National Institute for Health and Care Excellence

Chronic kidney disease

[K] Evidence reviews for managing anaemia with IV iron in people with GFR category G5 who are on dialysis

NICE guideline <number>

Evidence reviews underpinning recommendation 1.9.18 and research recommendations in the NICE guideline

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1 Managing anaemia with IV iron in people
2 with GFR category G5 who are on dialysis

3 1.1 Review question

4 For people with glomerular filtration rate (GFR) category G5 who are on dialysis, what
5 amount of intravenous (IV) iron is most clinically and cost effective in managing anaemia and
6 its associated outcomes?

7 1.1.1 Introduction

8 Many people with chronic kidney disease (CKD) or established renal failure also develop
9 associated anaemia. The prevalence of anaemia associated with CKD increases
10 progressively with GFR category, especially when the patient reaches category G4 or G5.
11 Anaemia of CKD contributes significantly to the burden of CKD. However, it is potentially
12 reversible and manageable with appropriate identification and treatment.

13 The NICE guideline on chronic kidney disease: managing anaemia (NICE guideline NG8)
14 was reviewed in 2017 as part of NICE's surveillance programme. As part of the scoping
15 process, NICE identified new areas not included in the surveillance report for which the
16 evidence needed to be reviewed. One of these areas was IV iron for the treatment of
17 anaemia associated with CKD.

18 The aim of this review is to determine what amount of IV iron is most clinically and cost
19 effective in managing anaemia and its associated outcomes for people with GFR category
20 G5who are on dialysis. This review identified randomised controlled trials (RCTs) that fulfilled
21 the conditions specified in Table 1. For full details of the review protocol, see Appendix A.

22 1.1.2 Summary of the protocol

23 **Table 1: PICO table for IV iron in people with GFR category G5 who are on dialysis**

Population	Inclusion: Adults, children and young people with a clinical diagnosis of anaemia and GFR category G5 and who are on dialysis. Exclusion: Management of anaemia in people whose anaemia is not principally caused by CKD. Ferumoxytol (withdrawn due to safety concerns)
Intervention	**IV iron** • Ferric carboxymaltose • Iron dextran • Iron isomaltoside 1000 • Iron polymaltose • Iron sucrose • Sodium ferric gluconate complex (SFGC)
Comparator	• Other doses/schedules/formulations of IV iron
Outcome	All measured over the follow up time of the studies: **Primary outcomes:** • Haemoglobin (Hb) level • Other markers of anaemia (for example serum ferritin) • All-cause mortality

- CV specific mortality
- Adverse events (infection, vascular access thrombosis, hypertension, hospitalization, anaphylaxis)

Secondary outcomes:
- Incidence of blood transfusions
- QoL

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods section in Appendix B.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

The following methods were specific for this review:

1. The evidence is reported separately for adults and for children and young people (up to the age of 18 years) and pooled within the same age group.

2. Some of the evidence was divided based on IV iron dose into high and low dose based on the higher and lower doses given in the trials. This included 3 trials for children and young people (Goldstein 2013, Ruiz-Jaramillo 2004, and Warady 2005) and 5 trials for adults (Besarab 2000, Charytan 2013, MacDougall 2019, Nissenson 1999, and Wan 2018). The committee agreed that since it was interested in the relative effects, the actual dose and iron preparation were less important. Therefore, this evidence was divided into high and low dose irrespective of the IV iron preparation and based on what the trial reported as high or low.

3. The rest of trials reported different IV iron preparations in each arm with the same dose for all arms (Roe 1996, Bhandari 2015, Hsiao 2016, and Akcicek 1997). These trials were reported separately.

4. Wan (2018) was a crossover trial but the committee did not consider the washout period to be appropriate for patients receiving Erythropoeitin Stimulating Agents. Therefore, data were only extracted from the first study period.

5. For Akcicek (1997), data was taken only from the first study period from this crossover trial because paired t-tests were not reported and there was not enough data from the study to approximate a paired analysis. Therefore, this trial was regarded as a parallel trial rather than as a crossover trial.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A systematic search was carried out to identify RCTs and systematic reviews of RCTs, which found 554 references (see Appendix C for the literature search strategy). After screening at title and abstract level, 482 references were excluded. Full texts were ordered to be screened for 72 references. In total, 12 RCTs were included based on their relevance to the review protocol (Appendix A). The clinical evidence study selection is presented as a PRISMA diagram in Appendix D.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies, to capture papers published whilst the guideline was being developed. This search returned 26 references for this review question, these were screened on title and abstract. Two references were ordered for full text screening. None of these references were included based on their relevance to the review protocol (Appendix A).

1   See section <u>1.1.12 References – included studies</u> for a list of references for included studies.

2   **1.1.4.2 Excluded studies**

3   See <u>Appendix K</u> for a list of excluded studies with the primary reason for exclusion.

4   **1.1.5 Summary of RCTs included in the effectiveness evidence**

5   **Table 2: IV iron high dose vs low dose in children and young people**

Study	Population	Intervention	Comparator	Outcome measure(s)
Goldstein (2013) N=145 Follow-up: 12 weeks	• Age: 2 to 21 years • Haemoglobin ≥11.0 to ≤13.5 g/dL • Ferritin 800 ng/mL≤ • Transferrin saturation ≥20% to ≤50% • Erythropoietic stimulating agent: stable therapy (±25% of current dose) for 8 weeks or longer prior to the qualifying screening visit • Other parameters: dialysis stable regimen for at least 3 months	IV iron sucrose (high dose = 2.0 mg/kg)	IV iron sucrose (very low dose = 0.5 mg/kg) IV iron sucrose (low dose = 1.0 mg/kg)	• Hb level

Ruiz-Jaramillo (2004) N=40
 	
Follow-up: 6 months
	• Age: <16 years
	• Other parameters
	  o Anaemia and absolute iron deficiency (ferritin <100 µg/l and transferrin saturation <20%) or functional iron deficiency (ferritin >100 µg/l and transferrin saturation <20% or haematocrit <33%)
		IV Iron dextran (dose depended on ferritin levels = low dose [6 mg/kg per month])	IV Iron dextran (10-dose courses on body weight = high dose [14.4 mg/g per month])	• Hb level
				• Other markers of anaemia
				  o Ferritin
				• Blood transfusion

Warady (2005) N=66	• Age: 2 to 15 years	IV sodium ferric gluconate	IV sodium ferric gluconate complex	• Hb level

Study	Population	Intervention	Comparator	Outcome measure(s)

Follow-up: 4 weeks	• Erythropoietic stimulating agent: receiving concomitant recombinant human erythropoietin therapy with stable dosing regimen (defined as ≤25% change in the dose during the 4 weeks before treatment assignment)
	 • Other parameters
	   o need for iron-repletion therapy as reflected by a transferrin saturation of <20% and/or a serum ferritin of <100 ng mL-1
		complex (low dose = 1.5 mg kg-1)	(high dose = 3.0 mg kg-1)	• Other markers of anaemia
				   o Serum ferritin
				 • Adverse events

1 **Table 3: IV iron high dose vs low dose in adults**

Study	Population	Intervention	Comparator	Outcome measure(s)
Besarab (2000) N=47 Follow-up: 6 weeks	• Age: >18 years • Haemoglobin ≥9.5 g/dl • Ferritin between 150 and 600 ng/ml • Transferrin saturation between 19 and 30% • Erythropoietic stimulating agent: stable dose for anaemia management over the previous 3 mo (±25%) • Medications: no prior adverse reactions to parenteral iron	IV iron dextran (low dose = TSAT 20 to 30%)	IV iron dextran (high dose = TSAT 30 to 50%)	• Hb level • Other markers of anaemia o Ferritin • All-cause mortality • CV specific mortality • Adverse events

Study	Population	Intervention	Comparator	Outcome measure(s)
	• Other parameters: mean cell volume of >80 fl			
Charytan (2013) N=97 Follow-up: 30 days	• Age: 18–85 years of age if they had at least a 6- month history of dialysis CKD • Haemoglobin ≤12.5 g/dL • Ferritin ≤500 ng/mL • Transferrin saturation ≤30% • Other parameters: eligible if they did not anticipate needing repletion therapy (>200 mg of IV iron) during the 30-day study period.	IV ferric carboxymaltose (low dose = mean dose 200 mg)	Standard medical care (high dose = mean dose 561 mg)	• Hb level • Other markers of anaemia ○ Ferritin • CV specific mortality • Adverse events
MacDougall (2019) N=2141 Follow-up: Median 2.1 years	• Age: >18 years • Ferritin <400 µg/L • Transferrin saturation <30% • Erythropoietic stimulating agent: on ESA therapy • Other parameters: Patients established on a chronic haemodialysis program for end-stage renal failure; Clinically stable per the judgment of the investigator; 0–12 months since commencing haemodialysis;	IV iron sucrose (high dose-proactive = 400 mg monthly)	IV iron sucrose (low dose-reactive = 0 to 400 mg monthly)	• All-cause mortality • CV specific mortality • Adverse events • Blood transfusion • Subgroup analysis

Study	Population	Intervention	Comparator	Outcome measure(s)
	Patients who have switched to haemodialysis from peritoneal dialysis or have received previous haemodialysis or renal transplants are eligible to enter the study. • Consent: Written informed consent			
Nissenson (1999) N=88 Follow-up: 30 days	• Age: Adults • Haemoglobin <10 g/dL • Haematocrit ≤32% • Ferritin <100 ng/m • Transferrin saturation <18%	IV sodium ferric gluconate complex in sucrose (high dose = 1000mg)	IV sodium ferric gluconate complex in sucrose (low dose = 500mg)	• Hb level • Other markers of anaemia ○ Serum ferritin; haematocrit

Wan (2018)
N=47
 	
Follow-up:
3 months
	• Age: Adults
	• Haemoglobin maintained at 100–130 (g/l)
	• Ferritin 100–500 (ng/ml)
	• Erythropoietic stimulating agent: treated with recombinant human erythropoietin
	• Other parameters
	  ○ Regular haemodialysis patients (4 h per session and three times a week) with duration of stable haemodialysis more than 6 months; intact parathyroid hormone < 800 (pg/ml);
		IV iron sucrose (continuous administration = high dose [1000 mg reached at 1 month])	IV iron sucrose (intermittent administration = low dose [1000 mg reached at 3 months])	• Hb level
				• Other markers of anaemia
				  ○ Serum ferritin reported as median (25th, 75th range); haematocrit

Study	Population	Intervention	Comparator	Outcome measure(s)
	Kt/V of each haemodialysis session >1.2 during the screening period	11		

1 **Table 4: IV iron dextran MW 267,000 vs IV iron dextran MW 96,000, adults**

Study	Population	Intervention	Comparator	Outcome measure(s)

Roe (1996) N=20 Follow-up: 30 days	• Ag: 18 years or older
	• Ferritin <100 µg/L
	• Transferrin saturation <20%
	• Other parameters
	  ○ life expectancy greater than 60 days, were receiving erythropoietin therapy for dialysis associated anaemia (haemoglobin 9 to 12 g/dL)
		IV iron dextran MW 267,000 (500 mg)	IV iron dextran MW 96,000 (500 mg)	• Hb level
				• Other markers of anaemia
				  ○ Serum ferritin

2 **Table 5: IV iron sucrose (500mg) vs IV iron isomaltoside 1000 (500mg), adults, week 6**

Study	Population	Intervention	Comparator	Outcome measure(s)
Bhandari (2015) Follow-up: 6 weeks	• Age: ≥18 years of age with a diagnosis of CKD and on haemodialysis therapy for at least 90 days • Haemoglobin between 9.5 and 12.5 g/dL • Ferritin <800 ng/mL • Transferrin saturation <35% • Erythropoietic stimulating agent: • dose stable for the previous 4	IV iron isomaltoside 1000 (500mg)	IV iron sucrose (500mg)	• Hb level • All-cause mortality • Adverse events

