Treatments for Anemia in Chronic Kidney Disease: Effectiveness and Value

Research Protocol

August 24, 2020

Institute for Clinical and Economic Review

Table of Contents

1. Background, Objectives, and Research Questions

1.1 Background

Anemia is described as "a condition in which the number of red blood cells or their oxygen-carrying capacity is insufficient to meet physiological needs."[1] In anemia, insufficient numbers of circulating red blood cells or inadequate quantities of iron or functional hemoglobin (Hb) are available to transport and release oxygen to tissues. Anemia is common in patients with chronic kidney disease (CKD). The World Health Organization and the 2012 Kidney Disease Improving Global Outcomes guidelines define anemia as an Hb level of <12 g/dL (grams per deciliter) in females and <13 g/dL in adult males.[2,3] However, this definition does not provide goals of treatment for different patient groups.

The definition and classification of CKD was established and endorsed by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative and the international Kidney Disease Improving Global Outcomes guideline group.[3] Decreased kidney function refers to a decrease in glomerular filtration rate (GFR), which is usually estimated using serum creatinine and one of several available equations.[4,5] This definition is widely accepted and used among patients, clinicians, researchers, and regulatory agencies. Patients who are diagnosed with CKD can be categorized into different stages according to the cause, their GFR (five G-stages: I, II, III, IV, and V), and the amount of albumin or protein in the urine (three A-stages: 1, 2, and 3). Additionally, patients with CKD can advance from being dialysis independent (DI-CKD) to end-stage kidney disease (ESKD), which is defined as severely reduced kidney function or treatment with dialysis (dialysis dependent [DD-CKD]) or transplantation. Risk factors for CKD include genetic or sociodemographic predisposition, or the presence of diseases that can initiate and propagate kidney disease such as diabetes and hypertension. CKD is a worldwide public health problem. The number of patients enrolled in the ESKD Medicare-funded program has increased from approximately 10,000 beneficiaries in 1973 to 703,243 as of 2015.[6]

Anemia in patients with CKD can be due to reduced production of erythropoietin by the kidneys, iron deficiency, inflammation, and the accumulation of uremic toxins that leads to shortened red blood cell survival.[7-9] Anemia causes many of the symptoms associated with CKD such as fatigue, depression, breathlessness, and reduced exercise tolerance. Anemia is also associated with increased morbidity and undesirable outcomes including mortality and hospitalizations.[10-13] In patients with DI-CKD, the prevalence of anemia increases with decline in kidney function and advancing stages of CKD.[14-16] For example, based on over 12,000 participants in the National Health and Nutrition Examination Survey, the prevalence of anemia (Hb <13 g/dL in men and <12 g/dL in

women) increased from 8.4% at CKD stage G-I to 53.4% at CKD stage G-V.[17] Nearly all patients with DD-CKD have anemia that must be managed.

Managing anemia in patients with CKD requires evaluating adequacy of iron stores. Additionally, up until now, managing anemia involved the use of recombinant erythropoietin and its synthetic derivatives (epoetin alfa, epoetin beta, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta; collectively known as erythropoiesis-stimulating agents [ESAs]). Recombinant human erythropoietin was developed in the late 1980s.[18] In the pre-ESA era, blood transfusion—with all of its potential risks including iron overload, antibody formation against blood cell antigens, sensitization to transplant antigens, and transfusion-related infections like viral hepatitis—was the main management strategy among CKD patients with anemia. The United States (US) Food and Drug Administration (FDA) approved recombinant human erythropoietin for the treatment of anemia in DD-CKD in 1989 and broadened approval to include anemia in DI-CKD in 1990. ESAs are administered intravenously or subcutaneously. After the FDA approval, there was a rapid and widespread uptake of ESA use in CKD patients, which was supported by recommendations in clinical practice guidelines.[19] However, despite the association between anemia and higher mortality in uncontrolled studies, subsequent evidence based on multiple randomized controlled trials (RCTs) emerged and showed that correction of anemia and maintenance of Hb to near normal levels with ESAs increased mortality and cardiovascular events without consistently improving quality of life.[20-23]

Hypoxia-inducible factor prolyl hydroxylase (HIF-PH) enzyme inhibitors have emerged as a new class of agents for the management of anemia in CKD. These agents work by stabilizing the HIF complex and stimulating endogenous erythropoietin production in patients with DI-CKD and DD-CKD. HIF-PH inhibitors are administered orally, which may be favorable for some patients, especially those who are not yet on dialysis. By inducing considerably lower, but more consistent, erythropoietin levels compared to ESAs, it is plausible that HIF-PH inhibitors may be associated with fewer adverse cardiovascular events. There are four HIF-PH inhibitors undergoing Phase II and III clinical trials in the US including roxadustat, vadadustat, daprodustat, and molidustat. This review will focus on roxadustat as it is the only agent that has been submitted to the FDA for consideration of approval.

