various timepoints used for follow-up during the study will be recorded. Outcomes will be collected as reported. Therefore, we will analyse and grade each agent on the following endpoints:

Primary outcome:

- Change in haemoglobin concentration between start of intervention and end of follow-up (g/L).

Secondary outcome:

- Biochemical: Change in ferritin and transferrin saturations; change in hepcidin level;
- Patient centred outcomes: health-related quality of life, disability free survival, functional status, days alive and at home, complications, mortality;
- Healthcare resource utilisation: length of stay, health care costs of treatment;
- Safety: post administration complications, major and minor adverse effects.

Table 1
Mechanism of action and physiological target of novel therapeutic agents for treatment of anaemia

Class *agent*	Mechanism	Relevant physiology
Agents that directly antagonise the effects of hepcidin		
Anticalins (hepcidin binding proteins) *PRS-080*	Pegylated lipocalin like proteins engineered to bind hepcidin thereby preventing adequate binding to ferroportin.	Overproduction of hepcidin due to aberrant inflammatory signals leads to increased ferroportin degradation and reduced iron absorption from the diet leading to iron restricted erythropoiesis and anaemia
Antihepcidin antibodies *AB12B9m, LY2787106*	Humanised monoclonal antibodies that bind hepcidin with high affinity causing degradation	
Spiegelmers (hepcidin-binding L-RNA Aptamers) *Lexaptepid pegol – NOX-H94*	Blocks hepcidin indued ferroportin internalisation L enantiomers of oligonucleotide that interact like antibodies binding human hepcidin and blocking its function	
Short Interfering and Short Hairpin RNA (siRNA and shRNA) *H6, H10, ALN-HPN*	RNA based technology leading to hepcidin gene silencing thereby reducing production of hepcidin mRNA	
Agents that interact with the BMP6-HJV-SMAD signalling cascade		
ALK2/3 (activin-like kinase receptor) inhibitors *OD66, TP-0184, INCB00928, Momelotinib, Indazole, DS79182026 (ALK3)*	Inhibition of the ALK2/3 receptors (a form of BMP receptor) prevents coupling with HJV and BMP6 thereby reducing intracellular signalling for hepcidin expression = decreased hepcidin production	Hemojuvelin (HJV) is a bone morphogenetic protein (BMP) co receptor High iron stimulates binding of circulating BMP6 to BMP receptor types I and II with co-receptor HJV on the hepatocyte membrane. This stable multiplex causes the activation of SMAD signal cascade Intracellular SMAD1/5/8 proteins complex with SMAD4 that then translocates to the nucleus causing induction of hepcidin expression
Inhibitors of BMP type 1 receptor *Dorsomorphin, LDN-193189, LDN-212854*	Inhibit BMP-, HJV-, and IL-6-stimulated hepcidin expression in hepatocytes and block iron induced hepcidin mRNA - Dorsomorphin is also a nonselective kinase inhibitor of AMP kinase (off-target effects) - LDN-193189 with increased potency and selectivity for BMP inhibition	
BMP6 sequestering agents *Anticoagulant and non-anticoagulant hepcidins*	Sequester BMP activity, inhibit BMP6-mediated hepcidin transcription and decrease SMAD phosphorylation thereby reducing hepcidin expression	
Hemojuvelin (BMP co-receptor) *sHJV.Fc, h5F9.23, h5F9-AM, ABT-207*	Antibodies that cause cleavage of hemojuvelin and interferes with BMP binding to the BMPR thereby decreasing hepcidin transcription.	
Transferrin receptor (TRF2) *RNAi*	Experimental gene silencing technology aimed towards the transferrin receptor	

Agents that interact with the IL-6/STAT3 signalling pathway		
JAK/STAT3 inhibition *AG490* *PpYLKTK*	AG490 inhibits the phosphorylation of STAT3 by JAK2 thereby no binding of STAT3 responsive element and reduced hepcidin expression PpYLKTK is a peptide agent that disrupts pSTAT3 dimerization required for binding of hepcidin promoting target genes	Proinflammatory cytokines released due to a variety of stimulants e.g. malignancy. IL-6 binds IL-6 receptor on hepatocyte activating the JAK1/2 cascade causing phosphorylation of STAT3 transcription factor (STAT3-TF) that then translocates to the nucleus In the nucleus STAT3-TF binds STAT3 responsive element (STAT-RE) on hepcidin promoter region STAT3-RE must be coupled with BMP-RE (which is activated via the BMP/HJV/SMAD pathway) for IL-6 mediated hepcidin expression to occur Once coupled hepcidin translation occurs with hepcidin release and degradation of ferroportin
AMPK activator *Metformin* , DS79182026	AMP-activated protein kinase (AMPK) promotes JAK2 degradation reducing STAT3 phosphorylation and hepcidin expression	
IL-6 inhibitors *Toclizumab, Siltuximab*	Inhibit the IL-6/STAT3 pathway via antibodies to the IL-6 receptor (toclizumab) or via antibodies to the IL-6 ligand - Limited by increased infective risks	
IL1-β inhibitors *Canakinumab*	Monoclonal antibody against IL1- β involved in the inflammatory pathway	
Erythroferrone	Erythroferrone (ERFE) is responsible for early hepcidin suppression during erythropoietic activity stimulated by endogenous or exogenous EPO.	Erythroferron suppresses hepcidin to promote the mobilization of stored iron and the absorption of dietary iron, so that the increased iron demands of developing erythrocytes can be met.
Agents upregulating erythropoiesis (negative regulator of hepcidin)		
HIF-prolyl hydroxylase inhibitors (EGLN inhibitors) *Roxadustat, Vadadustat, Daprodustat, Enarodustat, FG-4692, AKB-6548, GSK1278863, JTZ-951, BAY85-3934*	Propyl hydroxylase domain-2 (PDH2) inhibitors stabilize HIF-1 and HIF-2 → stable HIF stimulates endogenous erythropoietin production which suppresses hepcidin leading to greater iron availability for erythropoiesis - Activates HIF in presence of oxygen (normocemic conditions)	Hypoxia stimulates the production of EPO via signalling by hypoxia inducible factor (HIF) which also suppresses hepcidin production. Under normoxic conditions, prolyl hydroxylases constitutively degrade HIF, allowing hepcidin production to occur.
Agents interacting with Ferroportin		
Ferroportin agonists/ stabilisers *LY2928057* *Fursultiamine*	Humanized antibody to ferroportin that block the hepcidin-ferroportin interaction while maintaining ferroportin function thereby maintain iron influx. - Fursultiamine prevents hepcidin-FPN interactions by competing with hepcidin to bind FPN on the hepcidin binding site	FPN is a transmembrane protein that is expressed by duodenal enterocytes, splenic macrophages, and hepatocytes ↑ hepcidin causes degradation of ferroportin leading to inability to mobilise store iron

Note. Mechanism and relevant physiology description are adapted from The Hepcidin-Ferroportin System as a Therapeutic Target in Anemias and Iron Overload Disorders, by Ganz et al *Hematology* 2011(32), "Hepcidin Therapeutics" by Katsarou et al, *Pharmaceuticals* 2018(33), pharmacological targeting of the hepcidin/ferroportin axis by Sebastiani et al, *Frontiers in pharmacology* 2016(36), and "Targeting the hepcidin–ferroportin axis to develop new treatment strategies for anemia of chronic disease and anemia of inflammation" by Sun et al. *American Journal of Hematology* 2012(37)

Publication type, study design, language, and timeframe

We will include prospective and retrospective observational studies and randomised and pseudo-randomised controlled trials. Controlled trials can be of any design including parallel, cross over and cluster randomised trials. Open-label clinical trials will be eligible for inclusion. Preclinical safety and dose finding studies in humans will be included. Commentaries, letters, and conference abstracts will be included. Case reports, case studies and animal studies will be excluded. No limitation will be placed on the setting or time frame of follow up or on language or country of study. We will only include studies published since January 1, 2010.