Study	Population	Intervention	Comparator	Outcome measure(s)
	weeks prior to screening • Medications: No IV iron or an average of no >100 mg/week for the previous 4 weeks • Other parameters: Life expectancy beyond 12 months • Consent: Willing to provide written informed consent			

Table 6: IV iron sucrose (1000mg) vs IV ferric chloride hexahydrate (1000mg), adults, week 10

Study	Population	Intervention	Comparator	Outcome measure(s)

Hsiao (2016)
N=56
 	
Follow-up:
10 weeks
	• Age: ≥18 years
	• Haematocrit between 22% and 32%
	• Ferritin <200 µg/L
	• Transferrin saturation <40%
	• Other parameters: regular haemodialysis for at least 3 months; normal serum Vitamin B12 and folic acid concentrations; no blood transfusion in the last 3 months
		IV iron sucrose (1000mg)	IV ferric chloride hexahydrate (1000mg)	• Other markers of anaemia
				  ○ Serum ferritin
				  ○ Haematocrit

Table 7: IV ferric saccharate (100mg/week) vs IV ferric saccharate (2 x 50mg/week), adults, 2 months

Study	Population	Intervention	Comparator	Outcome measure(s)

Akcicek (1997)
N=17
	• Age: Adults
	• Haemoglobin <10 g/dL
		IV ferric saccharate (100mg/week)	IV ferric saccharate (2 x 50mg/week)	• Other markers of anaemia
				  ○ Ferritin
				  ○ Haematocrit

Study	Population	Intervention	Comparator	Outcome measure(s)
Follow-up: 6 weeks	• Haematocrit equivalent levels to haemoglobin levels • Erythropoietic stimulating agent: average dose 80 ±28 U/kg/week			

1 See Appendix E for full evidence tables.

2 **1.1.6 Summary of the effectiveness evidence**

3 **Children and young people**

4 **Table 8: IV iron high dose vs low dose**

Outcome	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Hb g/dL - Week 2	56	MD 0.00 (-0.64, 0.64)	MODERATE[a]	Could not differentiate
Hb g/dL - Week 4	56	MD 0.10 (-0.78, 0.98)	LOW[b]	Could not differentiate
Hb 10.5-14.0 g/dL – Week 12	53	RR 0.76 (0.42, 1.34)	VERY LOW[c]	Could not differentiate
Hb 10.5-14.0 g/dL – Week 12	53	RR 0.71 (0.40, 1.25)	VERY LOW[c]	Could not differentiate
Hb 10.5-14.0 g/dL – Week 12	58	RR 0.94 (0.60, 1.47)	VERY LOW[c]	Could not differentiate
Serum ferritin µg/L or ng mL - Week 2	56	MD 117.20 (5.37, 229.03)	LOW[b]	Favours high dose. Clinically significant effect higher than the MID (113.7)
Serum ferritin µg/L or ng mL - Week 4	56	MD 65.30 (-62.19, 192.79)	LOW[b]	Could not differentiate
Serum ferritin µg/L or ng mL – 4 months	40	MD 268.00 (51.81, 484.19)	LOW[b]	Favours high dose. Clinically significant effect higher than the MID (143.15)
Blood transfusions, 6 months	40	RR 7.00 (0.38, 127.32)	VERY LOW[c]	Could not differentiate
Adverse events, week 4	66	RR 0.94 (0.06, 14.42)	VERY LOW[c]	Could not differentiate

5 *(a) Serious risk of bias*

1 (b) *Serious risk of bias; serious imprecision*
2 (c) *Serious risk of bias; very serious imprecision*

3 **Adults**

4 **Table 9: IV iron high dose vs low dose**

Outcome	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Hb level ≤12.5 g/dL - Day 30	93	RR 1.15 (0.67, 1.97)	VERY LOW[a]	Could not differentiate
Hb g/dL - Day 2	83	MD 0.70 (0.14, 1.26)	LOW[b]	Favours high dose. Clinically significant effect higher than the MID (0.50)
Hb g/dL - Day 14	83	MD 0.80 (0.21, 1.39)	LOW[b]	Favours high dose. Clinically significant effect higher than the MID (0.50)
Hb g/dL - Day 30	175	MD 0.43 (-0.14, 1.00)	VERY LOW[c]	Could not differentiate
Hb g/dL - Month 3	34	MD 0.38 (-0.41, 1.17)	LOW[b]	Could not differentiate
Ferritin ng/mL - Day 2	80	MD 190.00 (32.89, 347.11)	LOW[b]	Favours high dose. Clinically significant effect higher than the MID (90.40)
Ferritin ng/mL - Day 14	80	MD 67.00 (-54.82, 188.82)	VERY LOW[a]	Could not differentiate
Ferritin ng/mL - Day 30	173	MD 59.03 (21.41, 96.65)	MODERATE[d]	Favours high dose. There is an effect, but it is less than the defined MID (125.99)
Haematocrit % - Day 2	83	MD 2.00 (0.20, 3.80)	LOW[b]	Favours high dose. Clinically significant effect higher than the MID (1.77)
Haematocrit % - Day 14	83	MD 2.20 (0.22, 4.18)	LOW[b]	Favours high dose. Clinically significant effect higher than the MID (1.76)
Haematocrit % - Day 30	83	MD 2.10 (0.12, 4.08)	LOW[b]	Favours high dose. Clinically significant effect higher than the MID (1.85)
Haematocrit % - Month 3	34	MD 1.35 (-0.89, 3.59)	LOW[b]	Could not differentiate
All-cause mortality - 6 months	42	RR 2.50 (0.11, 58.06)	LOW[b]	Could not differentiate
All-cause mortality - time-to-first event (median follow-up 2.1 years)	2,141	RR 0.88 (0.75, 1.02)	MODERATE[e]	Could not differentiate
All-cause mortality: subgroups - Catheter access	884	RR 0.77 (0.61, 0.96)	HIGH	Favours high dose. Clinically significant

Outcome	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
				effect exceeding the line of no effect
All-cause mortality: subgroups - Fistula access	1,257	RR 0.97 (0.79, 1.19)	MODERATE[e]	Could not differentiate
All-cause mortality: subgroups - Diabetes	944	RR 0.86 (0.71, 1.04)	MODERATE[e]	Could not differentiate
All-cause mortality: subgroups - Non-diabetes	1,198	RR 0.89 (0.70, 1.12)	MODERATE[e]	Could not differentiate
All-cause mortality: subgroups - Duration of dialysis <5 months	986	RR 0.87 (0.69, 1.10)	MODERATE[e]	Could not differentiate
All-cause mortality: subgroups - Duration of dialysis ≥5 months	1,155	RR 0.88 (0.73, 1.07)	MODERATE[e]	Could not differentiate
CV mortality - Day 30	97	RR 5.31 (0.26, 107.85)	LOW[b]	Could not differentiate
CV mortality - 6 months	42	RR 0.17 (0.01, 3.27)	LOW[b]	Could not differentiate
CV mortality - time-to-first event (median follow-up 2.1 years)	2,141	RR 0.91 (0.69, 1.20)	MODERATE[e]	Could not differentiate
Adverse events - ≥1 event, day 30	97	RR 0.96 (0.60, 1.55)	VERY LOW[a]	Could not differentiate
Adverse events - time-to-first event (median follow-up 2.1 years)	2,141	RR 1.01 (0.95, 1.08)	HIGH	No meaningful difference
Adverse events: infection - 6 months	36	RR 0.77 (0.32, 1.83)	VERY LOW[a]	Could not differentiate
Adverse events: infection - time-to-first event (median follow-up 2.1 years)	2,141	RR 1.00 (0.88, 1.13)	HIGH	No meaningful difference
Adverse events: hospitalisations - 6 months	36	RR 0.89 (0.50, 1.60)	VERY LOW[a]	Could not differentiate
Adverse events: hospitalisations - time-to-first event (median follow-up 2.1 years)	2,141	RR 1.01 (0.94, 1.09)	HIGH	No meaningful difference
Adverse events: vascular access thrombosis - time-to-first event (median follow-up 2.1 years)	2,141	RR 1.15 (0.98, 1.35)	MODERATE[e]	Could not differentiate
Blood transfusion - time-to-first event (median follow-up 2.1 years)	2,141	RR 0.84 (0.71, 1.00)	MODERATE[e]	Could not differentiate

1   *(a) Serious risk of bias; very serious imprecision*
2   *(b) Serious risk of bias; serious imprecision*
3   *(c) Serious risk of bias; serious inconsistency; serious imprecision*
4   *(d) Serious risk of bias*
5   *(e) Serious imprecision*

1   **Table 10: IV iron dextran MW 267,000 vs IV iron dextran MW 96,000, adults**

Outcome	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Hb g/dL - week 1	20	MD 0.59 (-0.16, 1.34)	VERY LOW[a]	Could not differentiate
Hb g/dL - week 2	20	MD 0.30 (-0.49, 1.09)	VERY LOW[b]	Could not differentiate
Hb g/dL - week 3	20	MD 0.77 (0.08, 1.46)	VERY LOW[a]	Favours MW 267,000. Clinically significant effect higher than the MID (0.42)
Hb g/dL - week 4	20	MD 0.77 (0.06, 1.48)	VERY LOW[a]	Favours MW 267,000. Clinically significant effect higher than the MID (0.46)
Serum ferritin µg/L - week 1	20	MD 341.50 (-386.54, 1069.54)	VERY LOW[b]	Could not differentiate
Serum ferritin µg/L - week 2	20	MD 5.20 (-85.87, 96.27)	VERY LOW[b]	Could not differentiate
Serum ferritin µg/L - week 3	20	MD 3.70 (-84.66, 92.06)	VERY LOW[b]	Could not differentiate
Serum ferritin µg/L - week 4	20	MD -24.10 (-113.35, 65.15)	VERY LOW[b]	Could not differentiate

2   *(a) Very serious risk of bias; serious imprecision*
3   *(b) Very serious risk of bias; very serious imprecision*

4   **Table 11: IV iron sucrose (500mg) vs IV iron isomaltoside 1000 (500mg), adults, week 6**

Outcome	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Hb >12.5 g/dL	341	RR 0.98 (0.49, 1.96)	LOW[a]	Could not differentiate
All-cause mortality	351	RR 0.28 (0.01, 5.46)	MODERATE[b]	Could not differentiate
Adverse events	346	RR 1.06 (0.85, 1.33)	MODERATE[b]	Could not differentiate

5   *(a) Very serious imprecision*
6   *(b) Serious imprecision*

7   **Table 12: IV iron sucrose (1000mg) vs IV ferric chloride hexahydrate (1000mg), adults,**
8   **week 10**

Outcome	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Serum ferritin µg/L	56	MD 129.00 (-34.41, 292.41)	LOW[a]	Could not differentiate
Haematocrit (%)	56	MD 1.00 (-0.83, 2.83)	LOW[a]	Could not differentiate

9   *(a) Serious risk of bias; serious imprecision*

Table 13: IV ferric saccharate (100mg/week) vs IV ferric saccharate (2 x 50mg/week), adults, 2 months

Outcome	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Serum ferritin μg/L	17	MD 9.00 (-49.90, 67.90)	VERY LOW[a]	Could not differentiate
Haematocrit (%)	17	MD -2.80 (-6.20, 0.60)	VERY LOW[b]	Could not differentiate

(a) *Very serious risk of bias; very serious imprecision*
(b) *Very serious risk of bias; serious imprecision*

See Appendix G for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

A search was conducted to identify economic evaluations relevant to the review question (see Appendix C). The search was not date limited. A total of 530 records were returned, 519 of which were excluded on the basis of title and abstract. The remaining 11 studies were fully inspected, and none were included in the synthesis. No additional studies were identified during inspection of the full publications and reference lists.