1.2 Objectives

The scope of this project was previously available for public comment and has been revised upon further discussions and input from stakeholders. In accordance with the revised scope, this project will assess both the comparative clinical effectiveness and economic impacts of roxadustat for the treatment of anemia in chronic kidney disease. The assessment aims to systematically evaluate the existing evidence, taking uncertainty into account. To that aim, the assessment is informed by two research components: a systematic review of the existing evidence and an economic evaluation. This document presents the protocol for the systematic review of existing evidence (i.e., the clinical review). The model analysis plan will include details on the proposed methodology and model

structure that will be used for the economic evaluation (expected publication date: October 14, 2020).

1.3 Research Questions

To inform our review of the clinical evidence, we have developed the following research questions:

- What is the net health benefit of roxadustat versus darbepoetin alfa, epoetin alfa, methoxy polyethylene glycol-epoetin beta, and usual care (estimated by placebo arms of clinical trials) in the population(s) described below?

1.4 PICOTS Criteria

In line with the above research questions, the following specific criteria have been defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting and Study Design) elements.

Population

The population of focus for this review will be adult patients with anemia associated with CKD. Data permitting, we will consider evidence across two relevant populations of patients:

1. Patients with DI-CKD
2. Patients with DD-CKD

In patients with DI-CKD (population one), we will plan to evaluate subgroups of patients defined by stages of CKD: G-stages III, IV, and V. In patients with DD-CKD (population two), we will plan to evaluate a subgroup of patients newly initiated on dialysis. Other subgroups of interest may be defined according to iron status, inflammation status and ESA-hyporesponsiveness, presence of cardiovascular disease, or cancer.

Interventions

The intervention of interest is roxadustat (AstraZeneca and FibroGen).

Comparators

We intend to compare roxadustat to:

- Darbepoetin alfa (Aranesp®, Amgen)
- Epoetin alfa (Epogen®, Amgen; Procrit®, Janssen)

- Methoxy polyethylene glycol-epoetin beta (Mircera®, Roche)
- Usual care (estimated by placebo arms of clinical trials)

Outcomes

The outcomes of interest are described in the list below.

- Patient-important outcomes:
    - All-cause mortality
    - Cardiovascular mortality
    - Stroke
    - Myocardial infarction
    - Unstable angina
    - Heart failure
    - Hospitalization
    - Blood transfusion
    - Rescue therapy
    - ESKD
    - Health-related quality of life
    - Improvement in symptoms or function (e.g., fatigue, dyspnea)
    - Adverse events including
        - Serious adverse events
        - Treatment-emergent adverse events
        - Adverse events leading to treatment discontinuation
- Other outcomes:
    - Anemia (as assessed by Hb and/or hematocrit)
    - Measures of iron storage and availability
    - Measures of inflammation
    - Lipid levels
    - CKD progression (as assessed by eGFR)

Timing

Evidence on intervention efficacy, safety, and effectiveness will be collected from studies of any duration.

Setting

Evidence from all relevant settings will be considered, with a focus on outpatient settings in the US.

Study Design

RCTs, non-RCTs, and observational studies of roxadustat with any sample size will be included. In addition, RCTs of ESAs with any sample size will be included.

2. Evidence Review Methods

2.1 Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on roxadustat for anemia in CKD will follow established best methods.[24,25] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[26] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE and EMBASE for relevant studies. Each search will be limited to English language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We will include abstracts from conference proceedings identified from the systematic literature search. All search strategies will be generated utilizing the Population, Intervention, Comparator, and Study Design elements described above.

We will conduct a de novo search for roxadustat with no time restriction (Tables 2.1 and 2.2). Additionally, we identified a systematic literature review and network meta-analysis (NMA) of ESAs that followed a similar scope to the one planned for this review, with a literature search end date of 2014.[27] We will identify RCTs of darbepoetin alfa, epoetin alfa, and methoxy polyethylene glycol-epoetin beta that meet our criteria from the systematic literature review and search for new evidence by conducting an updated systematic literature search. In order to account for delays in indexing, we will overlap the search timeframe with that of the previous systematic literature review, starting with January 2014 (Tables 2.3 and 2.4). The proposed search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE) as well as free-text terms.