Information sources

The search will be run in Scopus, MEDLINE (Ovid) and Excerpta Medica database (Ovid) to account for variability in the indexing in each database. We will supplement the electronic database search by searching for ongoing or recently completed trial protocols in international trial registries including clinicaltrials.gov, the Australian New Zealand Clinical Trials Registry (ANZCTR), the European Union Clinical Trial register and the International Clinical Trials Registry Platform (ICTRP). Each article included in the review will have its reference list scanned to ensure literature saturation.

Search strategy

We conducted an initial abbreviated search to refine and define our search terms and to avoid duplication of any existing systematic reviews. This was subsequently used to develop a systematic search strategy using medical subject headings (MeSH) with Boolean operations.

The search strategy was developed with the help of the information specialists from the University of Western Australia, was piloted against a random search of 50 abstracts, and

refined subsequently. Search results will be limited to abstracts published after 2010 with no language or jurisdiction limitations. The international clinical trial registry platform search portal and clinical trial.gov will be search for ongoing or recently completed trials. PROSPERO will be reviewed for any ongoing or recent systematic reviews. The search includes general terms to describe anaemia and potential pathways to management, as well as more specific terms (i.e., prolyl hydroxylase inhibitors). The full version of the search strategy can be found in Supplemental File 1.

Study records

Data management

The scoping review will be conducted using the framework as described by Arksey and O'Malley (48) and reported against the PRISMA-ScR checklist.(44) The literature search results will be imported into a systematic review management program (Covidence, Melbourne, Australia) to facilitate the study selection process. Abstracts and citations will be uploaded and screened against inclusion criteria. A data extraction form was developed and piloted by the review team based on the study inclusion and exclusion criteria (Supplemental File 2).

Selection process

Two independent review authors (AD and PD) will screen all titles and abstracts yielded by the search against the inclusion criteria. For any abstract where consensus is not achieved a third reviewer (CD or LFM) will adjudicate its suitability for inclusion. For any article that meets the inclusion criteria, a full text extraction will be obtained. For any full text articles that do not meet the inclusion criteria the reason for exclusion will be documented.

Data collection process

Data will be independently extracted by two authors (AD and PD) using a predeveloped and piloted data extraction form (Supplemental File 2). Again, for any extraction where there is no consensus between the two authors, a third author (CD or LFM) will adjudicate. To ensure consistency between reviewers a calibration exercise has been performed prior to commencing the formal data collection process. In keeping with established scoping review methodology ongoing consultation with the senior members of the scoping team (TR and LFM) will occur to guide additional data extraction from the papers as deemed necessary. Where data requires further confirmation, all attempts will be made to seek clarification from the corresponding author of the study and where it is unable to be confirmed will be documented in the results.

Data items

Data will be sought for the following variables:

1. Participant information including n value, treatment setting and descriptive data of participants (age, gender, diagnostic criteria, treatment history, documented comorbidities);
2. Study methodology including study design, country, setting and design limitations;

3. Study intervention and comparator including duration of treatment, timepoints for follow-up, route of intervention (oral or intravenous), frequency of intervention;
4. Primary and secondary outcomes as defined above.

Outcomes and prioritisations

We have chosen to identify and define our outcome measures *a priori*, however, given the scoping nature of this systematic review, revision of these outcomes and expansion or refinement as necessary will occur through the full text review and data extraction process.

The primary outcome of this review will be to investigate which agents facilitate an increase in haemoglobin concentration from baseline as defined by the individual study criteria. Change in haemoglobin concentration is used frequently as an indication of treatment efficacy in clinical trials that aim to treat anaemia. It is therefore expected to be an endpoint in any study investigating novel agents for use in anaemia. Change in haemoglobin concentration is not without limitations, most importantly the potential lack of consistent associations with meaningful clinical changes such as complication rates, particularly in a peri-operative patient cohort. Therefore, this measure will be considered in addition to secondary outcomes to determine the suitability of a potential novel agent for use in a peri-operative patient cohort. The time taken to demonstrate a change in haemoglobin concentration will be of importance, given that these patients often require an intervention that offers benefit within a limited time period prior to surgery.(49) Therefore, any timepoint for which haemoglobin concentration is recorded following a baseline measurement will be reviewed. Similarly the optimal time to intervene in patients with pre-operative anaemia is not yet known, further highlighting the need to characterise the timeline of changes in haemoglobin concentration.

Where available, data pertaining to iron parameters (ferritin, transferrin saturation, soluble transferrin receptor) will be recorded and reviewed to further inform the potential patient cohorts in which the novel agents may be best suited. Patients will be considered as being iron deficient or having inadequate iron stores if they define a cut off of ferritin < 100 μmol/L or transferrin saturation < 20%.(50) As previously discussed, the cause of anaemia can be multifactorial and so understanding the interplay of a potential therapeutic agent with the concomitant cause of anaemia will be important in developing participant selection criteria for future prospective interventional studies.

In peri-operative research there is an imperative to ensure that research include clinically relevant patient centred outcome measures (47) to ensure that therapies have a significant effect on the functional and physical capacity of the patient in addition to procedural complications. Therefore, we will also determine to what extent patient centred outcomes have been investigated thus far. It is unknown if there will be any data on survival measures or healthcare resource utilisation. This review will address this by collecting data on patient mortality, morbidity, length of hospital and/or ICU stay and health care costs of treatment.

Safety of tested interventions will be assessed through documented major and minor adverse effects. Any immediate post-administration complications or side-effects will be reviewed. Charting of this data (particularly those data describing different interventions or combinations of interventions) will inform future clinical trial design.

Risk of bias

Given the scoping nature of this review a formal bias assessment will not be performed.

Data synthesis

The review will be reported in accordance with the PRISMA-ScR guidelines.(44) Demographic and methodological data will be charted in a tabulated form. Study interventions and outcome data will be charted as a combination of narrative discussion and an alluvial diagram. An alluvial diagram is a type of flow diagram designed to represent dynamic relationships in a system. We intend to use this to cluster the different variables from our data set to show the relationship and volume of evidence in a particular area; Simple frequency analysis will inform the size of the components between each stream. A stream will be a novel drug or drugs with similar mechanism. Streams will then be 'blocked' according to the following: agent; patient population; study type; comparator; added treatment; outcomes. In keeping with scoping review methodology, a meta-analysis will not be performed.

Meta-bias

This scoping review has been undertaken to inform if there is a need for a more formal systematic review; accordingly, a meta-bias analysis is beyond the scope of this review.

Confidence in cumulative evidence

A through assessment of the risk of bias and other factors that can be used to describe the quality of evidence falls beyond the capacity of this review and lies outside the proposed scoping methodology. Such an assessment will not be included.

Patient and public involvement

No patient involved

ETHICS AND DISSEMINATION

This scoping review will be conducted and reported following the PRISMA-ScR criteria. Ethics approval is not required as the study will only review previously published literature. The findings of this scoping review will be published in a peer-reviewed scientific journal. As indicated throughout this manuscript the results of this study will inform the methodology of future prospective studies utilising novel agents for the management of anaemia in the perioperative setting.