1.1.7.2 Excluded studies

Details of excluded studies are provided in Appendix K.

1.1.8 Summary of included economic evidence

No economic evaluations relevant to the review question were found.

1.1.9 Economic model

No economic modelling was undertaken for this review question.

1.1.10 The committee's discussion and interpretation of the evidence

1.1.10.1. The outcomes that matter most

The committee agreed that even though the majority of the studies included in the review only reported short term follow-ups and improvements in Hb or serum ferritin (most frequently reported outcomes), longer term outcomes were the key outcomes for people (adults, children and young people) with a clinical diagnosis of anaemia and CKD 5 who are on dialysis. This includes long term maintenance of Hb level and serum ferritin level as well as events such as all-cause mortality and CV mortality. The committee also agreed that Hb level, other markers of anaemia, adverse events, incidence of blood transfusions, and quality of life were also important outcomes.

1.1.10.2 The quality of the evidence

Overall, the quality of the evidence varied from high to very low (most of the evidence was low and very low), with the main reasons for downgrading being due to imprecision of the evidence on the effect size of the amount of IV iron in managing anaemia and risk of bias of included studies. In most of the pairwise comparisons, imprecision was considered to be serious (95% confidence interval crossing one end of the defined MID interval [0.8, 1.25 for dichotomous outcomes or 0.2 for continuous outcomes]) or very serious (95% confidence

1 interval crossing both ends of the defined MID interval). Risk of bias for some of the included
2 studies was due to lack of detailed report of the randomisation process, lack of report that
3 protocols were pre-registered, or the assignment of interventions was not well described. The
4 committee expressed some concern that the maximum follow-up for Hb measurements was
5 3 months.

6 The committee noted that many of the included studies had a small sample size, short follow-
7 up and reported only biochemical or surrogate outcomes. One study of high quality was large
8 and had long follow-up for most of the outcomes including all-cause mortality and CV
9 mortality (PIVOTAL trial, MacDougall et al. 2019).

10 The committee noted that there was limited evidence for quality of life and that only 2 studies
11 reported data on this outcome, and the data was not reported in an extractable format (raw
12 data was not reported).

13 **1.1.10.3 Benefits and harms**

14 For the purposes of the review, the evidence was divided based on the amount of IV iron into
15 'high' and 'low' dose (when possible). The committee agreed that since they were interested
16 in relative effects, this was an appropriate thing to do.

17 The evidence for adults showed that high-dose intravenous iron was clinically and
18 significantly better than a low-dose regimen at increasing levels of serum ferritin and
19 haemoglobin as well as increasing the percentage of haematocrit in the short to medium
20 term. The committee agreed that the type of iron preparation was not relevant and that there
21 was no reason to recommend a specific preparation. It did however note that not all iron
22 compounds are the same and a bio-equivalent amount of iron would be needed. The
23 committee provided an example regimen for adults using a high dose of iron sucrose. The
24 example regimen was chosen because it was the dose and formulation used in a recent,
25 large high-quality, UK based randomised controlled trial (PIVOTAL trial, MacDougall et al.
26 2019). The committee agreed that providing a clear example from the evidence could help
27 guide practice, however they were also very clear that the choice of preparation should be
28 based on local availability and policies and that they did not want to recommend a specific
29 formulation. Therefore, the committee highlighted that iron sucrose was only an example and
30 this was the reason why they suggested to use a bioequivalent dose of iron. The committee
31 further noted that the inclusion criteria for the trial (transferrin saturation <30%, serum ferritin
32 400 micrograms/litre) differed from the criteria for diagnosing iron deficiency in this NICE
33 guideline (transferrin saturation <20%, serum ferritin <100 micrograms/litre). It agreed that
34 the regimen was still appropriate when using the NICE diagnostic criteria. Therefore, it made
35 a strong recommendation to use high dose iron in people diagnosed with iron deficiency
36 because the trial was a large trial at low risk of bias that improved the certainty of the
37 evidence.

38 The evidence for adults also showed that adverse events were not meaningfully different
39 between high-dose and low-dose of intravenous iron. Therefore, it is likely that high-dose
40 intravenous iron does not increase the risk of adverse events compared to low-dose.

41 The evidence for children and young people showed that high-dose intravenous iron was
42 clinically and significantly better than a low-dose regimen at increasing levels of serum ferritin
43 in the short to medium term. Based on this limited evidence, the committee agreed that using
44 the highest value of IV iron recommended by the BNF for children was the appropriate
45 amount of iron to give to children and young people, but noted that IV iron use in children is
46 off license either in all children and young people, or in children under 14 (depending on the
47 preparation). The committee also noted that for children and young people it was not
48 uncommon to see a 'functional iron deficiency' with normal or high ferritin levels but low Hb
49 and profound anaemia who only respond to very high doses of iron. It agreed that clinicians
50 do not withhold the iv iron where ferritin is high if other, more precise estimates of iron status
51 (e.g. reticulocyte haemoglobin, hypochromic red blood cells) are out of range In these cases

1 clinical judgment would dictate whether or not to give or withhold IV iron. The committee
2 were unsure of the long-term consequences of high ferritin levels in these children and young
3 people and made a research recommendation to address this uncertainty.

4 The committee was aware that, in some areas, for people who are on home dialysis, the first
5 dose of IV iron is administered in hospital or in a dialysis centre and the rest of the treatment
6 is given at home or self-administered. The committee discussed the benefits and risks of this,
7 but it was also aware of a MHRA alert on intravenous iron and serious hypersensitivity
8 reactions. The MHRA information on administering intravenous iron states that 'intravenous
9 iron products should only be administered when staff trained to evaluate and manage
10 anaphylactic or anaphylactoid reactions – as well as resuscitation facilities – are immediately
11 available.' The committee therefore agreed that intravenous iron should not be administered
12 at home.

13 Most of the evidence was from studies including participants who were on haemodialysis and
14 receiving ESA therapy. Therefore, the committee agreed that more research would help to
15 inform future guidance on intravenous iron for people with GFR category G5 who are on
16 peritoneal dialysis or who are on dialysis but not having ESA therapy.

17 **1.1.10.4 Cost effectiveness and resource use**

18 The committee was not presented with any formal cost effectiveness evidence.
19 Recommendations are not expected to result in a substantial resource impact, as the
20 committee advised that recommendations are consistent with current practice and IV iron is
21 reasonably inexpensive. Furthermore, in the PIVOTAL trial, people in the high-dose iron
22 group received a lower dose of erythropoiesis-stimulating agent compared with people in the
23 low-dose iron group (Macdougall et al. 2019). Given the high costs associated with
24 erythropoiesis-stimulating agents, any excess treatment costs associated with high-dose
25 compared with low-dose iron are likely to be offset by the reduction in erythropoiesis-
26 stimulating agent dose.

27 **1.1.10.5 Other factors the committee took into account**

28 The committee agreed that there were no equality issues that could arise from the
29 recommendations they made. They highlighted that there were no physiological differences
30 that could affect the response to treatment with IV iron.

31 **1.1.11 Recommendations supported by this evidence review**

32 This evidence review supports recommendations 1.9.18 and the research recommendation
33 on IV iron for adults, children and young people with GFR category 5 who are on peritoneal
34 dialysis (see Appendix L for further details about the research recommendation).

35 **1.1.12 References – included studies**

36 **1.1.12.1 Effectiveness**

37 Akcicek, F, Ozkahya, M, Cirit, M et al. (1997) The efficiency of fractionated parenteral iron
38 treatment in CAPD patients.. Advances in peritoneal dialysis. Conference on Peritoneal
39 Dialysis 13: 109-12

40 Besarab, A, Amin, N, Ahsan, M et al. (2000) Optimization of epoetin therapy with intravenous
41 iron therapy in hemodialysis patients.. Journal of the American Society of Nephrology : JASN
42 11(3): 530-8

43 Bhandari, Sunil, Kalra, Philip A, Kothari, Jatin et al. (2015) A randomized, open-label trial of
44 iron isomaltoside 1000 (Monofer) compared with iron sucrose (Venofer) as maintenance

1   therapy in haemodialysis patients.. Nephrology, dialysis, transplantation : official publication
2   of the European Dialysis and Transplant Association - European Renal Association 30(9):
3   1577-89

4   Charytan, Chaim, Bernardo, Marializa V, Koch, Todd A et al. (2013) Intravenous ferric
5   carboxymaltose versus standard medical care in the treatment of iron deficiency anemia in
6   patients with chronic kidney disease: a randomized, active-controlled, multi-center study..
7   Nephrology, dialysis, transplantation : official publication of the European Dialysis and
8   Transplant Association - European Renal Association 28(4): 953-64

9   Goldstein, Stuart L; Morris, David; Warady, Bradley A (2013) Comparison of the safety and
10   efficacy of 3 iron sucrose iron maintenance regimens in children, adolescents, and young
11   adults with CKD: a randomized controlled trial.. American journal of kidney diseases : the
12   official journal of the National Kidney Foundation 61(4): 588-97

13   Hsiao P.-J., Chan J.-S., Wu K.-L. et al. (2016) Comparison of short-term efficacy of iron
14   sucrose with those of ferric chloride in hemodialysis patients: An open-label study. Journal of
15   Research in Medical Sciences 21(7): 102

16   Macdougall, Iain C, White, Claire, Anker, Stefan D et al. (2019) Intravenous Iron in Patients
17   Undergoing Maintenance Hemodialysis.. The New England journal of medicine 380(5): 447-
18   458

19   Nissenson, A R, Lindsay, R M, Swan, S et al. (1999) Sodium ferric gluconate complex in
20   sucrose is safe and effective in hemodialysis patients: North American Clinical Trial..
21   American journal of kidney diseases : the official journal of the National Kidney Foundation
22   33(3): 471-82

23   Roe, D J, Harford, A M, Zager, P G et al. (1996) Iron utilization after iron dextran
24   administration for iron deficiency in patients with dialysis-associated anemia: a prospective
25   analysis and comparison of two agents.. American journal of kidney diseases : the official
26   journal of the National Kidney Foundation 28(6): 855-60

27   Ruiz-Jaramillo, Ma de la Cruz, Guizar-Mendoza, Juan Manuel, Gutierrez-Navarro, Maria de
28   Jesus et al. (2004) Intermittent versus maintenance iron therapy in children on hemodialysis:
29   a randomized study.. Pediatric nephrology (Berlin, Germany) 19(1): 77-81

30   Wan, Li and Zhang, Dongliang (2018) Effect of frequency of intravenous iron administration
31   on hemoglobin variability in maintenance hemodialysis patients.. International urology and
32   nephrology 50(8): 1511-1518

33   Warady, Bradley A, Zobrist, R Howard, Wu, Jingyang et al. (2005) Sodium ferric gluconate
34   complex therapy in anemic children on hemodialysis.. Pediatric nephrology (Berlin,
35   Germany) 20(9): 1320-7

36   **1.1.12.2 Other**

37   Pergola PE, Pecoits-Filho R, Winkelmayer WC, et al. (2019) Economic Burden and Health-
38   Related Quality of Life Associated with Current Treatments for Anaemia in Patients with CKD
39   not on Dialysis: A Systematic Review. Pharmacoecon Open. 2019 Apr 9 [Epub ahead of
40   print]

41   Norman GR, Sloan JA, Wyrwich KW (2003) Interpretation of changes in health-related
42   quality of life: the remarkable universality of half a standard deviation. Med Care. 2003
43   May;41(5):582-92.