To supplement the database searches, we will perform a manual check of the reference lists of included trials and reviews and invite key stakeholders to share references germane to the scope of this project. We will also supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Table 2.1. Search Strategy of MEDLINE via Ovid* for Roxadustat

1	exp Anemia/ OR exp Anemia, Hypochromic/ OR exp Anemia, Refractory/
2	(an?emi* OR chronic anemia).ti,ab.
3	1 OR 2
4	exp Renal Insufficiency, Chronic/
5	(chronic kidney disease OR end*stage kidney disease OR end*stage kidney failure OR ESKD OR chronic renal disease OR end*stage renal dysfunction OR end*stage renal failure OR ESRD or stage 5 renal disease).ti,ab.
6	4 OR 5
7	3 AND 6
8	(roxadustat OR roxa OR FG-4592 OR FG4592 OR FG 4592 ASP-1517 OR ASP1517 OR ASP 1517 OR AZD-9941 OR AZD9941 OR AZD 9941 OR ai rui zhuo OR evrenzo).ti,ab.
9	7 AND 8
10	(addresses OR autobiography OR bibliography OR biography OR clinical trial, phase I OR comment OR congresses OR consensus development conference OR duplicate publication OR editorial OR guideline OR in vitro OR interview OR lecture OR legal cases OR legislation OR letter OR news OR newspaper article OR patient education handout OR periodical index OR personal narratives OR portraits OR practice guideline OR review OR video audio media).pt.
11	9 NOT 10
12	(exp animals/ OR exp animal/ OR exp nonhuman/ OR exp animal experiment/ OR animal model/ OR animal tissue/ OR non human/ OR (rat OR rats OR mice OR mouse OR swine OR porcine OR murine OR sheep OR lambs OR pigs OR piglets OR rabbit OR rabbits OR cat OR cats OR dog OR dogs OR cattle OR bovine OR monkey OR monkeys OR trout OR marmoset$1 OR basic research OR cell lines OR in vitro OR animal model OR canine).tw.) NOT (humans/ OR human/ OR human experiment/ OR (human* OR men OR women OR patients OR subjects).tw.)
13	11 NOT 12
14	limit 13 to english language
15	remove duplicates from 14

*Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present

Table 2.2. Search Strategy of EMBASE for Roxadustat

#1	'anemia'/exp OR 'iron deficiency anemia'/exp OR 'refractory anemia'/exp OR 'refractory anemia with excess blasts'/exp
#2	'an?emi*':ti,ab OR 'chronic anemia':ti,ab
#3	#1 OR #2
#4	'chronic kidney failure'/exp OR 'end stage renal disease'/exp
#5	'chronic kidney disease':ti,ab OR 'end*stage kidney disease':ti,ab OR 'end*stage kidney failure':ti,ab OR 'ESKD':ti,ab OR 'chronic renal disease':ti,ab OR 'end*stage renal dysfunction':ti,ab OR 'end*stage renal failure':ti,ab OR 'ESRD':ti,ab OR 'stage 5 renal disease':ti,ab
#6	#4 OR #5
#7	#3 AND #6
#8	'roxadustat'/exp
#9	'roxadustat':ti,ab OR 'roxa':ti,ab OR 'fg-4592':ti,ab OR 'fg4592':ti,ab OR 'fg 4592':ti,ab OR 'asp-1517':ti,ab OR 'asp1517':ti,ab OR 'asp 1517':ti,ab OR 'azd-9941':ti,ab OR 'azd9941':ti,ab OR 'azd 9941':ti,ab OR 'ai rui rhuo':ti,ab OR 'evrenzo':ti,ab
#10	#8 OR #9
#11	#7 AND #10
#12	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#13	#11 NOT #12
#14	('case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#15	#13 NOT #14
#16	#15 AND [english]/lim