Authors statement

LFM is the guarantor. AD, PD and LFM drafted the manuscript. TR was involved with critical revision of the abstract for important intellectual content. All authors contributed to the development of the selection criteria, the data extraction criteria, and the charting methodology. AD and CD developed the search strategy. All authors read, provided feedback, and approved the final manuscript. The authors acknowledge the assistance of the information specialists of the University of Western Australia University Library in devising the search strategy.

Amendments

In the event of protocol amendments, the date of the amendment will be accompanied by a description of the change and the rationale in the listing on the Open Science Framework Registry.

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Competing interests

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Future Health Research and Innovation Fund (Western Australia), grants and personal fees from Pfizer Pty Ltd (Australia), and personal fees from BioAge Labs Inc., outside the submitted work; TR is a regular speaker at national and international conferences on anaemia, blood transfusion, wound healing and vascular disease for which he has received expenses for travel, accommodation and sundries, TR has worked with several agencies promoting meetings or healthcare, TR is a director of The Iron Clinic Ltd, director of Veincare London Ltd and Vein Care WA. TR is the Vascular lead for 18-week wait Ltd. LM reports grants from Vifor Pharma Pty Ltd, the Australian and New Zealand College of Anaesthetists, the Victorian Department of Health, the Epworth Medical foundation and the Austin Medical Research foundation, outside the submitted work. LM has a leadership or fiduciary role with the National Medical Advisory Committee, Red Cross Lifeblood, Australia and Blood Matters Advisory Committee, Department of Health, Victorian State Government. PD, AD and CD declare no financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

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Medline:

1 iron defic*.ti.
2 an*emia not (leuk*emia or h*emolytic or sickle or malaria or myelodysplas* or sideroblast* or thalassemia*).ti.
3 h*emoglobin.tw.
4 treatment* or therap* or drug* or pharm*.tw.
5 1 or 2
6 5 and 3 and 4
7 STAT3 inhibi* or AG490 or ppYLKTK.tw.
8 AMPK activ* or metformin or DS79182026.tw.
9 IL-6 inhibi* or interleukin-6 inhibi* or toclizumab or siltuximab.tw.
10 IL-1 inhibit* or interleukin 1 inhibit* or canakinumab.tw. 1372
11 erythroferron*.tw.
12 Prolyl-Hydroxylase Inhibitors/ or hypoxia inducible factor prolyl hydroxylase inhibitors.mp. or Hypoxia-Inducible Factor-Proline Dioxygenases/
13 hypoxia inducible factor stabili*er*.tw.
14 roxadustat.tw.
15 daprodustat.tw.
16 vadadustat.tw.
17 molidustat.tw.
18 enarodustat.tw.
19 desidustat.tw.
20 FG-4592.tw.
21 ASP1517.tw.
22 AZD9941.tw.
23 BAY85-3934.tw.
24 GSK1278863.tw.
25 AKB-6548.tw.
26 JTZ-951.tw.
27 ZYAN-1.tw.
28 ferroportin stabili*er* or ferroportin agonist* or LY298057 or fursultiamine.tw.
29 anticalin* or hepcidin binding protein* or PRS-080.tw.
30 antihepcidin antibod* or A12B9m or Ly2787106.tw.
31 hepcidin spiegelmer* or hepcidin binding L-RNA aptamer* or lexapetid pegol NOX-H94.tw. 2
32 (short interfering RNA or shRNA or siRNA or short hairpin RNA or H6 or H10 or ALN-HPN) and hepcidin.mp.
33 activin like kinase receptor inhibit* or ALK2 inhibit* or ALK3 inhibit* or OD66 or TP-0184 or INCB00928 or momelotinib or indazole or DS79182026.tw.
34 bone morphogenic protein type 1 receptor inhibit* or BMP type 1 receptor inhibit* or dorsomorphin or LDN-193189 or LDN-212854.tw.
35 BMP6 inhibit* or bone morphogenic protein 6 inhibit* or imatinib or spironolactone.tw.
36 hemojuvelin inibit* or hemojuvelin antibod* or sHJV or h5F923 or h5F9-AM or ABT-207.tw.
37 transferrin receptor RNAi.tw.
38 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 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
39 5 and 38
40 6 or 39

41 limit 40 to (humans and yr="2010 -Current")

Embase Classic + Embase:

1 iron defic*.ti.
2 an*emia not (leuk*emia or h*emolytic or sickle or malaria or myelodysplas* or sideroblast* or thalassemia*).ti.
3 h*emoglobin.tw.
4 treatment* or therap* or drug* or pharm*.tw.
5 1 or 2
6 5 and 3 and 4
7 STAT3 inhibi* or AG490 or ppYLKTK.tw.
8 AMPK activ* or metformin or DS79182026.tw.
9 IL-6 inhibi* or interleukin-6 inhibi* or toclizumab or siltuximab.tw.
10 IL-1 inhibit* or interleukin 1 inhibit* or canakinumab.tw. 1372
11 erythroferron*.tw.
12 Prolyl-Hydroxylase Inhibitors/ or hypoxia inducible factor prolyl hydroxylase inhibitors.mp. or Hypoxia-Inducible Factor-Proline Dioxygenases/
13 hypoxia inducible factor stabili*er*.tw.
14 roxadustat.tw.
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24 GSK1278863.tw.
25 AKB-6548.tw.
26 JTZ-951.tw.
27 ZYAN-1.tw.
28 ferroportin stabili*er* or ferroportin agonist* or LY298057 or fursultiamine.tw.
29 anticalin* or hepcidin binding protein* or PRS-080.tw.
30 antihepcidin antibod* or A12B9m or Ly2787106.tw.
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35 BMP6 inhibit* or bone morphogenic protein 6 inhibit* or imatinib or spironolactone.tw.
36 hemojuvelin inibit* or hemojuvelin antibod* or sHJV or h5F923 or h5F9-AM or ABT-207.tw.
37 transferrin receptor RNAi.tw.

38 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 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
39 5 and 38
40 6 or 39
41 limit 40 to (humans and yr="2010 -Current")

Scopus

1. TITLE-ABS-KEY (treatment OR therap* OR pharm* OR safe* OR efficacy OR drug*) AND
2. TITLE (an*emia) OR TITLE ("iron defic*") AND
3. TITLE-ABS-KEY (h*emoglobin) OR
4. TITLE-ABS-KEY ("stat3 inhibi*" OR "ag490" OR "ppylktk" "ampk activ*" OR "metformin" OR "ds78182026" OR "il-6 inhibit*" OR "interleukin-6 inhibit*" OR "toclizumab" OR "siltuximab" OR "il-1 inhibit*" OR "interleukin 1 inhibit*" OR "canakinumab" OR "erythroferron*" OR "prolyl hydroxylase inhibit*" OR "hypoxia inducible factor prolyl hydroxylase inhibit*" OR "hypoxia inducible factor proline dioxygenase*" OR "hif prolyl hydroxylase inhibit*" OR "hypoxia inducible factor stabili*er*" OR "roxadustat" OR "daprodustat" OR "vadadustat" OR "molidustat " OR "enarodustat" OR "desidustat" OR "fg-4592" OR "asp1517" OR "azd9941" OR "bay85-3934" OR "gsk1278863" OR "akb-6548" OR "jtz-951" OR "zyan-1" OR "ferroportin stabili*er*" OR "ferroportin agonist*" OR "ly298057" OR "fursultiamine" OR "anticalin*" OR "hepcidin binding protein*" OR "prs-080" OR "antihepcidin antibod*" OR "a12b9m" OR "ly2787106" OR "hepcidin spiegelmer*" OR "hepcidin binding l-rna aptamer*" OR "lexapetid pegol nox-h94" OR "short interfering rna" OR "shrna" OR "sirna" OR "short hairpin rna" OR "activin like kinase receptor inhibit*" OR "alk2 inhibit*" OR "alk3 inhibit*" OR "od66" OR "tp-0184" OR "incb00928" OR "momelotinib" OR "indazole" OR "ds79182026" OR "bone morphogenic protein type 1 receptor inhibit*" OR "bmp type 1 receptor inhibit*" OR "dorsomprhin" OR "ldn-193189" OR "ldn-212854" OR "hemojuvelin inhibit*" OR "shjv" OR "imatinib" OR "spironolactone" OR "h5f923" OR "h5f9-am" OR "abt-207" OR "transferrin receptor rnai" AND "an*emia") AND
5. PUBYEAR > 2009