44

1 Appendices

2 Appendix A – Review protocols

3 Review protocol for managing anaemia with IV iron in people with GFR category G5 who are on dialysis

ID	Field	Content
0.	PROSPERO registration number	CRD42019141004
1.	Review title	Diagnosis and management of anaemia in CKD: the use of IV iron for the treatment of anaemia associated with CKD.
2.	Review question	For people with GFR category G5 who are on dialysis, what amount of IV iron is most clinically and cost effective in managing anaemia and its associated outcomes?
3.	Objective	To determine what amount of IV iron is most clinically and cost effective in managing anaemia and its associated outcomes for people with GFR category G5 who are on dialysis.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Database of Abstracts of Reviews of Effect (DARE) • Embase (Ovid) • MEDLINE (Ovid) • MEDLINE In-Process (Ovid) • MEDLINE Epub Ahead of Print Searches will be restricted by:

		• English language • Human studies
		The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Many people with CKD or established renal failure also develop associated anaemia. The prevalence of anaemia associated with CKD increases progressively with the GFR category, especially when the patient reaches GFR category G4 or G5. Anaemia of CKD contributes significantly to the burden of CKD. However, it is potentially reversible and manageable with appropriate identification and treatment.
6.	Population	**Inclusion**: Adults, children and young people with a clinical diagnosis of anaemia and CKD 5 and who are on dialysis. **Exclusion**: Management of anaemia in people whose anaemia is not principally caused by CKD or who do not have CKD5 or dialysis.

7.	Intervention/Exposure/Test	IV iron • Ferric carboxymaltose • Iron dextran • Iron isomaltoside 1000 • Iron polymaltose • Iron sucrose • Sodium ferric gluconate complex (SFGC)
8.	Comparator	• Other doses/schedules/formulations of IV iron
9.	Types of study to be included	• RCTs • SRs of RCTs If there are no RCTs then non-randomised controlled trials and comparative cohort studies will be considered.
10.	Other exclusion criteria	• Non-English language • Abstracts and conference proceedings • Theses • Non-human studies • Studies of ferumoxytol (withdrawn due to safety concerns)
11.	Context	NICE guideline NG8 chronic kidney disease: managing anaemia will be updated by this question. This guideline will be combined with guidelines CG182 chronic kidney disease in adults: assessment and management and CG157 chronic kidney disease (stage 4 or 5):

		management of hyperphosphataemia. The guideline will be extended to cover the assessment and management of chronic kidney disease in children and young people.
12.	Primary outcomes (critical outcomes)	All measured over the follow up time of the studies: • Hb level • Other markers of anaemia (for example serum ferritin) • All-cause mortality • CV specific mortality • Adverse events (infection, vascular access thrombosis, hypertension, hospitalization, anaphylaxis)
13.	Secondary outcomes (important outcomes)	• Incidence of blood transfusions • QoL
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer 5 and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow.

15.	Risk of bias (quality) assessment	Risk of bias for RCTs will be assessed using the Cochrane RoB (2.0) checklist as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Meta-analyses of interventional data will be conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011). Fixed- and random-effects models (der Simonian and Laird) will be fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model is clearly not met, even after appropriate pre-specified subgroup analyses is conducted, random-effects results are presented. Fixed-effects models are deemed to be inappropriate if one or both of the following conditions was met: • Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$. Meta-analyses will be performed in Cochrane Review Manager V5.3
17.	Analysis of sub-groups	Where data allow, and if there is heterogeneity, the following subgroups analyses will be undertaken:

		• People on ESA vs not on ESA • Catheter vs fistula access • Diabetes vs non-diabetes • Duration of dialysis	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	[For the purposes of PROSPERO, the date of commencement for the systematic review can be defined as any point after completion of a protocol but before formal screening of the identified studies against the eligibility criteria begins. A protocol can be deemed complete after sign-off by the NICE team with responsibility for quality assurance.]	

22.	Anticipated completion date	[Give the date by which the guideline is expected to be published. This field may be edited at any time. All edits will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.]		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** [Give development centre name] **5b Named contact e-mail** [Guideline email]@nice.org.uk [Developer to check with Guideline Coordinator for email address]		

		5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) Guideline Updates Team
25.	Review team members	From the Guideline Updates Team: • Mr Chris Carmona • Dr Yolanda Martinez • Ms Hannah Nicholas • Ms Lynda Ayiku
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team, which is part of NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10118

29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	anaemia, chronic kidney disease, iron therapy, intravenous iron
33.	Details of existing review of same topic by same authors	This review is a partial update of NICE guideline CG182: Chronic kidney disease in adults: assessment and management
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None

36.	Details of final publication	www.nice.org.uk

1

Appendix B – Methods

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstract can be stopped, assuming a defined threshold for the proportion of relevant papers it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- In every review, at least 50% of the identified abstract (or 1,000 records, if that is a greater number) were always screened.
- After this point, screening was only terminated if a pre-specified threshold was met for a number of abstracts being screened without a single new include being identified. This threshold was set according to the expected proportion of includes in the review (with reviews with a lower proportion of includes needing a higher number of papers without an identified study to justify termination), and was always a minimum of 250.
- A random 10% sample of the studies remaining in the database when the threshold were additionally screened, to check if a substantial number of relevant studies were not being correctly classified by the algorithm, with the full database being screened if concerns were identified.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of included systematic reviews were searched to identify any papers not identified through the primary search.

Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. For continuous outcomes analysed as mean differences, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. These studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences at baseline these studies were not included in any meta-analysis and were reported separately. For continuous outcomes analysed as standardised mean differences, where only baseline and final time point values were available, change from baseline standard deviations were estimated, assuming a correlation coefficient of 0.5.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Other study designs were quality assessed using the ROBINS-I tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.

- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.

- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.

- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.

- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event, and a pooled incidence rate ratio was calculated for dichotomous outcomes reporting total numbers of events. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis (all pooled trials).

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.

- The presence of significant statistical heterogeneity in the fixed-effect meta-analysis, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager V5.3, with the exception of incidence rate ratio analyses which were carried out in R version 3.3.4.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin. Confidence intervals were taken into account for clinical importance and uncertainty around the effect to make final decisions for recommendations.

MIDs found through this process and used to assess imprecision in the guideline are given in Table 14. For other continuous outcomes not specified in the table below, no MID was defined.

Table 14: Identified MIDs

Outcome	MID	Source
Quality of life SF-12/36	4	Pergola PE (2019)
Quality of life KDQoL-12/36	4	Pergola PE (2019)
Quality of life KDQ	0.5	Pergola PE (2019)
Quality of life EQ-5D	0.07	Pergola PE (2019)
Quality of life LASA	15	Pergola PE (2019)
Quality of life FACIT-Fatigue scale	3.0	Pergola PE (2019)
Quality of life FACT-Fatigue scale	3.0	Pergola PE (2019)

For mean differences where no other MID was available, an MID of +/- 0.5 standard deviations from the mean value was used (see Norman 2003). For relative risks where no other MID was available, a default MID interval for dichotomous outcomes of 0.8 to 1.25 was used. For mortality, the line of no effect was used as the MID.

When decisions were made in situations where MIDs were not available for overall effect size, the 'Evidence to Recommendations' section of that review should make explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from all study designs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 15.

Table 15: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded.
	Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level.
	Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.
	Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded.
	Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level.
	Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.
	Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic.
	N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study.
	Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded.
	Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level.
	Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels.
	Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID.
	If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected.
	Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if any of the following three conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts, trial protocols or trial records without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 16.

Table 16 Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 17.

Table 17 Methodological criteria

Level	Explanation
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

Appendix C – Literature search strategies

RQ: For people with GFR category G5 who are on dialysis, what amount of intravenous (IV) iron is most clinically and cost effective in managing anaemia and its associated outcomes?

Background to the search

A NICE information specialist conducted the literature searches for the evidence review. The searches were originally run between the 17th and 20th of June 2019 and updated between the 15th and 16th of September 2020. This search report is compliant with the requirements of PRISMA-S.

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

The MEDLINE strategy below was quality assured (QA) by trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude conferences in Embase were applied in adherence to standard NICE practice and the review protocol.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Clinical searches

Databases	Date searched	Version/files	No. retrieved
Cochrane Central Register of Controlled Trials (CENTRAL)	19th June 2019	Issue 6 of 12, June 2019	284
Cochrane Database of Systematic Reviews (CDSR)	19th June 2019	Issue 6 of 12, June 2019	3
Database of Abstracts of Reviews of Effect (DARE)	19th June 2019	Up to 2019	13

Embase (Ovid)	19th June 2019	Embase <1974 to 2019 Week 24>	413
MEDLINE (Ovid)	17th June 2019	Ovid MEDLINE(R) <1946 to June 14, 2019>	231
MEDLINE In-Process (Ovid)	17th June 2019	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to June 14, 2019>	22
MEDLINE Epub Ahead of Print	17th June 2019	Ovid MEDLINE(R) Epub Ahead of Print <June 14, 2019>	2

The following search filters were applied in MEDLINE and Embase to identify RCTs and systematic reviews:

- RCT filters:
  - McMaster Therapy – Medline - "best balance of sensitivity and specificity" version.
    Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.

  - McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

    Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association, 94(1), 41-47.

- Systematic reviews filters:
  - Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. *BMC Medical Research Methodology,* 12(1), 51.

    In MEDLINE, the standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.

    In Embase, the standard NICE modifications were used: pubmed.tw added to line medline.tw.

Search strategies
Database: Ovid MEDLINE(R) <1946 to June 14, 2019>
Search Strategy:
----
1   exp Renal Insufficiency, Chronic/ (107959)
2   ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (68743)
3   ((kidney* or renal*) adj1 insufficien*).tw. (20908)
4   ckd*.tw. (20780)

5   ((kidney* or renal*) adj1 fail*).tw. (84732)

6   ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (33680)

7   (esrd* or eskd*).tw. (13435)

8   "Chronic Kidney Disease-Mineral and Bone Disorder"/ (3381)

9   or/1-8 (204989)

10   exp Renal Replacement Therapy/ (197090)

11   (haemodialys* or hemodialys* or dialys* or predialys* or pre-dialys*).tw. (138733)

12   ((kidney* or renal*) adj1 replac*).tw. (10604)

13   or/10-12 (244846)

14   9 or 13 (360946)

15   exp Anemia/ (156350)

16   (anemi* or anaemi*).tw. (126939)

17   15 or 16 (204816)

18   exp Administration, Intravenous/ (139586)

19   (iv or i-v or intraven*).tw. (630829)

20   18 or 19 (685027)

21   iron/ (90665)

22   exp iron compounds/ (67132)

23   (iron or ferric or ferrous or ferritin*).tw. (164632)

24   (ferumoxytol or rienso or fersaday or galfer or ferrosuccinate or fefol or feospan or ferinject or cosmofer or monofer or venofer).tw. (371)

25   or/21-24 (227574)

26   20 and 25 (10956)

27   14 and 17 and 26 (1110)

28   randomized controlled trial.pt. (483592)

29   randomi?ed.mp. (745900)

30   placebo.mp. (185889)

31   or/28-30 (795884)

32   (MEDLINE or pubmed).tw. (141527)

33   systematic review.tw. (100773)

34   systematic review.pt. (107996)

35   meta-analysis.pt. (101875)

36   intervention$.ti. (112431)

37   or/32-36 (335269)

38   31 or 37 (1034745)

39   27 and 38 (243)

40   animals/ not humans/ (4556558)

41   39 not 40 (242)

42   limit 41 to english language (231)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to June 14, 2019>
Search Strategy:

----

1   exp Renal Insufficiency, Chronic/ (0)

2   ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (8899)

3   ((kidney* or renal*) adj1 insufficien*).tw. (1064)

4   ckd*.tw. (4240)

5   ((kidney* or renal*) adj1 fail*).tw. (6120)

6   ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (4486)

7   (esrd* or eskd*).tw. (1846)

8   "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9   or/1-8 (17492)

10   exp Renal Replacement Therapy/ (0)

11   (haemodialys* or hemodialys* or dialys* or predialys* or pre-dialys*).tw. (11306)

12   ((kidney* or renal*) adj1 replac*).tw. (1748)