Table 2.3. Search Strategy of MEDLINE via Ovid* for ESAs

1	exp Anemia/ OR exp Anemia, Hypochromic/ OR exp Anemia, Refractory/
2	(an?emi* OR chronic anemia).ti,ab.
3	1 OR 2
4	exp Renal Insufficiency, Chronic/
5	(chronic kidney disease OR end*stage kidney disease OR end*stage kidney failure OR ESKD OR chronic renal disease OR end*stage renal dysfunction OR end*stage renal failure OR ESRD or stage 5 renal disease).ti,ab.
6	4 OR 5
7	3 AND 6
8	exp Erythropoietin/ OR exp Epoetin Alfa/
9	(epo OR rhepo OR epoetin alfa OR procrit OR epogen OR darbepoetin alfa OR aranesp OR methoxy polyethylene glycol epoetin beta OR methoxy polyethylene glycol-epoetin beta OR cera OR mircera).ti,ab.
10	(erythropoie* OR epo?etin).ti,ab.
11	8 OR 9 OR 10
12	7 AND 11
13	(addresses OR autobiography OR bibliography OR biography OR clinical trial, phase I OR comment OR congresses OR consensus development conference OR duplicate publication OR editorial OR guideline OR in vitro OR interview OR lecture OR legal cases OR legislation OR letter OR news OR newspaper article OR patient education handout OR periodical index OR personal narratives OR portraits OR practice guideline OR review OR video audio media).pt.
14	exp cohort studies/ OR comparative study.pt.
15	control groups/ OR (control* adj2 (clinical OR group* OR trial* OR study OR studies OR design* OR arm*)).ti,ab. OR (clinical trial OR clinical trial, phase ii OR clinical trial, phase iii OR clinical trial, phase iv OR controlled clinical trial OR multicenter study OR randomized controlled trial).pt. OR (randomi?ed adj6 (study OR trial* OR (clinical adj2 trial*))).ti,ab.
16	14 OR 15
17	16 NOT 13
18	12 AND 17
19	(exp animals/ OR exp animal/ OR exp nonhuman/ OR exp animal experiment/ OR animal model/ OR animal tissue/ OR non human/ OR (rat OR rats OR mice OR mouse OR swine OR porcine OR murine OR sheep OR lambs OR pigs OR piglets OR rabbit OR rabbits OR cat OR cats OR dog OR dogs OR cattle OR bovine OR monkey OR monkeys OR trout OR marmoset$1 OR basic research OR cell lines OR in vitro OR animal model OR canine).tw.) NOT (humans/ OR human/ OR human experiment/ OR (human* OR men OR women OR patients OR subjects).tw.)
20	18 NOT 19
21	limit 20 to English language
22	remove duplicates from 21
23	limit 22 to yr="2014 -Current"

*Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present

Table 2.4. Search Strategy of EMBASE for ESAs

#1	'anemia'/exp OR 'iron deficiency anemia'/exp OR 'refractory anemia'/exp OR 'refractory anemia with excess blasts'/exp
#2	'an?emi*':ti,ab OR 'chronic anemia':ti,ab
#3	#1 OR #2
#4	'chronic kidney failure'/exp OR 'end stage renal disease'/exp
#5	'chronic kidney disease':ti,ab OR 'end*stage kidney disease':ti,ab OR 'end*stage kidney failure':ti,ab OR 'ESKD':ti,ab OR 'chronic renal disease':ti,ab OR 'end*stage renal dysfunction':ti,ab OR 'end*stage renal failure':ti,ab OR 'ESRD':ti,ab OR 'stage 5 renal disease':ti,ab
#6	#4 OR #5
#7	#3 AND #6
#8	'erythropoietin'/exp OR 'recombinant erythropoietin'/exp OR 'epoetin alpha'/exp
#9	'erythropoeie*':ti,ab OR 'epo?etin':ti,ab OR 'epo':ti,ab OR 'rhepo':ti,ab OR 'epoetin alfa':ti,ab OR 'procrit': ti, ab OR 'epogen':ti,ab OR 'darbepoetin alfa':ti,ab OR 'aranesp':ti,ab OR 'methoxy polyethylene glycol-epoetin beta':ti,ab OR 'methoxy polyethylene glycol epoetin beta':ti,ab OR 'cera':ti,ab OR 'mircera':ti,ab
#10	#8 OR #9
#11	#7 AND #10
#12	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#13	#11 NOT #12
#14	('case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#15	#13 NOT #14
#16	('clinical':ti,ab AND 'trial':ti,ab) OR 'clinical trial'/exp OR 'randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR random*:ti,ab or control*:ti,ab OR 'control group'/exp OR 'drug therapy':lnk
#17	#15 AND #16
#18	#17 AND [english]/lim
#19	#18 AND [medline]/lim
#20	#18 NOT #19
#21	#20 AND [2014-2020]/py

2.2 Eligibility Criteria

We will exclude studies that do not meet the PICOTS criteria defined above. We will also exclude studies that focus on children or adolescent patients in addition to studies that include biosimilars.