Data extraction form

Date:		Investigator: AD PD CD LM		DOI	
Title					
Author (s)					
Citation					
Year of pub.		Country		Pub. Type	
Research question					
Outcomes					
Population					
Inclusion criteria	[ ] adult pts (>18 y/o) [ ] anemia [ ] novel agents				
Exclusion criteria	[ ] anemia 2'another hematological condition [ ] primary bone marrow disorder [ ] renal disease [ ]hemolysis [ ]infection e.g. malaria				
Setting					
Sample size					
Methodology	[ ] prospective [ ] retrospective [ ]blinded [ ] open label [ ] randomized [ ] non- randomized				
Intervention					
Comparator	[ ] placebo [ ] SOC [ ] ESA [ ] PO iron [ ] IV iron [ ] no comparator				
Duration of intervention					

Outcome and measures:					
Timepoints	Baseline	1	2	End	Significance
Δ Hb					
Δ Ferritin					
Δ T sats					
Δ hepcidin					
Major AE		Minor AE		Admin comp	
HRQL	Y/N		Disability free survival		
Functional status			DAAAH		
Mortality			Complications		
LOS			Health care costs		

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Information reported (Y/N)	Page(s)
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Y	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Y	
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Y	2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Y	20
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA	NA
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Y	20
Sponsor	5b	Provide name for the review funder and/or sponsor	NA	20
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Y	20
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	Y	6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Y	8
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Y	9-13
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Y	13
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Y	Sup. file 1

Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Y	14
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Y	15
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Y	15
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Y	15-16
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Y	16-17
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Y	17
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Y	18
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	NA	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	NA	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Y	18
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	NA	18
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA	18

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Non-erythropoiesis stimulating agent, non-iron therapies for the management of anaemia: protocol for a scoping review

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Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Haematology (incl blood transfusion), Surgery
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Non-erythropoiesis stimulating agent, non-iron therapies for the management of anaemia: protocol for a scoping review

Paula Devlin, Amelia Davies, Cory Dugan, Toby Richards, and Lachlan F. Miles

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Keywords: Anaemia; Inflammation; Hypoxia Inducing Factors; Hepcidin

ABSTRACT

Introduction

Pre-operative anaemia is associated with poor postoperative outcomes and is the strongest predictor of allogenic blood transfusion, which contributes further to patient morbidity. Emphasis has been placed on correcting anaemia prior to surgery to mitigate these outcomes. Conflicting evidence exists regarding the benefit of currently recommended interventions. With greater understanding of iron haemostasis and erythropoiesis, novel therapies have been identified. These are at varying stages of development with some demonstrating promising results in patients with chronic kidney disease. It is not known how these agents have been studied outside this population, particularly in the peri-operative context. To address this, we will conduct a scoping review of the published literature to chart the evidence.

Methods and analysis

The scoping review will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews framework. The electronic database search will include Scopus, MEDLINE (Ovid) and Excerpta Medica database (Ovid), with no language restrictions and will include all publications since January 1 2010. This review will have three objectives; (1) describe the mechanisms of action for novel agents; (2) describe the level of evidence and stage of development of novel agents in a perioperative setting; and (3) determine the potential agents suitable for prospective controlled trials in a pre- or postoperative patient cohort and aiming to improve patient centred outcomes. The review process will involve two reviewers with a third reviewer resolving disagreements. Data will be extracted and organised with subsequent analysis.

Ethics and dissemination

This scoping review does not require research ethics approval. The results will be published in a peer-reviewed journal and inform the development of future prospective trials based on established evidence from potential therapeutic agents.

Registration

This protocol has been registered prospectively on the Open Science Framework registry (DOI:10.17605/OSF.IO/SM3UH; https://osf.io/sm3uh/?view_only=39876ccf7a4348dfbd566535b957a7db).

Strengths and limitations of this study

- The exclusion of papers published prior to 2010 will focus the study on contemporary evidence specific to our research aims; namely, the stage of development of novel drugs.
- The exclusion of studies related to patients with chronic kidney disease will limit indirectness in assessing the evidence outside this population.
- The exclusion of the chronic kidney disease population from our search may in turn limit the results yielded and thus the applicability of our results.
- The scoping review methodology will reflect the extent of gaps in the literature, however, will lack the robustness of a traditional systematic review with meta-analysis.

INTRODUCTION

Rationale

While the global prevalence of anaemia is decreasing, the global burden of disease remains high. Approximately 25% of the general population have anaemia (1), which has been associated with worse outcomes and greater health care costs across a range of specific patient populations.(1-7) There is an independent association between pre-operative anaemia and worse postoperative outcomes.(5, 8-10) Pre-operative anaemia is also the strongest predictor of allogeneic red cell transfusion, which is also associated with worse postoperative outcomes, including risk of delirium, wound complications, sepsis, acute kidney injury and increased length of hospital stay.(11, 12) Absolute or functional iron deficiency (and by extension the 'anaemia of inflammation' [AOI]) is the underlying cause of anaemia in most hospitalised patients.(13) AOI occurs due to disruption of the hepcidin-ferroportin axis resulting in iron restricted erythropoiesis, functional iron deficiency and anaemia despite 'sufficient' iron stores.(11, 14) AOI confers a poorer prognosis and worsens quality of life.(14, 15)

Renal medicine has treated anaemia previously as a modifiable risk factor that can be targeted to improve patient outcomes. Indeed, intravenous iron and erythropoietin stimulating agents (ESAs) are now standard of care when haemoglobin concentration falls below 100 g/L in this cohort.(9, 16) Intravenous iron has since been shown to improve biochemical and patient centred outcome measures in patients with anaemia without renal disease; however, these results are yet to be translated consistently to the surgical setting.(17-24) As an example, a 2019 Cochrane review and meta-analysis by Ng *et al.* concluded there was no difference in transfusion rates between those who did and those who did not receive iron prior to surgery.(25) These results differ to previous studies in specific surgical populations investigating the same intervention.(26-28) Furthermore, this conclusion contradicts a meta-analysis performed in

2013 which – while having a higher sample size – was not restricted to the peri-operative setting.(29) More recently, the PREVENTT trial reported similar results in a larger sample.(30) Like Ng *et al*., the PREVENTT investigators concluded that pre-operative intravenous iron was not superior to placebo in reducing the need for blood transfusion or death in patients with anaemia prior to open, major, elective abdominal surgery. This evidence suggests that intravenous iron in isolation, to reduce allogenic blood transfusion and subsequent poor patient outcomes, is an inadequate management option for the anaemia of inflammation commonly seen in the surgical setting. ESAs similarly improve biochemical outcomes outside the renal population; however, implementation as part of wider patient blood management programs has been limited in recent years due to the perceived increased risks of thrombosis, stroke, and mortality and – particularly in Australia – the lack of a government pharmaceutical subsidy for this indication.(31) Kei *et al*. addressed some of these concerns with a meta-analysis conducted in 2019 that reviewed the relative efficacy and safety of ESA and iron (as recommended in guidelines) *vs* iron alone.(31) While limited by significant heterogeneity and potential confounding from the inclusion of studies with non-anaemic patients, their results suggest a reduced risk of allogenic red cell transfusion in the intervention group. Importantly, their analysis noted no difference regarding safety.