13   or/10-12 (12306)

14   9 or 13 (24844)

15   exp Anemia/ (0)

16   (anemi* or anaemi*).tw. (12120)

17   15 or 16 (12120)

18   exp Administration, Intravenous/ (0)

19   (iv or i-v or intraven*).tw. (57808)

20   18 or 19 (57808)

21   iron/ (0)

22   exp iron compounds/ (0)

23   (iron or ferric or ferrous or ferritin*).tw. (28663)

24   (ferumoxytol or rienso or fersaday or galfer or ferrosuccinate or fefol or feospan or ferinject or cosmofer or monofer or venofer).tw. (84)

25   or/21-24 (28684)

26   20 and 25 (1138)

27   14 and 17 and 26 (80)

28   randomized controlled trial.pt. (276)

29   randomi?ed.mp. (65565)

30   placebo.mp. (16174)

31   or/28-30 (71364)

32   (MEDLINE or pubmed).tw. (29441)

33   systematic review.tw. (23996)

34   systematic review.pt. (215)

35   meta-analysis.pt. (37)

36   intervention$.ti. (18442)

37   or/32-36 (57463)

38   31 or 37 (115978)

39   27 and 38 (22)

40   animals/ not humans/ (0)

41   39 not 40 (22)

42   limit 41 to english language (22)

Database: Ovid MEDLINE(R) Epub Ahead of Print <June 14, 2019>

Search Strategy:

----

1   exp Renal Insufficiency, Chronic/ (0)

2   ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (1403)

3   ((kidney* or renal*) adj1 insufficien*).tw. (165)

4   ckd*.tw. (735)

5   ((kidney* or renal*) adj1 fail*).tw. (755)

6   ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (702)

7   (esrd* or eskd*).tw. (332)

8   "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9   or/1-8 (2620)

10   exp Renal Replacement Therapy/ (0)

11   (haemodialys* or hemodialys* or dialys* or predialys* or pre-dialys*).tw. (1569)

12   ((kidney* or renal*) adj1 replac*).tw. (282)

13   or/10-12 (1743)
14   9 or 13 (3673)
15   exp Anemia/ (0)
16   (anemi* or anaemi*).tw. (1621)
17   15 or 16 (1621)
18   exp Administration, Intravenous/ (0)
19   (iv or i-v or intraven*).tw. (8312)
20   18 or 19 (8312)
21   iron/ (0)
22   exp iron compounds/ (0)
23   (iron or ferric or ferrous or ferritin*).tw. (3272)
24   (ferumoxytol or rienso or fersaday or galfer or ferrosuccinate or fefol or feospan or ferinject or cosmofer or monofer or venofer).tw. (16)
25   or/21-24 (3276)
26   20 and 25 (177)
27   14 and 17 and 26 (12)
28   randomized controlled trial.pt. (1)
29   randomi?ed.mp. (12521)
30   placebo.mp. (2971)
31   or/28-30 (13546)
32   (MEDLINE or pubmed).tw. (6226)
33   systematic review.tw. (5847)
34   systematic review.pt. (19)
35   meta-analysis.pt. (3)
36   intervention$.ti. (3738)
37   or/32-36 (12320)
38   31 or 37 (23015)
39   27 and 38 (2)
40   animals/ not humans/ (0)
41   39 not 40 (2)
42   limit 41 to english language (2)

Database: Embase <1974 to 2019 Week 24>
Search Strategy:
----
1   exp kidney failure/ (330000)
2   ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (114839)
3   ((kidney* or renal*) adj1 insufficien*).tw. (29231)
4   ckd*.tw. (44813)
5   ((kidney* or renal*) adj1 fail*).tw. (127944)
6   ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (54676)
7   (esrd* or eskd*).tw. (25454)
8   or/1-7 (419514)
9   exp renal replacement therapy/ (176566)
10   exp dialysis/ (172791)
11   (haemodialys* or hemodialys* or dialys* or predialys* or pre-dialys*).tw. (203730)
12   ((kidney* or renal*) adj1 replac*).tw. (20310)
13   or/9-12 (269476)
14   8 or 13 (557459)
15   exp anemia/ (334011)
16   (anemi* or anaemi*).tw. (192047)

17   15 or 16 (370418)
18   exp intravenous drug administration/ (353252)
19   (iv or i-v or intraven*).tw. (942497)
20   18 or 19 (1159421)
21   exp iron/ (144159)
22   exp antianemic agent/ (115990)
23   (iron or ferric or ferrous or ferritin*).tw. (233322)
24   (ferumoxytol or rienso or fersaday or galfer or ferrosuccinate or fefol or feospan or ferinject or cosmofer or monofer or venofer).tw. (1547)
25   21 or 22 or 23 or 24 (375491)
26   20 and 25 (25365)
27   14 and 17 and 26 (3005)
28   random:.tw. (1419010)
29   placebo:.mp. (433709)
30   double-blind:.tw. (198611)
31   or/28-30 (1666704)
32   (MEDLINE or pubmed).tw. (222595)
33   exp systematic review/ or systematic review.tw. (250496)
34   meta-analysis/ (164333)
35   intervention$.ti. (180412)
36   or/32-35 (576816)
37   31 or 36 (2062864)
38   27 and 37 (565)
39   nonhuman/ not human/ (4399730)
40   38 not 39 (561)
41   limit 40 to english language (542)
42   limit 41 to (conference abstract or conference paper or "conference review") (129)
43   41 not 42 (413)

Cochrane Library

ID   Search Hits
#1   MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees 5944
#2   (((chronic* or progressi*) near/1 (renal* or kidney*))):ti,ab,kw   9491
#3   (((kidney* or renal*) near/1 insufficien*)):ti,ab,kw 4617
#4   (ckd*):ti,ab,kw   4336
#5   (((kidney* or renal*) near/1 fail*)):ti,ab,kw   15414
#6   (((endstage* or end-stage* or "end stage*") near/1 (renal* or kidney*))):ti,ab,kw   4179
#7   ((esrd* or eskd*)):ti,ab,kw   1907
#8   MeSH descriptor: [Chronic Kidney Disease-Mineral and Bone Disorder] this term only   80
#9   #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8   24140
#10   MeSH descriptor: [Renal Replacement Therapy] explode all trees   8449
#11   (haemodialys* or hemodialys* or dialys* or predialys* or pre-dialys*):ti,ab,kw   16928
#12   ((kidney* or renal*) near/1 replac*):ti,ab,kw   2047
#13   #10 or #11 or #12   21294
#14   #9 or #13   35692
#15   MeSH descriptor: [Anemia] explode all trees   4775
#16   (anemi* or anaemi*):ti,ab,kw   19047
#17   #15 or #16   19427
#18   MeSH descriptor: [Administration, Intravenous] explode all trees 17927
#19   (iv or i-v or intraven*):ti,ab,kw   133091

#20   #18 or #19   133091

#21   MeSH descriptor: [Iron] this term only   2280

#22   MeSH descriptor: [Iron Compounds] explode all trees   2302

#23   (iron or ferric or ferrous or ferritin*):ti,ab,kw   10382

#24   (ferumoxytol or rienso or fersaday or galfer or ferrosuccinate or fefol or feospan or ferinject or cosmofer or monofer or venofer):ti,ab,kw   337

#25   #21 or #22 or #23 or #24   11262

#26   #20 and #25   2021

#27   #14 and #17 and #26   441

#28   "conference":pt 152012

#29   "clinicaltrials.gov":so   140837

#30   #28 or #29   292849

#31   #27 not #30   346

#32   "www.who.int":so   114462

#33   #31 not #32   287 (3- CDSR, 284 – Central)

CRD databases

1   MeSH DESCRIPTOR Renal Insufficiency, Chronic EXPLODE ALL TREES   538
Delete

2   ((chronic* or progressi*) near1 (renal* or kidney*))   489   Delete

3   ((kidney* or renal*) near1 insufficien*)   320   Delete

4   (ckd*) 93   Delete

5   ((kidney* or renal*) near1 fail*)   836   Delete

6   ((endstage* or end-stage* or "end stage*") near1 (renal* or kidney*))   354
Delete

7   ((esrd* or eskd*))   150   Delete

8   MeSH DESCRIPTOR Chronic Kidney Disease-Mineral and Bone Disorder EXPLODE
ALL TREES   0   Delete

9   (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)   1407   Delete

10   MeSH DESCRIPTOR Renal Replacement Therapy EXPLODE ALL TREES   881
Delete

11   (haemodialys* or hemodialys* or dialys* or predialys* or pre-dialys*)   1015
Delete

12   ((kidney* or renal*) near1 replac*)   151   Delete

13   (#10 or #11 or #12)   1351   Delete

14   (#9 or #13)   2102   Delete

15   MeSH DESCRIPTOR Anemia EXPLODE ALL TREES   380   Delete

16   (anemi* or anaemi*)   731   Delete

17   (#15 or #16)   791   Delete

18   MeSH DESCRIPTOR Administration, Intravenous EXPLODE ALL TREES   596
Delete

19   (iv or i-v or intraven*)   4124   Delete

20   #18 OR #19   4124   Delete

21   MeSH DESCRIPTOR Iron   68   Delete

22   MeSH DESCRIPTOR Iron Compounds EXPLODE ALL TREES 73   Delete

23   (iron or ferric or ferrous or ferritin*)   343   Delete

24   (ferumoxytol or rienso or fersaday or galfer or ferrosuccinate or fefol or feospan or
ferinject or cosmofer or monofer or venofer)   10   Delete

25   (#21 or #22 or #23 or #24)   357   Delete

26   (#20 and #25) 73   Delete

| 27 | (#14 and #17 and #26) 30 | Delete |
| 28 | (#14 and #17 and #26) IN DARE | 13 | Delete |

Cost-effectiveness searches

Databases	Date searched	Version/files	No. retrieved
MEDLINE (Ovid)	20th June 2019	Ovid MEDLINE(R) <1946 to June 18, 2019>	212
MEDLINE in Process (Ovid)	20th June 2019	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to June 18, 2019>	20
MEDLINE epub (Ovid)	20th June	Ovid MEDLINE(R) Epub Ahead of Print <June 18, 2019>	4
Embase (Ovid)	20th June 2019	Embase <1974 to 2019 June 19>	449
EconLit (Ovid)	20th June 2019	Econlit <1886 to June 13, 2019>	0
NHS Economic Evaluation Database (NHS EED) (legacy database)	20th June 2019	Up to 2015	10
CRD HTA	20th June 2019	Up to 2018	4
Database of Abstracts of Reviews of Effect (DARE)	19th June 2019	Up to 2019	13

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

- Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Several modifications have been made to these filters over the years that are standard NICE practice.

