PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Non-erythropoiesis stimulating agent, non-iron therapies for the management of anaemia: protocol for a scoping review
AUTHORS	Devlin, Paula; Davies, Amelia; Dugan, Cory; Richards, Toby; Miles, Lachlan

VERSION 1 – REVIEW

REVIEWER	Ipsiroglu, Osman The University of British Columbia, Pediatrics, Sleep/Wake-Behaviours
REVIEW RETURNED	13-Dec-2021

GENERAL COMMENTS	Thank you for allowing us to review the manuscript, "Non-erythropoiesis stimulating agent, non-iron therapies for the management of anaemia: a protocol for a systematic scoping review". The authors have developed a protocol for their scoping review, which is to follow the methodological framework outlined by Arksey & O'Malley, and reported using the PRISMA-Scr checklist. The protocol is well-structured and provides a good overview of the rationale, methodology, and implications for this review. Further, the supplementary materials including the search strategy and data collection sheet appear to be very thorough, and help to increase the transparency of this scoping review protocol. Inclusion Criteria. While the authors did provide a rationale for including studies only published >2010, as a scoping review, it would be beneficial to obtain a wider array of literature, which may consequently allow for a comment on any trends with non-ESA, non-iron therapies over time. However, we would suggest consulting a hematologist to provide a comment on this specific criterion, as it is out of the scope of our knowledge. Similarly, the authors have stated that case studies/series will be excluded. While the level of evidence from such studies is considered to be relatively low, the inclusion of such studies would allow for a more well-rounded and comprehensive review. This is particularly important given that research question 2 ("What is the level of evidence and stage of development for non-ESA, non-iron novel anaemia therapies in a peri-operative setting?") directly relates to levels of evidence. Analysis of outcome measures. When reviewing ferritin levels, CRP/ESR should also be included because ferritin is an acute phase reactant that can increase in the presence of inflammation/infection. In summary, this is a well-written and comprehensive scoping review protocol on an important topic that will be of interest to many readers. Expanding the scope to include studies published earlier than 2010 and including case studies/series may enable the authors to draw more concrete conclusions.

REVIEWER	lasocki, sigismond

	Centre Hospitalier Universitaire d'Angers, Département Anesthésie Réanimation consulting fees from VIFOR PHARMA and PFIZER
REVIEW RETURNED	28-Jan-2022

GENERAL COMMENTS	Dr Devlin and collaborators propose a study protocol for a systematic review of the interest of non-erythropoiesis stimulating agent and non-iron therapies for the management of anaemia. The subject of the review is really up-to-date, with new players coming in the field of anaemia treatment (outside erythropoiesis stimulating agent and iron). The studied population (ie surgical patients) is well chosen. The authors should be congratulated for their proposed methodology and their manuscript. I have only some minor comments: - Introduction: please cite the two recently published in the NEJM RCTs: PRO2TECT Study (N Engl J Med. 2021 Apr 29;384(17):1589-1600) and ASCEND-D (N Engl J Med. 2021 Dec 16;385(25):2325-2335) that demonstrated the non-inferiority of HIF inhibitors (but not the safety for Vadadustat). - Although there are conflicting results regarding the effect of IRON in reducing blood transfusion, other benefits have been reported (less hospital readmissions, lower LOS, higher Hb levels…), even in the postoperative periods (when anaemia of inflammation is very likely). The sentence P9L12-17 "This evidence suggests that intravenous iron in isolation is an inadequate management option for the anaemia of inflammation commonly seen in the surgical setting. " show be tempered. - Please correct author names in REF 15

REVIEWER	Sholzberg, Michelle Université de Toronto
REVIEW RETURNED	02-Feb-2022

GENERAL COMMENTS	This is a well written and thought out protocol by Devlin et al. for a scoping reviewing non-ESA, non-iron therapies for the management of pre-operative anemia. Some minor comments for your consideration: 1. Please provide rationale on why the search starts January 1st, 2010. 2. In addition to publishing this protocol, it would be helpful to register this scoping review. 3. Please include a concluding paragraph regarding the possible significance of the findings of the scoping review.

VERSION 1 – AUTHOR RESPONSE

Response to reviewer 1: Dr Ipsiroglu

Thank you for your comments and suggestions. Where available we will include CRP/ESR in our data extraction to reflect the subsequent elevation of ferritin in the presence of infection/inflammation.

2010 has been chosen as a time limit to allow us to best assess novel and contemporary therapies rather than historical practices. Further, we have hematologists who are integrally involved in our

research, including the PREVENTT, ITACS, CAVIAR and IRONMAN trial groups. We can confirm they have advised on this. Of note, Professor Richards PhD was on HIF-1, and he has been integrally involved in trials on iron, EPO and HIF-PHI.

Regarding the exclusion of case studies/series, while the presence of these would allow for a more comprehensive review, we believe that the low evidence quality of these study designs would not be robust enough to preclude future prospective investigation into any identified agent. The objective of a scoping review is to determine if there is a sufficient body of evidence to justify a systematic review and ideally meta-analysis, in which single-arm case series and case reports are not traditionally included. Consequently, inclusion of these designs would dramatically increase the size of the literature review to no appreciable effect.

Response to reviewer 2: Prof. Lasocki

Thank you for your comments and the suggested papers that contain further evidence supporting further investigation into the HIF prolyl hydroxylase inhibitors. We have now referenced these articles in the introduction. Reference 15 has also been corrected.

I have also clarified in the manuscript that our position is that intravenous iron in isolation to reduce allogenic blood transfusion is inadequate, as to not dismiss the other patient benefits.

1. **Response to reviewer 3: Dr Sholzberg**

Thank you for your comments. We have chosen to limit our search to the literature after January 1st 2010 to allow us to best assess contemporary practice. After all, the objective is to assess new or novel agents, particularly those that act on newer molecules in the pathway. As hepcidin was not discovered until 1998, and erythroferrone not discovered until 2014, searching before 2010 is highly unlikely to reveal any agents that will act upon these pathways.

Our current protocol and previous iterations are currently available on the open science framework database. Unfortunately, other registries, such as PROSPERO, do not accept protocols for scoping reviews.

BMJopen journal policy is to not include a conclusion or speculate about potential results and as such this has been omitted. However, we suspect that by excluding the CKD population there will be limited (if any) literature in an anaemic surgical population which would provide avenues for future prospective investigations.