Given the heterogeneous results of trials examining intravenous iron as an intervention for anaemia in surgical patients and the lack of uptake of ESAs as part of standard practice, attention has shifted to novel agents that purport to treat the causes of anaemia (particularly the anaemia of inflammation) more directly. These agents have varied mechanisms of action that attempt to balance the multifactorial nature of anaemia in a multimorbid patients.(32-37) Trials of one such class of agents, the hypoxia inducible factor – prolyl hydroxylase inhibitors (HIF-PHIs) have suggested that these agents improve haemoglobin concentration reliably in the

chronic kidney disease (CKD) population.(38-41) However, a recent meta-analysis concluded that while HIF-PHIs demonstrate biochemical efficacy and safety, they lack evidence of benefit for patient-centred outcome measures.(42) Trials in individual agents (Vadadustat and Daprodustat) do suggest non inferiority when compared to ESAs, but are inconsistent in regards to safety.(43, 44) Furthermore, it is unclear what studies have been conducted in a population outside of patients with CKD. As such, a scoping review of the literature is necessary to chart the available evidence for novel therapeutics (that is, non-ESA, non-iron therapies) in the management of anaemia in non-CKD patient cohorts.

Objectives

The objectives of this scoping review will be to identify, appraise and map the existing evidence for any available non-ESA, non-iron agents that can be utilised in patients with pre-operative anaemia to improve outcomes, guide future research and determine the need for a full systematic review and meta-analysis. The proposed review will therefore answer the following questions:

1. What are the described mechanisms of action for non-ESA, non-iron therapies to increase haemoglobin?
2. What is the level of evidence and stage of development for non-ESA, non-iron novel anaemia therapies in a peri-operative setting?
3. Which potential agents are suitable for prospective controlled trials in a pre- or postoperative patient cohort with aims to improve peri-operative patient centred outcomes (including patient-centred outcome measures)?

METHODS AND ANALYSIS

This protocol draws from the Preferred Reporting Items for Systematic Review and Meta-Analysis – Protocols 2015 (PRISMA-P) checklist (45) and is refined for reporting via the application of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR).(46) Where aspects of the PRISMA-P checklist are not applicable, a brief discussion and rationale for exclusion will be given. In the event of a protocol amendments, the date of the amendment will be accompanied by a description of the change and the rationale in the listing on the Open Science Framework Registry.

Eligibility Criteria

We have used a PICO format to develop our eligibility criteria and outline our outcome measures:

Population

We will include studies examining adults ≥ 18 years of age with anaemia. Given the varied definition of anaemia used in reporting and to ensure we capture all relevant literature we will define anaemia as any haemoglobin concentration < 130 g/L regardless of sex.(47, 48) Studies in which anaemia is caused by primary renal dysfunction, infection (i.e., malaria) or haemolysis will be excluded. Studies will be excluded if the patient population is restricted to a specific haematological disorder such as sickle cell disease; thalassaemia subgroups; sideroblastic anaemia; haematological malignancy and primary disease of the bone marrow such as myelodysplasia. Any study not performed in humans will be excluded.

Intervention

All studies in which anaemia is treated using a non-ESA or iron-based therapy will be reviewed. Primarily, novel agents (those that are neither marketed nor utilised for another primary

indication) will be sought. Examples of such interventions and their mechanisms of action are shown in Table 1. Studies that utilise a novel agent in addition to standard or routine care will be included.

Comparison

Comparisons will be made to iron preparations (oral or intravenous), ESAs, routine care (i.e., no intervention in addition to standard management) or placebo. We will include studies that do not have a defined comparator for appraisal and charting as appropriate in line with the scoping review methodology

Outcome

We recognise the recent development of standardised outcome measures defined by the COMPAC-StEP group as the current standard for research in peri-operative medicine; however, as the development of these measures is relatively recent, it is unlikely that many studies will have been performed utilising these endpoints.(49) As such, biochemical surrogates will be used to determine efficacy, and the potential for further study of identified agents in a peri-operative context. Where available, patient-related outcomes will be included in the evidence mapping. Similarly, where possible, the total duration of follow-up, as well as the various timepoints used for follow-up during the study will be recorded. Outcomes will be collected as reported. Therefore, we will analyse and grade each agent on the following endpoints:

Primary outcome:

- Change in haemoglobin concentration between start of intervention and end of follow-up (g/L).

Secondary outcome:

- Biochemical: Change in ferritin and transferrin saturations; change in hepcidin level;

- Patient centred outcomes: health-related quality of life, disability free survival, functional status, days alive and at home, complications, mortality;
- Healthcare resource utilisation: length of stay, health care costs of treatment;
- Safety: post administration complications, major and minor adverse effects.

Table 1
Mechanism of action and physiological target of novel therapeutic agents for treatment of anaemia

Class *agent*	Mechanism	Relevant physiology
Agents that directly antagonise the effects of hepcidin		
Anticalins (hepcidin binding proteins) *PRS-080*	Pegylated lipocalin like proteins engineered to bind hepcidin thereby preventing adequate binding to ferroportin.	Overproduction of hepcidin due to aberrant inflammatory signals leads to increased ferroportin degradation and reduced iron absorption from the diet leading to iron restricted erythropoiesis and anaemia
Antihepcidin antibodies *AB12B9m, LY2787106*	Humanised monoclonal antibodies that bind hepcidin with high affinity causing degradation	
Spiegelmers (hepcidin-binding L-RNA Aptamers) *Lexaptepid pegol – NOX-H94*	Blocks hepcidin indued ferroportin internalisation L enantiomers of oligonucleotide that interact like antibodies binding human hepcidin and blocking its function	
Short Interfering and Short Hairpin RNA (siRNA and shRNA) *H6, H10, ALN-HPN*	RNA based technology leading to hepcidin gene silencing thereby reducing production of hepcidin Mrna	
Agents that interact with the BMP6-HJV-SMAD signalling cascade		
ALK2/3 (activin-like kinase receptor) inhibitors *OD66, TP-0184, INCB00928, Momelotinib, Indazole, DS79182026 (ALK3)*	Inhibition of the ALK2/3 receptors (a form of BMP receptor) prevents coupling with HJV and BMP6 thereby reducing intracellular signalling for hepcidin expression = decreased hepcidin production	Hemojuvelin (HJV) is a bone morphogenetic protein (BMP) co receptor High iron stimulates binding of circulating BMP6 to BMP receptor types I and II with co-receptor HJV on the hepatocyte membrane. This stable multiplex causes the activation of SMAD signal cascade Intracellular SMAD1/5/8 proteins complex with SMAD4 that then translocates to the nucleus causing induction of hepcidin expression
Inhibitors of BMP type 1 receptor *Dorsomorphin, LDN-193189, LDN-212854*	Inhibit BMP-, HJV-, and IL-6-stimulated hepcidin expression in hepatocytes and block iron induced hepcidin mRNA - Dorsomorphin is also a nonselective kinase inhibitor of AMP kinase (off-target effects) - LDN-193189 with increased potency and selectivity for BMP inhibition	
BMP6 sequestering agents *Anticoagulant and non-anticoagulant hepcidins*	Sequester BMP activity, inhibit BMP6-mediated hepcidin transcription and decrease SM AD phosphorylation thereby reducing hepcidin expression	
Hemojuvelin (BMP co-receptor) *sHJV.Fc, h5F9.23, h5F9-AM, ABT-207*	Antibodies that cause cleavage of hemojuvelin and interferes with BMP binding to the BMPR thereby decreasing hepcidin transcription.	
Transferrin receptor (TRF2) *RNAi*	Experimental gene silencing technology aimed towards the transferrin receptor	