Search strategies
Database: Ovid MEDLINE(R) <1946 to June 18, 2019>

Search Strategy:

----

1   exp Renal Insufficiency, Chronic/ (108003)

2   ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (68783)

3   ((kidney* or renal*) adj1 insufficien*).tw. (20911)

4   ckd*.tw. (20799)

5   ((kidney* or renal*) adj1 fail*).tw. (84754)

6   ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (33701)

7   (esrd* or eskd*).tw. (13445)

8   "Chronic Kidney Disease-Mineral and Bone Disorder"/ (3381)

9   or/1-8 (205070)

10   exp Renal Replacement Therapy/ (197146)

11   (haemodialys* or hemodialys* or dialys* or predialys* or pre-dialys*).tw. (138783)

12   ((kidney* or renal*) adj1 replac*).tw. (10616)

13   or/10-12 (244923)

14   9 or 13 (361071)

15   exp Anemia/ (156372)

16   (anemi* or anaemi*).tw. (126969)

17   15 or 16 (204857)

18   exp Administration, Intravenous/ (139620)

19   (iv or i-v or intraven*).tw. (631018)

20   18 or 19 (685227)

21   iron/ (90691)

22   exp iron compounds/ (67162)

23   (iron or ferric or ferrous or ferritin*).tw. (164686)

24   (ferumoxytol or rienso or fersaday or galfer or ferrosuccinate or fefol or feospan or ferinject or cosmofer or monofer or venofer).tw. (371)

25   or/21-24 (227650)

26   20 and 25 (10963)

27   14 and 17 and 26 (1110)

28   Economics/ (27051)

29   exp "Costs and Cost Analysis"/ (225613)

30   Economics, Dental/ (1902)

31   exp Economics, Hospital/ (23637)

32   exp Economics, Medical/ (14103)

33   Economics, Nursing/ (3986)

34   Economics, Pharmaceutical/ (2865)

35   Budgets/ (11123)

36   exp Models, Economic/ (14190)

37   Markov Chains/ (13460)

38   Monte Carlo Method/ (26824)

39   Decision Trees/ (10586)

40   econom$.tw. (219867)

41   cba.tw. (9553)

42   cea.tw. (19645)

43   cua.tw. (940)

44   markov$.tw. (16687)

45   (monte adj carlo).tw. (28196)

46   (decision adj3 (tree$ or analys$)).tw. (12071)

47   (cost or costs or costing$ or costly or costed).tw. (426323)

48   (price$ or pricing$).tw. (31144)

49   budget$.tw. (22402)

50   expenditure$.tw. (46143)

51   (value adj3 (money or monetary)).tw. (1938)

52   (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3346)

53   or/28-52 (866013)

54   "Quality of Life"/ (177356)

55   quality of life.tw. (209021)

56   "Value of Life"/ (5648)

57   Quality-Adjusted Life Years/ (11115)

58   quality adjusted life.tw. (9719)

59   (qaly$ or qald$ or qale$ or qtime$).tw. (7990)

60   disability adjusted life.tw. (2363)

61   daly$.tw. (2174)

62   Health Status Indicators/ (22904)

63   (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (21049)

64   (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1251)

65   (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (4441)

66   (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (28)

67   (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (369)

68   (euroqol or euro qol or eq5d or eq 5d).tw. (7731)

69   (qol or hql or hqol or hrqol).tw. (39725)

70   (hye or hyes).tw. (58)

71   health$ year$ equivalent$.tw. (38)

72   utilit$.tw. (158121)

73   (hui or hui1 or hui2 or hui3).tw. (1202)

74   disutili$.tw. (350)

75   rosser.tw. (82)

76   quality of wellbeing.tw. (11)

77   quality of well-being.tw. (367)

78   qwb.tw. (186)

79   willingness to pay.tw. (3922)

80   standard gamble$.tw. (762)

81   time trade off.tw. (979)

82   time tradeoff.tw. (223)

83   tto.tw. (844)

84   or/54-83 (453808)

85   53 or 84 (1256965)

86   27 and 85 (239)

87   limit 86 to english language (212)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to June 18, 2019>

Search Strategy:

----

1   exp Renal Insufficiency, Chronic/ (0)

2   ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (8961)

3   ((kidney* or renal*) adj1 insufficien*).tw. (1068)

4   ckd*.tw. (4278)

5   ((kidney* or renal*) adj1 fail*).tw. (6144)

6   ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (4508)

7   (esrd* or eskd*).tw. (1852)

8   "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9   or/1-8 (17594)

10   exp Renal Replacement Therapy/ (0)

11   (haemodialys* or hemodialys* or dialys* or predialys* or pre-dialys*).tw. (11376)

12   ((kidney* or renal*) adj1 replac*).tw. (1758)

13   or/10-12 (12384)

14   9 or 13 (24995)

15   exp Anemia/ (0)

16   (anemi* or anaemi*).tw. (12173)

17   15 or 16 (12173)

18   exp Administration, Intravenous/ (0)

19   (iv or i-v or intraven*).tw. (58146)

20   18 or 19 (58146)

21   iron/ (0)

22   exp iron compounds/ (0)

23   (iron or ferric or ferrous or ferritin*).tw. (29027)

24   (ferumoxytol or rienso or fersaday or galfer or ferrosuccinate or fefol or feospan or ferinject or cosmofer or monofer or venofer).tw. (86)

25   or/21-24 (29048)

26   20 and 25 (1142)

27   14 and 17 and 26 (80)

28   Economics/ (0)

29   exp "Costs and Cost Analysis"/ (0)

30   Economics, Dental/ (0)

31   exp Economics, Hospital/ (0)

32   exp Economics, Medical/ (0)

33   Economics, Nursing/ (0)

34   Economics, Pharmaceutical/ (0)

35   Budgets/ (0)

36   exp Models, Economic/ (0)

37   Markov Chains/ (0)

38   Monte Carlo Method/ (0)

39   Decision Trees/ (0)

40   econom$.tw. (39078)

41   cba.tw. (378)

42   cea.tw. (1640)

43   cua.tw. (169)

44   markov$.tw. (4944)

45   (monte adj carlo).tw. (15277)

46   (decision adj3 (tree$ or analys$)).tw. (2016)

47   (cost or costs or costing$ or costly or costed).tw. (84430)

48   (price$ or pricing$).tw. (5161)

49   budget$.tw. (4415)

50   expenditure$.tw. (5760)

Chronic kidney disease: evidence reviews for managing anaemia with IV iron DRAFT (Jan 2021)

51   (value adj3 (money or monetary)).tw. (323)

52   (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (508)

53   or/28-52 (146158)

54   "Quality of Life"/ (0)

55   quality of life.tw. (34633)

56   "Value of Life"/ (0)

57   Quality-Adjusted Life Years/ (0)

58   quality adjusted life.tw. (1500)

59   (qaly$ or qald$ or qale$ or qtime$).tw. (1262)

60   disability adjusted life.tw. (450)

61   daly$.tw. (404)

62   Health Status Indicators/ (0)

63   (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (2479)

64   (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (659)

65   (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (666)

66   (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (4)

67   (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (19)

68   (euroqol or euro qol or eq5d or eq 5d).tw. (1517)

69   (qol or hql or hqol or hrqol).tw. (6578)

70   (hye or hyes).tw. (5)

71   health$ year$ equivalent$.tw. (2)

72   utilit$.tw. (27575)

73   (hui or hui1 or hui2 or hui3).tw. (161)

74   disutili$.tw. (61)

75   rosser.tw. (13)

76   quality of wellbeing.tw. (6)

77   quality of well-being.tw. (25)

78   qwb.tw. (8)

Chronic kidney disease: evidence reviews for managing anaemia with IV iron DRAFT (Jan 2021)

79   willingness to pay.tw. (818)

80   standard gamble$.tw. (52)

81   time trade off.tw. (107)

82   time tradeoff.tw. (10)

83   tto.tw. (117)

84   or/54-83 (64339)

85   53 or 84 (202152)

86   27 and 85 (20)

87   limit 86 to english language (20)

Database: Ovid MEDLINE(R) Epub Ahead of Print <June 18, 2019>

Search Strategy:

----

1   exp Renal Insufficiency, Chronic/ (0)

2   ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (1382)

3   ((kidney* or renal*) adj1 insufficien*).tw. (170)

4   ckd*.tw. (724)

5   ((kidney* or renal*) adj1 fail*).tw. (745)

6   ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (696)

7   (esrd* or eskd*).tw. (334)

8   "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9   or/1-8 (2597)

10   exp Renal Replacement Therapy/ (0)

11   (haemodialys* or hemodialys* or dialys* or predialys* or pre-dialys*).tw. (1559)

12   ((kidney* or renal*) adj1 replac*).tw. (281)

13   or/10-12 (1731)

14   9 or 13 (3650)

15   exp Anemia/ (0)

16   (anemi* or anaemi*).tw. (1626)

17   15 or 16 (1626)

18   exp Administration, Intravenous/ (0)

19   (iv or i-v or intraven*).tw. (8230)

20   18 or 19 (8230)

21   iron/ (0)

22   exp iron compounds/ (0)

23   (iron or ferric or ferrous or ferritin*).tw. (3016)

24   (ferumoxytol or rienso or fersaday or galfer or ferrosuccinate or fefol or feospan or ferinject or cosmofer or monofer or venofer).tw. (14)

25   or/21-24 (3020)

26   20 and 25 (180)

27   14 and 17 and 26 (12)

28   Economics/ (0)

29   exp "Costs and Cost Analysis"/ (0)

30   Economics, Dental/ (0)

31   exp Economics, Hospital/ (0)

32   exp Economics, Medical/ (0)

33   Economics, Nursing/ (0)

34   Economics, Pharmaceutical/ (0)

35   Budgets/ (0)

36   exp Models, Economic/ (0)

37   Markov Chains/ (0)

38   Monte Carlo Method/ (0)

39   Decision Trees/ (0)

40   econom$.tw. (5970)

41   cba.tw. (71)

42   cea.tw. (323)

43   cua.tw. (23)

44   markov$.tw. (804)

45   (monte adj carlo).tw. (1694)

46   (decision adj3 (tree$ or analys$)).tw. (363)

47   (cost or costs or costing$ or costly or costed).tw. (12163)

48   (price$ or pricing$).tw. (917)

49   budget$.tw. (569)

50   expenditure$.tw. (1159)

51   (value adj3 (money or monetary)).tw. (68)

52   (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (56)

53   or/28-52 (20752)

54   "Quality of Life"/ (0)

55   quality of life.tw. (6377)

56   "Value of Life"/ (0)

57   Quality-Adjusted Life Years/ (0)

58   quality adjusted life.tw. (354)

59   (qaly$ or qald$ or qale$ or qtime$).tw. (312)

60   disability adjusted life.tw. (86)

61   daly$.tw. (78)

62   Health Status Indicators/ (0)

63   (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (426)

64   (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (73)

65   (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (139)

66   (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (0)

67   (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (5)

68   (euroqol or euro qol or eq5d or eq 5d).tw. (327)

69   (qol or hql or hqol or hrqol).tw. (1231)

70   (hye or hyes).tw. (3)

71   health$ year$ equivalent$.tw. (0)

72   utilit$.tw. (4812)

73   (hui or hui1 or hui2 or hui3).tw. (20)

74   disutili$.tw. (20)

75   rosser.tw. (0)

76   quality of wellbeing.tw. (1)

77   quality of well-being.tw. (5)

78   qwb.tw. (2)

79   willingness to pay.tw. (144)

80   standard gamble$.tw. (10)

81   time trade off.tw. (32)

82   time tradeoff.tw. (7)

83   tto.tw. (17)

84   or/54-83 (11476)

85   53 or 84 (30590)

86   27 and 85 (4)

87   limit 86 to english language (4)

Database: Embase <1974 to 2019 June 19>

Search Strategy:

----

1   exp kidney failure/ (330476)

2   ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (115029)

3   ((kidney* or renal*) adj1 insufficien*).tw. (29256)

4   ckd*.tw. (44913)

5   ((kidney* or renal*) adj1 fail*).tw. (128051)

6   ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (54749)

7   (esrd* or eskd*).tw. (25482)

8   or/1-7 (420009)

9   exp renal replacement therapy/ (176681)

10   exp dialysis/ (172931)

11   (haemodialys* or hemodialys* or dialys* or predialys* or pre-dialys*).tw. (203911)

12   ((kidney* or renal*) adj1 replac*).tw. (20353)

13   or/9-12 (269698)

14   8 or 13 (558064)

15   exp anemia/ (334303)

16   (anemi* or anaemi*).tw. (192285)

17   15 or 16 (370717)

18   exp intravenous drug administration/ (353394)

19   (iv or i-v or intraven*).tw. (943579)

20   18 or 19 (1160515)

21   exp iron/ (144406)

22   exp antianemic agent/ (116062)

23   (iron or ferric or ferrous or ferritin*).tw. (233639)

