


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

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## ABSTRACT

**Introduction** Preoperative 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 perioperative 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 1 January 2010. This review will have three objectives: (1) to describe the mechanisms of action for novel agents, (2) to describe the level of evidence and stage of development of novel agents in a perioperative setting, and (3) to determine the potential agents suitable for prospective controlled trials in a preoperative 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.

**Trial registration number** 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](https://osf.io/sm3uh/?view_only=39876ccf7a4348dfbd566535b957a7db)). Cite Now

## INTRODUCTION

### Rationale

While the global prevalence of anaemia is decreasing, the global burden of disease

## 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 (CKD) will limit indirectness in assessing the evidence outside this population.
- The exclusion of the CKD 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, but will lack the robustness of a traditional systematic review with meta-analysis.

remains high. Approximately 25% of the general population has anaemia,<sup>1</sup> which has been associated with worse outcomes and greater healthcare costs across a range of specific patient populations.<sup>1–7</sup> There is an independent association between preoperative anaemia and worse postoperative outcomes.<sup>5 8–10</sup> Preoperative anaemia is also the strongest predictor of allogenic 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.<sup>11 12</sup> Absolute or functional iron deficiency (and by extension the ‘anaemia of inflammation’ (AOI)) is the underlying cause of anaemia in most hospitalised patients.<sup>13</sup> AOI occurs due to disruption of the hepcidin–ferroportin axis resulting in iron-restricted erythropoiesis, functional iron deficiency and anaemia despite ‘sufficient’ iron stores.<sup>11 14</sup> AOI confers a poorer prognosis and worsens quality of life.<sup>14 15</sup>

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.<sup>9 16</sup> 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.<sup>17–24</sup> 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.<sup>25</sup> These results differ from previous studies in specific surgical populations investigating the same intervention.<sup>26–28</sup> Furthermore, this conclusion contradicts a meta-analysis performed in 2013 which—while having a higher sample size—was not restricted to the perioperative setting.<sup>29</sup> More recently, the preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTT) trial reported similar results in a larger sample.<sup>30</sup> Like Ng *et al*, the PREVENTT investigators concluded that preoperative 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 AOI commonly seen in the surgical setting. ESAs similarly improve biochemical outcomes outside the renal population; however, implementation as part of wider patient blood management programmes 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.<sup>31</sup> 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) versus iron alone.<sup>31</sup> 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 AOI) more directly. These agents have varied mechanisms of action that attempt to balance the multifactorial nature of anaemia in multimorbid patients.<sup>32–37</sup> 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.<sup>38–41</sup> 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.<sup>42</sup> Trials in individual agents (Vadadustat and Daprodustat) do suggest non-inferiority when compared with ESAs but are inconsistent in regard to safety.<sup>43 44</sup> 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 (ie, 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 used in patients with preoperative 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:

- ▶ What are the described mechanisms of action for non-ESA, non-iron therapies to increase haemoglobin?
- ▶ What is the level of evidence and stage of development for non-ESA, non-iron novel anaemia therapies in a perioperative setting?
- ▶ Which potential agents are suitable for prospective controlled trials in a preoperative or postoperative patient cohort with aims to improve perioperative 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<sup>45</sup> 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).<sup>46</sup> 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 amendment, 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 population–intervention–comparison–outcome format to develop our eligibility criteria and outline our outcome measures.

## Population

We will include studies examining adults  $\geq 18$  years of age with anaemia. Given the varied definitions of anaemia used in reporting and to ensure we capture all relevant literature, we will define anaemia as any haemoglobin concentration of  $< 130$  g/L regardless of sex.<sup>47 48</sup> Studies in which anaemia is caused by primary renal dysfunction, infection (ie, 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 used for another primary indication) will be sought. Examples of such interventions and their mechanisms of action are shown in [table 1](#). Studies that use 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 (ie, 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 Standardised Endpoints in Perioperative Medicine-Core Outcome Measures in Perioperative and Anaesthetic Care (StEP-COMPAC) group as the current standard for research in perioperative medicine; however, as the development of these measures is relatively recent, it is unlikely that many studies will have been performed using these endpoints.<sup>49</sup> As such, biochemical surrogates will be used to determine efficacy and the potential for further study of identified agents in a perioperative 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 (gram per litre).

#### Secondary outcome

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

### Publication type, study design, language and time frame

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 1 January 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, the European Union Clinical Trials Register and the International Clinical Trials Registry Platform. 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 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 Trials Registry Platform search portal and clinical trial.gov will be searched for ongoing or recently completed trials. The International Prospective Register of Systematic Reviews (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 (ie, prolyl hydroxylase inhibitors). The full version of the search strategy can be found in online supplemental file 1.