Agents that interact with the IL-6/STAT3 signalling pathway		
JAK/STAT3 inhibition *AG490* *PpYLKTK*	AG490 inhibits the phosphorylation of STAT3 by JAK2 thereby no binding of STAT3 responsive element and reduced hepcidin expression PpYLKTK is a peptide agent that disrupts pSTAT3 dimerization required for binding of hepcidin promoting target genes	Proinflammatory cytokines released due to a variety of stimulants e.g. malignancy. IL-6 binds IL-6 receptor on hepatocyte activating the JAK1/2 cascade causing phosphorylation of STAT3 transcription factor (STAT3-TF) that then translocates to the nucleus In the nucleus STAT3-TF binds STAT3 responsive element (STAT-RE) on hepcidin promoter region STAT3-RE must be coupled with BMP-RE (which is activated via the BMP/HJV/SMAD pathway) for IL-6 mediated hepcidin expression to occur Once coupled hepcidin translation occurs with hepcidin release and degradation of ferroportin
AMPK activator *Metformin*, DS79182026	AMP-activated protein kinase (AMPK) promotes JAK2 degradation reducing STAT3 phosphorylation and hepcidin expression	
IL-6 inhibitors *Tocilizumab, Siltuximab*	Inhibit the IL-6/STAT3 pathway via antibodies to the IL-6 receptor (toclizumab) or via antibodies to the IL-6 ligand - Limited by increased infective risks	
IL1-β inhibitors *Canakinumab*	Monoclonal antibody against IL1- β involved in the inflammatory pathway	
Erythroferrone	Erythroferrone (ERFE) is responsible for early hepcidin suppression during erythropoietic activity stimulated by endogenous or exogenous EPO.	Erythroferrone suppresses hepcidin to promote the mobilization of stored iron and the absorption of dietary iron, so that the increased iron demands of developing erythrocytes can be met.
Agents upregulating erythropoiesis (negative regulator of hepcidin)		
HIF-prolyl hydroxylase inhibitors (EGLN inhibitors) *Roxadustat, Vadadustat, Daprodustat, Enarodustat, FG-4692, AKB-6548, GSK1278863, JTZ-951, BAY85-3934*	Propyl hydroxylase domain-2 (PDH2) inhibitors stabilize HIF-1 and HIF-2 → stable HIF stimulates endogenous erythropoietin production which suppresses hepcidin leading to greater iron availability for erythropoiesis - Activates HIF in presence of oxygen (normocemic conditions)	Hypoxia stimulates the production of EPO via signalling by hypoxia inducible factor (HIF) which also suppresses hepcidin production. Under normocemic conditions, prolyl hydroxylases constitutively degrade HIF, allowing hepcidin production to occur.
Agents interacting with Ferroportin		
Ferroportin agonists/ stabilisers *LY2928057* *Fursultiamine*	Humanized antibody to ferroportin that block the hepcidin-ferroportin interaction while maintaining ferroportin function thereby maintain iron influx. - Fursultiamine prevents hepcidin-FPN interactions by competing with hepcidin to bind FPN on the hepcidin binding site	FPN is a transmembrane protein that is expressed by duodenal enterocytes, splenic macrophages, and hepatocytes ↑ hepcidin causes degradation of ferroportin leading to inability to mobilise store iron

Note. Mechanism and relevant physiology description are adapted from The Hepcidin-Ferroportin System as a Therapeutic Target in Anemias and Iron Overload Disorders, by Ganz et al *Hematology* 2011(32), "Hepcidin Therapeutics" by Katsarou et al, *Pharmaceuticals* 2018(33), pharmacological targeting of the hepcidin/ferroportin axis by Sebastiani et al, *Frontiers in pharmacology* 2016(36), and "Targeting the hepcidin–ferroportin axis to develop new treatment strategies for anemia of chronic disease and anemia of inflammation" by Sun et al. *American Journal of Hematology* 2012(37)

Publication type, study design, language, and timeframe

We will include prospective and retrospective observational studies and randomised and pseudo-randomised controlled trials. Controlled trials can be of any design including parallel, cross over and cluster randomised trials. Open-label clinical trials will be eligible for inclusion. Preclinical safety and dose finding studies in humans will be included. Commentaries, letters, and conference abstracts will be included. Case reports, case studies and animal studies will be excluded. No limitation will be placed on the setting or time frame of follow up or on language or country of study. We will only include studies published since January 1, 2010 to focus our search on contemporary evidence specific to our research aims; namely, the stage of development of novel drugs.

Information sources

The search will be run in Scopus, MEDLINE (Ovid) and Excerpta Medica database (Ovid) to account for variability in the indexing in each database. We will supplement the electronic database search by searching for ongoing or recently completed trial protocols in international trial registries including clinicaltrials.gov, the Australian New Zealand Clinical Trials Registry (ANZCTR), the European Union Clinical Trial register and the International Clinical Trials Registry Platform (ICTRP). Each article included in the review will have its reference list scanned to ensure literature saturation.

Search strategy

We conducted an initial abbreviated search to refine and define our search terms and to avoid duplication of any existing reviews. This was subsequently used to develop a search strategy using medical subject headings (MeSH) with Boolean operations.

The search strategy was developed with the help of the information specialists from the University of Western Australia, was piloted against a random search of 50 abstracts, and refined subsequently. Search results will be limited to abstracts published after 2010 with no language or jurisdiction limitations. The international clinical trial registry platform search portal and clinical trial.gov will be search for ongoing or recently completed trials. PROSPERO will be reviewed for any ongoing or recent reviews. The search includes general terms to describe anaemia and potential pathways to management, as well as more specific terms (i.e., prolyl hydroxylase inhibitors). The full version of the search strategy can be found in Supplemental File 1.

Study records

Data management

The scoping review will be reported using the framework as described by Arksey and O'Malley (50) and the PRISMA-ScR checklist.(46) The literature search results will be imported into a review management program (Covidence, Melbourne, Australia) to facilitate the study selection process. Abstracts and citations will be uploaded and screened against inclusion criteria. A data extraction form was developed and piloted by the review team based on the study inclusion and exclusion criteria (Supplemental File 2).

Selection process

Two independent review authors (AD and PD) will screen all titles and abstracts yielded by the search against the inclusion criteria. For any abstract where consensus is not achieved a third reviewer (CD or LFM) will adjudicate its suitability for inclusion. For any article that

meets the inclusion criteria, a full text extraction will be obtained. For any full text articles that do not meet the inclusion criteria the reason for exclusion will be documented.

Data collection process

Data will be independently extracted by two authors (AD and PD) using a predeveloped and piloted data extraction form (Supplemental File 2). Again, for any extraction where there is no consensus between the two authors, a third author (CD or LFM) will adjudicate. To ensure consistency between reviewers a calibration exercise has been performed prior to commencing the formal data collection process. In keeping with established scoping review methodology ongoing consultation with the senior members of the scoping team (TR and LFM) will occur to guide additional data extraction from the papers as deemed necessary. Where data requires further confirmation, all attempts will be made to seek clarification from the corresponding author of the study and where it is unable to be confirmed will be documented in the results.