24   (ferumoxytol or rienso or fersaday or galfer or ferrosuccinate or fefol or feospan or ferinject or cosmofer or monofer or venofer).tw. (1549)

25   21 or 22 or 23 or 24 (375911)

26   20 and 25 (25397)

27   14 and 17 and 26 (3005)

28   exp Health Economics/ (799530)

29   exp "Health Care Cost"/ (276691)

30   exp Pharmacoeconomics/ (193846)

31   Monte Carlo Method/ (36290)

32   Decision Tree/ (11130)

33   econom$.tw. (334844)

34   cba.tw. (12301)

35   cea.tw. (32425)

36   cua.tw. (1366)

37   markov$.tw. (27226)

38   (monte adj carlo).tw. (43392)

39   (decision adj3 (tree$ or analys$)).tw. (20641)

40   (cost or costs or costing$ or costly or costed).tw. (699427)

41   (price$ or pricing$).tw. (52397)

42   budget$.tw. (35612)

43   expenditure$.tw. (69165)

44   (value adj3 (money or monetary)).tw. (3180)

45   (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (8234)

46   or/28-45 (1622105)

47   "Quality of Life"/ (428429)

48   Quality Adjusted Life Year/ (23810)

49   Quality of Life Index/ (2626)

50   Short Form 36/ (25941)

51   Health Status/ (120090)

52   quality of life.tw. (394642)

53   quality adjusted life.tw. (17489)

54   (qaly$ or qald$ or qale$ or qtime$).tw. (17901)

55   disability adjusted life.tw. (3544)

56   daly$.tw. (3516)

57   (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (38695)

58   (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2164)

59   (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (8586)

60   (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (54)

61   (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (427)

62   (euroqol or euro qol or eq5d or eq 5d).tw. (17855)

63   (qol or hql or hqol or hrqol).tw. (86427)

64   (hye or hyes).tw. (126)

65   health$ year$ equivalent$.tw. (40)

66   utilit$.tw. (262695)

67   (hui or hui1 or hui2 or hui3).tw. (2082)

68   disutili$.tw. (829)

69   rosser.tw. (117)

70   quality of wellbeing.tw. (38)

71   quality of well-being.tw. (470)

72   qwb.tw. (237)

73   willingness to pay.tw. (7580)

74   standard gamble$.tw. (1054)

75   time trade off.tw. (1607)

76   time tradeoff.tw. (279)

77   tto.tw. (1527)

78   or/47-77 (901012)

79   46 or 78 (2380155)

80   27 and 79 (685)

81   limit 80 to english language (637)

82   limit 81 to (conference abstract or conference paper or "conference review" or letter or note or tombstone) (188)

83   81 not 82 (449)

Database: Econlit <1886 to June 13, 2019>

Search Strategy:

----

1   [exp Renal Insufficiency, Chronic/] (0)

2   ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (20)

3   ((kidney* or renal*) adj1 insufficien*).tw. (3)

4   ckd*.tw. (4)

5   ((kidney* or renal*) adj1 fail*).tw. (32)

6   ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (53)

7   (esrd* or eskd*).tw. (30)

8   ["Chronic Kidney Disease-Mineral and Bone Disorder"/] (0)

9   or/1-8 (97)

10   [exp Renal Replacement Therapy/] (0)

11   (haemodialys* or hemodialys* or dialys* or predialys* or pre-dialys*).tw. (102)

12   ((kidney* or renal*) adj1 replac*).tw. (13)

13   or/10-12 (106)

14   9 or 13 (159)

15   [exp Anemia/] (0)

16   (anemi* or anaemi*).tw. (186)

17   15 or 16 (186)

18   [exp Administration, Intravenous/] (0)

19   (iv or i-v or intraven*).tw. (5191)

20   18 or 19 (5191)

21   [iron/] (0)

22   [exp iron compounds/] (0)

23   (iron or ferric or ferrous or ferritin*).tw. (1439)

24   (ferumoxytol or rienso or fersaday or galfer or ferrosuccinate or fefol or feospan or feSinject or cosmofer or monofer or venofer).tw. (0)

25   or/21-24 (1439)

26   20 and 25 (8)

27   14 and 17 and 26 (0)

CRD databases

1   MeSH DESCRIPTOR Renal Insufficiency, Chronic EXPLODE ALL TREES   538   Delete

2   ((chronic* or progressi*) near1 (renal* or kidney*))   489   Delete

3   ((kidney* or renal*) near1 insufficien*) 320   Delete

4   (ckd*) 93   Delete

5   ((kidney* or renal*) near1 fail*) 836   Delete

6   ((endstage* or end-stage* or "end stage*") near1 (renal* or kidney*))   354   Delete

7   ((esrd* or eskd*))   150   Delete

8   MeSH DESCRIPTOR Chronic Kidney Disease-Mineral and Bone Disorder EXPLODE ALL TREES 0   Delete

9   (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)   1407   Delete

10   MeSH DESCRIPTOR Renal Replacement Therapy EXPLODE ALL TREES   881   Delete

11   (haemodialys* or hemodialys* or dialys* or predialys* or pre-dialys*)   1015   Delete

12   ((kidney* or renal*) near1 replac*)   151   Delete

13   (#10 or #11 or #12)   1351   Delete

14   (#9 or #13)   2102   Delete

15   MeSH DESCRIPTOR Anemia EXPLODE ALL TREES 380   Delete

16   (anemi* or anaemi*)   731   Delete

17   (#15 or #16)   791   Delete

18   MeSH DESCRIPTOR Administration, Intravenous EXPLODE ALL TREES   596   Delete

19   (iv or i-v or intraven*)   4124   Delete

20   #18 OR #19   4124   Delete

21   MeSH DESCRIPTOR Iron 68   Delete

22   MeSH DESCRIPTOR Iron Compounds EXPLODE ALL TREES   73   Delete

23   (iron or ferric or ferrous or ferritin*)   343   Delete

24   (ferumoxytol or rienso or fersaday or galfer or ferrosuccinate or fefol or feospan or ferinject or cosmofer or monofer or venofer)   10   Delete