2.3 Selection of Eligible Studies

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening, at the abstract and full-text level. Two reviewers will independently screen the titles and abstracts of all publications identified using DistillerSR (Evidence Partners, Ottawa, Canada); a third reviewer will

work with the initial two reviewers to resolve any issues of disagreement through consensus. No study will be excluded at abstract level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

2.4 Data Extraction Strategy

Data will be extracted into Excel. The basic design and elements of the extraction forms will follow those used for other ICER reports. Elements include a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and quality assessment for each study.

The data extraction will be performed in the following steps:

1. One reviewer will extract information from the full articles and a second reviewer will validate the extracted data.
2. Extracted data will be reviewed for logic, and a random proportion of data will be validated by a third investigator for additional quality assurance.

2.5 Quality Assessment Criteria

We will use criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor."[28]

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all-important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.*

2.6 Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, we will scan the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include "anemia," "chronic kidney disease," "roxadustat," "darbepoetin alfa," "epoetin alfa," and "methoxy polyethylene glycol-epoetin beta." We will select studies which would have met our inclusion criteria, and for which no findings have been published. We will provide qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

2.7 Evidence Synthesis

The purpose of the evidence synthesis is to estimate the clinical effectiveness of the interventions being compared. The analysis will be based on the data from all relevant studies identified from the systematic review. This section contains two components: 1) a summary of the evidence base, 2) synthesis of outcome results, and 3) heterogeneity and subgroups.

Summary of Evidence Base

The studies will be summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the evidence base pertaining to the topic. An evidence table shell is presented in Appendix B. Relevant data include those listed in the data extraction section. Any key differences between the studies in terms of the study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), and study quality will be noted in the text of the report.

Synthesis of Results

The results of the studies will be synthesized for each outcome and described narratively in the report. Analyses to be conducted will reflect the nature and quality of the evidence base (see below). Key considerations for interpreting the results will be specified and described in the Evidence Report.

In addition, for each outcome of interest, we will evaluate the feasibility of conducting a quantitative synthesis. If studies are sufficiently similar in terms of design, populations, and

outcomes, we will conduct pairwise meta-analysis and NMA. A pairwise meta-analysis quantitatively synthesizes results from multiple studies of the same two treatments.[29]. An NMA extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator[s]).[30,31]

NMAs will be conducted under a Bayesian framework. For continuous outcomes (e.g., change in Hb), the NMA model corresponds to a generalized linear model with identity link. For binary outcomes (e.g., cardiovascular events), the NMA model corresponds to a generalized linear model with a logit link. We will include fixed or random effects on the treatment parameters depending on the study set in the networks. Results for all pairwise comparisons will be presented tabularly in terms of a point estimate and 95% credible intervals.

Furthermore, for any network where there are "loops" in evidence, we will empirically compare the direct and indirect estimates to assess if the NMA consistency assumption is violated using a node-splitting approach.[32] If there is evidence of inconsistency, the results will be presented for the direct and indirect evidence separately. If there is no evidence of inconsistency, we will present the pooled results.

All analyses will be conducted using R using the *metafor* package[33] for pairwise meta-analysis and the *gemtc* package[34] for NMA.

Heterogeneity and Subgroups

To explore heterogeneity across studies, we will examine if there are differences in the distribution of key characteristics across studies. For this project, key characteristics include prior use of dialysis, stages of CKD, and study follow-up. If studies differ with respect to these characteristics, subgroup analyses or meta-regressions may be performed where sufficient data exist.