Data items

Data will be sought for the following variables:

1. Participant information including n value, treatment setting and descriptive data of participants (age, gender, diagnostic criteria, treatment history, documented comorbidities);
2. Study methodology including study design, country, setting and design limitations;
3. Study intervention and comparator including duration of treatment, timepoints for follow-up, route of intervention (oral or intravenous), frequency of intervention;
4. Primary and secondary outcomes as defined above.

Outcomes and prioritisations

We have chosen to identify and define our outcome measures *a priori*, however, given the scoping nature of this review, revision of these outcomes and expansion or refinement as necessary will occur through the full text review and data extraction process.

The primary outcome of this review will be to investigate which agents facilitate an increase in haemoglobin concentration from baseline as defined by the individual study criteria. Change in haemoglobin concentration is used frequently as an indication of treatment efficacy in clinical trials that aim to treat anaemia. It is therefore expected to be an endpoint in any study investigating novel agents for use in anaemia. Change in haemoglobin concentration is not without limitations, most importantly the potential lack of consistent associations with meaningful clinical changes such as complication rates, particularly in a peri-operative patient cohort. Therefore, this measure will be considered in addition to secondary outcomes to determine the suitability of a potential novel agent for use in a peri-operative patient cohort. The time taken to demonstrate a change in haemoglobin concentration will be of importance, given that these patients often require an intervention that offers benefit within a limited time period prior to surgery.(51) Therefore, any timepoint for which haemoglobin concentration is recorded following a baseline measurement will be reviewed. Similarly the optimal time to intervene in patients with pre-operative anaemia is not yet known, further highlighting the need to characterise the timeline of changes in haemoglobin concentration.

Where available, data pertaining to iron parameters (ferritin, transferrin saturation, soluble transferrin receptor) will be recorded and reviewed to further inform the potential patient cohorts in which the novel agents may be best suited. Patients will be considered as being iron deficient or having inadequate iron stores if they define a cut off of ferritin < 100 μmol/L or

transferrin saturation < 20%.(52) As previously discussed, the cause of anaemia can be multifactorial and so understanding the interplay of a potential therapeutic agent with the concomitant cause of anaemia will be important in developing participant selection criteria for future prospective interventional studies.

In peri-operative research there is an imperative to ensure that research include clinically relevant patient centred outcome measures (49) to ensure that therapies have a significant effect on the functional and physical capacity of the patient in addition to procedural complications. Therefore, we will also determine to what extent patient centred outcomes have been investigated thus far. It is unknown if there will be any data on survival measures or healthcare resource utilisation. This review will address this by collecting data on patient mortality, morbidity, length of hospital and/or ICU stay and health care costs of treatment.

Safety of tested interventions will be assessed through documented major and minor adverse effects. Any immediate post-administration complications or side-effects will be reviewed. Charting of this data (particularly those data describing different interventions or combinations of interventions) will inform future clinical trial design.

Risk of bias

Given the scoping nature of this review a formal bias assessment will not be performed.

Data synthesis

The review will be reported in accordance with the PRISMA-ScR guidelines.(46) Demographic and methodological data will be charted in a tabulated form. Study interventions and outcome data will be charted as a combination of narrative discussion and an alluvial

diagram. An alluvial diagram is a type of flow diagram designed to represent dynamic relationships in a system. We intend to use this to cluster the different variables from our data set to show the relationship and volume of evidence in a particular area; Simple frequency analysis will inform the size of the components between each stream. A stream will be a novel drug or drugs with similar mechanism. Streams will then be 'blocked' according to the following: agent; patient population; study type; comparator; added treatment; outcomes. In keeping with scoping review methodology, a meta-analysis will not be performed.

Meta-bias

This scoping review has been undertaken to inform if there is a need for a more formal review with meta-analysis; accordingly, a meta-bias analysis is beyond the scope of this review.

Confidence in cumulative evidence

A thorough assessment of the risk of bias and other factors that can be used to describe the quality of evidence falls beyond the capacity of this review and lies outside the proposed scoping methodology. Such an assessment will not be included.

Patient and public involvement

No patient or public involvement.

ETHICS AND DISSEMINATION

This scoping review will be reported following the PRISMA-ScR criteria. Ethics approval is not required as the study will only review previously published literature. The findings of this scoping review will be published in a peer-reviewed scientific journal. The results of this study will inform the methodology of future prospective studies utilising novel agents for the management of anaemia in the perioperative setting.

Contributors

LFM is the guarantor. AD, PD and LFM drafted the manuscript. TR was involved with critical revision of the abstract for important intellectual content. All authors contributed to the development of the selection criteria, the data extraction criteria, and the charting methodology. AD and CD developed the search strategy. All authors read, provided feedback, and approved the final manuscript. The authors acknowledge the assistance of the information specialists of the University of Western Australia University Library in devising the search strategy.

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Competing interests

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healthcare. TR is a director of The Iron Clinic Ltd, director of Veincare London Ltd and Vein Care WA. TR is the Vascular lead for 18-week wait Ltd. LFM reports grants from Vifor Pharma Pty Ltd, the Australian and New Zealand College of Anaesthetists, the Victorian Department of Health, the Epworth Medical foundation, and the Austin Medical Research foundation, outside the submitted work. LFM has a leadership or fiduciary role with the National Medical Advisory Committee, Red Cross Lifeblood, Australia and Blood Matters Advisory Committee, Department of Health, Victorian State Government. PD, AD and CD declare no financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

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Search Strategy

Medline:

1 iron defic*.ti.
2 an*emia not (leuk*emia or h*emolytic or sickle or malaria or myelodysplas* or sideroblast* or thalassemia*).ti.
3 h*emoglobin.tw.
4 treatment* or therap* or drug* or pharm*.tw.
5 1 or 2
6 5 and 3 and 4
7 STAT3 inhibi* or AG490 or ppYLKTK.tw.
8 AMPK activ* or metformin or DS79182026.tw.
9 IL-6 inhibi* or interleukin-6 inhibi* or toclizumab or siltuximab.tw.
10 IL-1 inhibit* or interleukin 1 inhibit* or canakinumab.tw. 1372
11 erythroferron*.tw.
12 Prolyl-Hydroxylase Inhibitors/ or hypoxia inducible factor prolyl hydroxylase inhibitors.mp. or Hypoxia-Inducible Factor-Proline Dioxygenases/
13 hypoxia inducible factor stabili*er*.tw.
14 roxadustat.tw.
15 daprodustat.tw.
16 vadadustat.tw.
17 molidustat.tw.
18 enarodustat.tw.
19 desidustat.tw.
20 FG-4592.tw.
21 ASP1517.tw.
22 AZD9941.tw.
23 BAY85-3934.tw.
24 GSK1278863.tw.
25 AKB-6548.tw.
26 JTZ-951.tw.
27 ZYAN-1.tw.
28 ferroportin stabili*er* or ferroportin agonist* or LY298057 or fursultiamine.tw.
29 anticalin* or hepcidin binding protein* or PRS-080.tw.
30 antihepcidin antibod* or A12B9m or Ly2787106.tw.
31 hepcidin spiegelmer* or hepcidin binding L-RNA aptamer* or lexapetid pegol NOX-H94.tw. 2
32 (short interfering RNA or shRNA or siRNA or short hairpin RNA or H6 or H10 or ALN-HPN) and hepcidin.mp.
33 activin like kinase receptor inhibit* or ALK2 inhibit* or ALK3 inhibit* or OD66 or TP-0184 or INCB00928 or momelotinib or indazole or DS79182026.tw.
34 bone morphogenic protein type 1 receptor inhibit* or BMP type 1 receptor inhibit* or dorsomorphin or LDN-193189 or LDN-212854.tw.
35 BMP6 inhibit* or bone morphogenic protein 6 inhibit* or imatinib or spironolactone.tw.
36 hemojuvelin inibit* or hemojuvelin antibod* or sHJV or h5F923 or h5F9-AM or ABT-207.tw.
37 transferrin receptor RNAi.tw.
38 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 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
39 5 and 38