### Study records

#### Data management

The scoping review will be reported using the framework as described by Arksey and O'Malley<sup>50</sup> and the PRISMA-ScR checklist.<sup>46</sup> The literature search results will be imported into a review management programme (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

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

Class agent	Mechanism	Relevant physiology
<b>Agents that directly antagonise the effects of hepcidin</b>		
Anticalins (hepcidin binding proteins) <i>PRS-080</i>	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 <i>AB12B9m</i> and <i>LY2787106</i>	Humanised monoclonal antibodies that bind hepcidin with high affinity causing degradation	
Spiegelmers (hepcidin-binding L-RNA Aptamers) <i>Lexaptepid pegol-NOX-H94</i>	Blocks hepcidin induced ferroportin internalisation L enantiomers of oligonucleotide that interact like antibodies binding human hepcidin and blocking its function	
Short interfering and short hairpin RNAs <i>H6, H10</i> and <i>ALN-HPN</i>	RNA-based technology leading to hepcidin gene silencing, thereby reducing production of hepcidin mRNA	
<b>Agents that interact with the BMP6-HJV-SMAD signalling cascade</b>		
ALK2/3 (activin-like kinase receptor) inhibitors <i>OD66, TP-0184, INCB00928, Momelotinib, Indazole</i> and <i>DS79182026 (ALK3)</i>	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	HJV is a bone morphogenetic protein (BMP) co receptor High iron stimulates binding of circulating BMP6 to BMP receptor types I and II with coreceptor 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 one receptor <i>Dorsomorphin, LDN-193189</i> and <i>LDN-212854</i>	Inhibit BMP-stimulated, HJV-stimulated and IL-6-stimulated hepcidin expression in hepatocytes and block iron induced hepcidin mRNA ▶ Dorsomorphin is also a non-selective 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 coreceptor) <i>shJV.Fc, h5F9.23, h5F9-AM, ABT-207</i>	Antibodies that cause cleavage of hemojuvelin and interferes with BMP binding to the BMPR, thereby decreasing hepcidin transcription	
Transferrin receptor (TRF2) <i>RNAi</i>	Experimental gene silencing technology aimed towards the transferrin receptor	
<b>Agents that interact with the IL-6/STAT3 signalling pathway</b>		
JAK/STAT3 inhibition <i>AG490</i> <i>PpYLKTK</i>	AG490 inhibits the phosphorylation of STAT3 by JAK2 thereby no binding of STAT-RE 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, for example, malignancy. IL-6 binds IL-6 receptor on hepatocyte activating the JAK1/2 cascade causing phosphorylation of STAT3-TF that then translocates to the nucleus In the nucleus, STAT3-TF binds 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 <i>Metformin, DS79182026</i>	AMPK promotes JAK2 degradation, reducing STAT3 phosphorylation and hepcidin expression.	
IL-6 inhibitors <i>Tocilizumab</i> and <i>siltuximab</i>	Inhibit the IL-6/STAT3 pathway via antibodies to the IL-6 receptor (tocilizumab) or via antibodies to the IL-6 ligand ▶ Limited by increased infective risks.	
IL-1-β inhibitors <i>Canakinumab</i>	Monoclonal antibody against IL-1-β involved in the inflammatory pathway	
Erythroferrone	Erythroferrone is responsible for early hepcidin suppression during erythropoietic activity stimulated by endogenous or exogenous EPO	Erythroferrone suppresses hepcidin to promote the mobilisation of stored iron and the absorption of dietary iron, so that the increased iron demands of developing erythrocytes can be met.
<b>Agents upregulating erythropoiesis (negative regulator of hepcidin)</b>		
HIF-prolyl hydroxylase inhibitors (EGLN inhibitors) <i>Roxadustat, vadadustat, daprodustat, enarodustat, FG-4692, AKB-6548, GSK1278863, JTZ-951</i> and <i>BAY85-3934</i>	Propyl hydroxylase domain-2 (PDH2) inhibitors stabilise 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 HIF, which also suppresses hepcidin production. Under normocemic conditions, prolyl hydroxylases constitutively degrade HIF, allowing hepcidin production to occur.
<b>Agents interacting with ferroportin</b>		

Continued

Table 1 Continued

Class agent	Mechanism	Relevant physiology
Ferroportin agonists/stabilisers <i>LY2928057</i> <i>Fursultiamine</i>	Humanised 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.

Mechanism and relevant physiology description are adapted from Ganz and Nemeth,<sup>32</sup> Katsarou and Pantopoulos,<sup>33</sup> Sebastiani *et al*<sup>36</sup> and Sun *et al*.<sup>37</sup> AMPK, AMP-activated protein kinase; HIF, hypoxia inducible factor; HJV, hemojuvelin; IL, interleukin; STAT-RE, STAT3 responsive element; STAT3-TF, STAT3 transcription factor.

the study inclusion and exclusion criteria (online 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 (online 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 require 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:

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

### 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 perioperative 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.<sup>51</sup> 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 preoperative 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 and 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 of <100 µmol/L or transferrin saturation of <20%.<sup>52</sup> 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 perioperative research, there is an imperative to ensure that research includes clinically relevant patient-centred outcome measures<sup>49</sup> 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 use. This review will address this by collecting data on patient mortality, morbidity, length of hospital and/or intensive care unit stay and healthcare costs of treatment.

Safety of tested interventions will be assessed through documented major and minor adverse effects. Any immediate postadministration complications or side effects will be reviewed. Charting of these 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.<sup>46</sup> 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.

### Metabias

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

There is no patient or public involvement in this study.

## 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 using novel agents for the management of anaemia in the perioperative setting.

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**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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