References

1. World Health Organization. Anemia. 2020; https://www.who.int/health-topics/anaemia#tab=tab_1. Accessed July 13, 2020.
2. World Health Organization. Worldwide prevalence of anaemia 1993-2005 : WHO global database on anaemia. / Edited by Bruno de Benoist, Erin McLean, Ines Egli and Mary Cogswell. In. Geneva: World Health Organization; 2008.
3. Chapter 1: Diagnosis and evaluation of anemia in CKD. *Kidney Int Suppl (2011).* 2012;2(4):288-291.
4. Levey AS, Titan SM, Powe NR, Coresh J, Inker LA. Kidney Disease, Race, and GFR Estimation. *Clinical Journal of the American Society of Nephrology.* 2020:CJN.12791019.
5. Stevens LA, Coresh J, Greene T, Levey AS. Assessing Kidney Function — Measured and Estimated Glomerular Filtration Rate. *New England Journal of Medicine.* 2006;354(23):2473-2483.
6. Gregorio T. Obrador M, MPH. Epidemiology of chronic kidney disease. 2018. https://www.uptodate.com/contents/epidemiology-of-chronic-kidney-disease. Accessed 7/17/20.
7. Smith RE, Jr. The clinical and economic burden of anemia. *The American journal of managed care.* 2010;16 Suppl Issues:S59-66.
8. Kidney Disease Outcomes Quality Initiative (KDOQI). KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2006;47(5 Suppl 3):S11-145.
9. Eschbach JW. Erythropoietin 1991--an overview. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 1991;18(4 Suppl 1):3-9.
10. Khan S, Pereira BJ. Hematocrit level associated mortality in hemodialysis patients, by Ma JZ, Ebben J, Xia H, Collins AJ. J Am Soc Nephrol 10:610-619, 1999. *Seminars in dialysis.* 2000;13(2):112-113.
11. Xia H, Ebben J, Ma JZ, Collins AJ. Hematocrit levels and hospitalization risks in hemodialysis patients. *Journal of the American Society of Nephrology : JASN.* 1999;10(6):1309-1316.
12. Collins AJ, Li S, St Peter W, et al. Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. *Journal of the American Society of Nephrology : JASN.* 2001;12(11):2465-2473.
13. Collins AJ, Ma JZ, Ebben J. Impact of hematocrit on morbidity and mortality. *Seminars in nephrology.* 2000;20(4):345-349.
14. Hsu CY. Epidemiology of anemia associated with chronic renal insufficiency. *Current opinion in nephrology and hypertension.* 2002;11(3):337-341.
15. Hsu CY, McCulloch CE, Curhan GC. Epidemiology of anemia associated with chronic renal insufficiency among adults in the United States: results from the Third National Health and Nutrition Examination Survey. *Journal of the American Society of Nephrology : JASN.* 2002;13(2):504-510.
16. Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994). *Archives of internal medicine.* 2002;162(12):1401-1408.
17. Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. *PloS one.* 2014;9(1):e84943-e84943.

18. Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *N Engl J Med.* 1987;316(2):73-78.
19. KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2007;50(3):471-530.
20. Palmer SC, Navaneethan SD, Craig JC, et al. Meta-analysis: erythropoiesis-stimulating agents in patients with chronic kidney disease. *Annals of internal medicine.* 2010;153(1):23-33.
21. Bohlius J, Schmidlin K, Brillant C, et al. Erythropoietin or Darbepoetin for patients with cancer--meta-analysis based on individual patient data. *The Cochrane database of systematic reviews.* 2009;2009(3):Cd007303.
22. Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. *Lancet (London, England).* 2007;369(9559):381-388.
23. Strippoli GF, Navaneethan SD, Craig JC. Haemoglobin and haematocrit targets for the anaemia of chronic kidney disease. *The Cochrane database of systematic reviews.* 2006(4):Cd003967.
24. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Annals of internal medicine.* 1997;126(5):376-380.
25. Higgins JP. Cochrane Collaboration Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. 2008.
26. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLOS Medicine.* 2009;6(7):e1000097.
27. Palmer SC, Saglimbene V, Mavridis D, et al. Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis. *The Cochrane database of systematic reviews.* 2014;2014(12):Cd010590.
28. Agency for Healthcare Research and Quality. U.S. Preventive Services Task Force Procedure Manual. 2008.
29. Deeks JJ, Higgins, J.P., Altman, D.G. Analysing data and undertaking meta-analyses. In: *Cochrane Handbook for Systematic Reviews of Interventions.*2019:241-284.
30. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med.* 2004;23(20):3105-3124.
31. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ.* 2005;331(7521):897-900.
32. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med.* 2010;29(7-8):932-944.
33. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *2010.* 2010;36(3):48.
34. van Valkenhoef G KJ. Network Meta-Analysis Using Bayesian Methods. R package version 0.8-7. 2020; Network meta-analyses (mixed treatment comparisons) in the Bayesian framework using JAGS. Includes methods to assess heterogeneity and inconsistency, and a number of standard visualizations. . 2020; https://cran.r-project.org/web/packages/gemtc/gemtc.pdf.
35. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.* 2009;339:b2700.

Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2009.[26] Additional explanation of each item can be found in Liberati et al. 2009.[35]

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

doi:10.1371/journal.pmed.1000097.t001

Appendix B. Data Extraction Summary Table Shell

Author & Year of Publication (Trial)	Study Design	Interventions (n) & Dosing Schedule	Inclusion & Exclusion Criteria	Patient Characteristics	Outcomes

Table Footnotes