40 6 or 39
41 limit 40 to (humans and yr="2010 -Current")

Embase Classic + Embase:

1 iron defic*.ti.
2 an*emia not (leuk*emia or h*emolytic or sickle or malaria or myelodysplas* or sideroblast* or thalassemia*).ti.
3 h*emoglobin.tw.
4 treatment* or therap* or drug* or pharm*.tw.
5 1 or 2
6 5 and 3 and 4
7 STAT3 inhibi* or AG490 or ppYLKTK.tw.
8 AMPK activ* or metformin or DS79182026.tw.
9 IL-6 inhibi* or interleukin-6 inhibi* or toclizumab or siltuximab.tw.
10 IL-1 inhibit* or interleukin 1 inhibit* or canakinumab.tw. 1372
11 erythroferron*.tw.
12 Prolyl-Hydroxylase Inhibitors/ or hypoxia inducible factor prolyl hydroxylase inhibitors.mp. or Hypoxia-Inducible Factor-Proline Dioxygenases/
13 hypoxia inducible factor stabili*er*.tw.
14 roxadustat.tw.
15 daprodustat.tw.
16 vadadustat.tw.
17 molidustat.tw.
18 enarodustat.tw.
19 desidustat.tw.
20 FG-4592.tw.
21 ASP1517.tw.
22 AZD9941.tw.
23 BAY85-3934.tw.
24 GSK1278863.tw.
25 AKB-6548.tw.
26 JTZ-951.tw.
27 ZYAN-1.tw.
28 ferroportin stabili*er* or ferroportin agonist* or LY298057 or fursultiamine.tw.
29 anticalin* or hepcidin binding protein* or PRS-080.tw.
30 antihepcidin antibod* or A12B9m or Ly2787106.tw.
31 hepcidin spiegelmer* or hepcidin binding L-RNA aptamer* or lexapetid pegol NOX-H94.tw. 2
32 (short interfering RNA or shRNA or siRNA or short hairpin RNA or H6 or H10 or ALN-HPN) and hepcidin.mp.
33 activin like kinase receptor inhibit* or ALK2 inhibit* or ALK3 inhibit* or OD66 or TP-0184 or INCB00928 or momelotinib or indazole or DS79182026.tw.
34 bone morphogenic protein type 1 receptor inhibit* or BMP type 1 receptor inhibit* or dorsomorphin or LDN-193189 or LDN-212854.tw.
35 BMP6 inhibit* or bone morphogenic protein 6 inhibit* or imatinib or spironolactone.tw.
36 hemojuvelin inibit* or hemojuvelin antibod* or sHJV or h5F923 or h5F9-AM or ABT-207.tw.
37 transferrin receptor RNAi.tw.

38 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 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
39 5 and 38
40 6 or 39
41 limit 40 to (humans and yr="2010 -Current")

Scopus

1. TITLE-ABS-KEY (treatment OR therap* OR pharm* OR safe* OR efficacy OR drug*) AND
2. TITLE (an*emia) OR TITLE ("iron defic*") AND
3. TITLE-ABS-KEY (h*emoglobin) OR
4. TITLE-ABS-KEY ("stat3 inhibi*" OR "ag490" OR "ppylktk" "ampk activ*" OR "metformin" OR "ds78182026" OR "il-6 inhibit*" OR "interleukin-6 inhibit*" OR "toclizumab" OR "siltuximab" OR "il-1 inhibit*" OR "interleukin 1 inhibit*" OR "canakinumab" OR "erythroferron*" OR "prolyl hydroxylase inhibit*" OR "hypoxia inducible factor prolyl hydroxylase inhibit*" OR "hypoxia inducible factor proline dioxygenase*" OR "hif prolyl hydroxylase inhibit*" OR "hypoxia inducible factor stabili*er*" OR "roxadustat" OR "daprodustat" OR "vadadustat" OR "molidustat " OR "enarodustat" OR "desidustat" OR "fg-4592" OR "asp1517" OR "azd9941" OR "bay85-3934" OR "gsk1278863" OR "akb-6548" OR "jtz-951" OR "zyan-1" OR "ferroportin stabili*er*" OR "ferroportin agonist*" OR "ly298057" OR "fursultiamine" OR "anticalin*" OR "hepcidin binding protein*" OR "prs-080" OR "antihepcidin antibod*" OR "a12b9m" OR "ly2787106" OR "hepcidin spiegelmer*" OR "hepcidin binding l-rna aptamer*" OR "lexapetid pegol nox-h94" OR "short interfering rna" OR "shrna" OR "sirna" OR "short hairpin rna" OR "activin like kinase receptor inhibit*" OR "alk2 inhibit*" OR "alk3 inhibit*" OR "od66" OR "tp-0184" OR "incb00928" OR "momelotinib" OR "indazole" OR "ds79182026" OR "bone morphogenic protein type 1 receptor inhibit*" OR "bmp type 1 receptor inhibit*" OR "dorsomprhin" OR "ldn-193189" OR "ldn-212854" OR "hemojuvelin inhibit*" OR "shjv" OR "imatinib" OR "spironolactone" OR "h5f923" OR "h5f 9-am" OR "abt-207" OR "transferrin receptor rnai" AND "an*emia") AND
5. PUBYEAR > 2009

Data extraction form

Date:		Investigator: AD PD CD LM			DOI	
Title						
Author (s)						
Citation						
Year of pub.		Country		Pub. Type		
Research question						
Outcomes						
Population						
Inclusion criteria	[ ] adult pts (>18 y/o) [ ] anemia [ ] novel agents					
Exclusion criteria	[ ] anemia 2'another hematological condition [ ] primary bone marrow disorder [ ] renal disease [ ]hemolysis [ ]infection e.g. malaria					
Setting						
Sample size						
Methodology	[ ] prospective [ ] retrospective [ ]blinded [ ] open label [ ] randomized [ ] non- randomized					
Intervention						
Comparator	[ ] placebo [ ] SOC [ ] ESA [ ] PO iron [ ] IV iron [ ] no comparator					
Duration of intervention						
Outcome and measures:						
Timepoints	Baseline	1	2	End	Significance	
Δ Hb						
Δ Ferritin						
Δ T sats						
Δ hepcidin						
Major AE		Minor AE		Admin comp		
HRQL	Y/N		Disability free survival			
Functional status			DAAAH			
Mortality			Complications			
LOS			Health care costs			

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Information reported (Y/N)	Page(s)
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Y	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Y	
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Y	2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Y	20
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA	NA
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Y	20
Sponsor	5b	Provide name for the review funder and/or sponsor	NA	20
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Y	20
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	Y	6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Y	8
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Y	9-13
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Y	13
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Y	Sup. file 1

Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Y	14
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Y	15
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Y	15
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Y	15-16
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Y	16-17
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Y	17
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Y	18
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	NA	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	NA	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Y	18
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	NA	18
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA	18

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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