25   (#21 or #22 or #23 or #24)   357   Delete

26   (#20 and #25)   73   Delete

27   (#14 and #17 and #26) 30   Delete

28   (#14 and #17 and #26) IN NHSEED   10   Delete

29   (#14 and #17 and #26) IN HTA   4   Delete

30   (#14 and #17 and #26) IN DARE 13   Delete

Appendix D – Effectiveness evidence study selection

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Databases                          Updated search
554 Citation(s)                    26 Citation(s)
      |                                  |
      v                                  v
554 Non-Duplicate                  26 Non-Duplicate
Citation Screened                  Citation Screened
      |                                  |
      v                                  v
Inclusion/Exclusion  -> 482 Articles Excluded After    Inclusion/Exclusion  -> 24 Articles Excluded After
Criteria Applied        Title/Abstract Screen          Criteria Applied        Title/Abstract Screen
      |                                  |
      v                                  v
72 Articles                        2 Articles
Retrieved                          Retrieved
      |                                  |
      v                                  v
Inclusion/Exclusion -> 60 Articles Excluded -> 0 Articles   Inclusion/Exclusion -> 2 Articles Excluded -> 0 Articles
Criteria Applied       After Full Text Screen  Excluded During Criteria Applied    After Full Text Screen  Excluded During
                                               Data Extraction                                             Data Extraction
      |                                  |
      v                                  v
12 Articles                        0 Articles
Included                           Included
```

Appendix E – Effectiveness evidence tables

Akcicek, 1997	
Bibliographic Reference	Akcicek, F; Ozkahya, M; Cirit, M; Ok, E; Unsal, A; Toz, H; Celik, A; Atabay, G; Basci, A; The efficiency of fractionated parenteral iron treatment in CAPD patients.; Advances in peritoneal dialysis. Conference on Peritoneal Dialysis; 1997; vol. 13; 109-12
Study details	
Study type	Randomised controlled trial (RCT) Data was taken only from the first intervention period from this crossover trial because paired t-tests were not reported and there was not enough data from the study to approximate a paired analysis. Therefore, this RCT was regarded as a parallel trial rather than as a cross-over trial.
Study location	Turkey
Study setting	Not reported
Study dates	Not reported
Duration of follow-up	Post-treatment (treatment was given for 6 weeks)
Sources of funding	Not reported
Inclusion criteria	Age Adults Haemoglobin <10 g/dL in 2 consecutive samples more than 2 months apart while on regular oral ferrous sulfate (2 mg/kg/day) for 6 months in addition to recombinant human erythropoietin treatment Haematocrit equivalent levels to the haemoglobin levels in 2 consecutive samples more than 2 months apart while on regular oral ferrous sulfate (2 mg/kg/day) for 6 months in addition to recombinant human erythropoietin treatment Erythropoietic stimulating agent The average recombinant human erythropoietin dose was 80 ±28 U/kg/week given in 2 divided doses, subcutaneous, for the first 6 months and the dose kept constant during the study

Exclusion criteria	None reported
Sample size	17
Loss to follow-up	None
% Female	59%
Mean age (SD)	47.5 (range 27 to 63 years)
Condition specific characteristics	Type of dialysis Continuous ambulatory peritoneal dialysis Duration of dialysis treatment 4.2 years in average (range 0.5 to 5 years)
Outcome measures	Other markers of anaemia Ferritin (μg/L) at ~2 months, haematocrit (%) at ~ 2 months

Study arms

	IV ferric saccharate (100mg/week) (N = 10) Intravenous ferric saccharate preparation (venofer) 100 mg/week until the total dosage of 600 mg was reached.
	IV ferric saccharate (2 x 50mg/week) (N = 7) Intravenous ferric saccharate preparation (venofer) 2 x 50 mg/week until the total dosage of 600 mg was reached.

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High *(unclear if allocation concealment; baseline data not reported for each arm; unclear blinding; protocol not reported)*
	Overall Directness	Directly applicable

Besarab, 2000

Bibliographic Reference	Besarab, A; Amin, N; Ahsan, M; Vogel, S E; Zazuwa, G; Frinak, S; Zazra, J J; Anandan, J V; Gupta, A; Optimization of epoetin therapy with intravenous iron therapy in hemodialysis patients.; Journal of the American Society of Nephrology : JASN; 2000; vol. 11 (no. 3); 530-8

Study details

Study type	Randomised controlled trial (RCT)
Study location	US
Study setting	Outpatient study
Study dates	Not reported
Duration of follow-up	Post-treatment (month 2) and months 3 to 6

	Treatment duration was 6 weeks
Sources of funding	Not reported
Inclusion criteria	Age >18 years Haemoglobin ≥9.5 g/dl Ferritin between 150 and 600 ng/ml Transferrin saturation between 19 and 30% Erythropoietic stimulating agent stable dose of recombinant human erythropoietin for anemia management over the previous 3 mo (±25%), but this baseline dose had to exceed 700 U intravenously three times per week Medications no prior adverse reactions to parenteral iron Other parameters mean cell volume of >80 fl
Exclusion criteria	Other conditions hemolytic anemia, known aluminum toxicity, the presence of acute infection/inflammation, hematologic malignancies, active known acute or chronic gastrointestinal bleeding, or moderate hyperparathyroidism (parathyroid hormone >450 pg/dl)
Sample size	42
Condition specific characteristics	Type of dialysis Haemodialysis
Outcome measures	Hb level Other markers of anaemia Ferritin All-cause mortality CV specific mortality Adverse events

Study arms

IV iron dextran (TSAT 20 to 30%) (N = 19)	
Intravenous iron dextran administered as weekly maintenance doses of 25 to 150 mg/wk to maintain transferrin saturation (TSAT) at 20 to 30%.	
Loss to follow-up	11%
% Female	47%
Mean age (SD)	60.7 (23.6)
Condition specific characteristics	Mean baseline Hb (SD) 10.5 g/dL (0.3) Mean baseline ferritin (SD) 287 ng/ml (36) Mean baseline transferrin saturation (SD) 23.9 % (1.8) ESA dose Mean dose (U, 3X/wk) 3782 (559)
IV iron dextran (TSAT 30 to 50%) (N = 23)	
Intravenous iron dextran administered initially as four to six 100 doses of 100 mg during consecutive haemodialysis sessions sufficient to increase transferrin saturation (TSAT) to .30% and thereafter as weekly maintenance doses of 25 to 150 mg/wk to maintain TSAT at 30 to 50%.	
Loss to follow-up	13%
% Female	35%
Mean age (SD)	60.9 (3.5)
Condition specific characteristics	Mean baseline Hb (SD) 10.6 g/dL (0.1) Mean baseline ferritin (SD) 285 ng/ml (35) Mean baseline transferrin saturation (SD)

24.6% (1.7)
ESA dose
Mean dose (U, 3X/wk) 3625 (419)

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns *(unclear randomisation method and allocation concealment; unclear blinding of participants; protocol not reported)*
	Overall Directness	Directly applicable

Bhandari, 2015

Bibliographic Reference	Bhandari, Sunil; Kalra, Philip A; Kothari, Jatin; Ambuhl, Patrice M; Christensen, Jeppe H; Essaian, Ashot M; Thomsen, Lars L; Macdougall, Iain C; Coyne, Daniel W; A randomized, open-label trial of iron isomaltoside 1000 (Monofer) compared with iron sucrose (Venofer) as maintenance therapy in haemodialysis patients.; Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association; 2015; vol. 30 (no. 9); 1577-89

Study details

Study type	Randomised controlled trial (RCT)
Study location	48 sites: 16 in India, 14 in the UK, 4 in Russia, 4 in Poland, 3 in Sweden, 3 in Switzerland, 2 in Romania, 1 in Denmark and 1 in the US.
Study setting	Hospitals or private dialysis clinics
Study dates	June 2011 to October 2013
Duration of follow-up	Follow-up was at week 6
Sources of funding	The trial was funded by Pharmacosmos A/S.
Inclusion criteria	Age ≥18 years of age with a diagnosis of CKD and on haemodialysis therapy for at least 90 days Haemoglobin between 9.5 and 12.5 g/dL (inclusive both values) both at screening visit 1a and screening visit 1b (screening visits were separated by at least 1 week) Ferritin <800 ng/mL Transferrin saturation <35% Erythropoietic stimulating agent dose stable for the previous 4 weeks prior to screening Medications No IV iron or an average of no >100 mg/week for the previous 4 weeks Other parameters Life expectancy beyond 12 months Consent

	Willing to provide written informed consent
Exclusion criteria	Anaemia
	Factors other than renal-related anaemia
	Iron
	Iron overload or disturbances in utilization of iron (i.e. haemochromatosis and hemosiderosis)
	Medications
	Currently undergoing active treatment with immunosuppressive agents
	Parameters
	Difference of Hb ≥1.0 g/dL between screening visit 1a and 1b;
	Other conditions
	A history of multiple allergies; Decompensated liver cirrhosis or active hepatitis; History of hepatitis B or C; Active acute or chronic infections; Rheumatoid arthritis with symptoms or signs of active joint inflammation; Pregnant or nursing women; Untreated vitamin B12 or folate deficiency; Any other medical condition that, in the opinion of the investigator, may have caused the patient to be unsuitable for completion of the trial or placed the patient at potential risk from being in the trial
	Other exclusion criteria
	Blood transfusion within the previous 12 weeks; Planned elective surgery in the next 8 weeks; Participation in any other clinical trial where the trial drug had not passed five half-lives prior to screening
Sample size	351
Condition specific characteristics	Type of dialysis
	Haemodialysis
Outcome measures	Hb level
	All-cause mortality
	Adverse events

Study arms

	IV iron isomaltoside 1000 (500mg) (N = 234)
	Group A1: single undiluted IV bolus injection of 500 mg over ~2 min at baseline Group A2: undiluted iron in split doses of 100 mg at baseline and 200 mg each at Weeks 2 and 4 as IV bolus injections over ~2 min
	Loss to follow-up Group A1: 8%

	% Female	32.5%
	Mean age (SD)	60.13 (16.21)
	Condition specific characteristics	Duration of dialysis treatment Mean dialysis time before entering the trial 3.46 years (3.95) Mean baseline Hb (SD) 11.2 g/dL (0.66) Mean baseline ferritin (SD) 367 ng/mL 367 (180) Mean baseline transferrin saturation (SD) 21.6% (5.95) Mean baseline C-reactive protein (SD) 6.85 ng/mL (7.33) Diabetes 35.5% ESA dose Treatment with ESA had to be kept stable during the trial. The patients received different dosing schedules with various ESAs including epoetin alfa, epoetin beta, darbepoetin alfa, erythropoietin and methoxy polyethylene glycol-epoetin beta.

IV iron sucrose (500mg) (N = 117)
Group B: split doses of 100 mg at baseline and 200 mg each at Weeks 2 and 4

	Loss to follow-up	3%
	% Female	36.8
	Mean age (SD)	59.50 (15.39)
	Condition specific characteristics	Duration of dialysis treatment Mean dialysis time before entering the trial 3.59 years (4.08) Mean baseline Hb (SD) 11.0 g/dL (0.76)

	Mean baseline ferritin (SD)
	384 ng/mL (184)
	Mean baseline transferrin saturation (SD)
	22.6% (6.76)
	Mean baseline C-reactive protein (SD)
	7.61 ng/mL (10.1)
	Diabetes
	30.8%
	ESA dose
	Treatment with ESA had to be kept stable during the trial. The patients received different dosing schedules with various ESAs including epoetin alfa, epoetin beta, darbepoetin alfa, erythropoietin and methoxy polyethylene glycol-epoetin beta.

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(trial was not blinded but primary outcome was a biochemical measurement)*
	Overall Directness	Directly applicable

Charytan, 2013

Bibliographic Reference	Charytan, Chaim; Bernardo, Marializa V; Koch, Todd A; Butcher, Angelia; Morris, David; Bregman, David B; Intravenous ferric carboxymaltose versus standard medical care in the treatment of iron deficiency anemia in patients with chronic kidney disease: a randomized, active-controlled, multi-center study.; Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association; 2013; vol. 28 (no. 4); 953-64

Study details

Study type	Randomised controlled trial (RCT)
Study location	US
Study setting	Not reported
Study dates	October 2007–January 2009
Duration of follow-up	Follow-up was at day 30
Sources of funding	Support for these studies was provided by Luitpold Pharmaceuticals, Inc.
Inclusion criteria	Age 18–85 years of age were eligible if they had at least a 6- month history of dialysis chronic kidney disease Haemoglobin ≤12.5 g/dL Ferritin ≤500 ng/mL Transferrin saturation ≤30%

	Other parameters
	eligible if they did not anticipate needing repletion therapy (>200 mg of IV iron) during the 30-day study period.
Exclusion criteria	Anaemia
	anemia other than that due to iron deficiency
	Medications
	current treatment for asthma
	Other conditions
	evidence of ongoing infection (including hepatitis B, hepatitis C or HIV), concomitant severe liver or cardiovascular diseases, iron storage disorders, pregnancy or lactation
	Other exclusion criteria
	recent hospitalisation; use of investigational drugs, GI bleeding, alcohol or drug abuse, known hypersensitivity to any component of ferric carboxymaltose; not using approved birth control methods and anticipated surgery during the study period
Sample size	97
Loss to follow-up	Not reported separately for dialysis and non-dialysis participants.
	3% were lost in IV ferric carboxymaltose.
	3% were lost in standard medical care.
Condition specific characteristics	Type of dialysis
	Reported as dialysis (HD)
Outcome measures	Hb level
	Other markers of anaemia
	Ferritin (ng/mL)
	CV specific mortality
	Adverse events

Study arms

	IV ferric carboxymaltose (N = 50)
	Undiluted IV push of 200 mg directly into the venous line of the dialyzer ~30–60 min into the dialysis session.
	% Female 44.0

Mean age (SD)	54.8 (14.4)	
Condition specific characteristics	Mean baseline Hb (SD) 11.2 g/dL (0.7) Mean baseline ferritin (SD) 273.2 ng/mL (112.3) Mean baseline transferrin saturation (SD) 22.6% (4.9) ESA dose Current ESA use 98.0%	

Standard medical care (N = 47)

Treatment for iron deficiency anemia determined by the investigator to be appropriate for the given patient, and could include IV or oral iron or no iron treatment. Type of standard medical care: No treatment (31.9%); Oral iron (0); IV iron (Iron sucrose [46.8%], Sodium ferric gluconate [50.0%], Iron dextran [3.1%]). Note: Percent within IV Iron group. Patients may have been administered more than one iron therapy.

Split between study groups	Type of standard medical care: No treatment
% Female	21.3
Mean age (SD)	57.1 12.6
Condition specific characteristics	Mean baseline Hb (SD) 11.3 g/dL (0.7) Mean baseline ferritin (SD) 247.9 ng/mL (135.6) Mean baseline transferrin saturation (SD) 24.6% (4.8) ESA dose Current ESA use 95.7%

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns *(unclear randomisation method; open-label trial)*
	Overall Directness	Directly applicable

Goldstein, 2013

Bibliographic Reference	Goldstein, Stuart L; Morris, David; Warady, Bradley A; Comparison of the safety and efficacy of 3 iron sucrose iron maintenance regimens in children, adolescents, and young adults with CKD: a randomized controlled trial.; American journal of kidney diseases : the official journal of the National Kidney Foundation; 2013; vol. 61 (no. 4); 588-97

Study details

Study type	Randomised controlled trial (RCT)
Study location	US and Russia
Study setting	Not reported
Study dates	Not reported

Duration of follow-up	12-week post-baseline. Treatment duration was 12 weeks.
Sources of funding	The study was funded by Luitpold Pharmaceuticals Inc.
Inclusion criteria	Age 2 to 21 years Haemoglobin ≥11.0 to ≤13.5 g/dL Ferritin 800 ng/mL≤ Transferrin saturation ≥20% to ≤50% Erythropoietic stimulating agent stable ESA therapy (±25% of current dose) for 8 weeks or longer prior to the qualifying screening visit Other parameters dialysis stable regimen for at least 3 months
Exclusion criteria	None reported
Sample size	145
Condition specific characteristics	ESA dose The type, dose, rate, route, and frequency of ESAwere to be held constant from the time of consent until study completion. ESA dosing could be increased or decreased for safety reasons only.
Outcome measures	Hb level Other markers of anaemia Ferritin was reported for all participants combined (haemodialysis, peritoneal dialysis and non-dialysis) Adverse events Adverse events were reported for all participants combined (haemodialysis, peritoneal dialysis and non-dialysis)

Study arms

	IV iron sucrose (0.5 mg/kg) (N = 49)

	0.5 mg/kg of iron sucrose; once every other week for 6 doses; undiluted over 5 minutes by IV push or diluted in 25 mL of 0.9% sodium chloride; solution and administered over 5-60 minutes; administered after an haemodialysis treatment. The duration of IV push/infusion was determined by local institutional protocol.
Loss to follow-up	16.3%
% Female	43
Mean age (SD)	13.8 (4.40)
Condition specific characteristics	Type of dialysis Haemodialysis (63%); peritoneal dialysis (25%) Mean baseline Hb (SD) 12.22 g/dL (0.79) Mean baseline ferritin (SD) 262 ng/mL (211) Mean baseline transferrin saturation (SD) 33.0% (10.1)

IV iron sucrose (1.0 mg/kg) (N = 47)

1.0 mg/kg of iron sucrose; once every other week for 6 doses; undiluted over 5 minutes by IV push or diluted in 25 mL of 0.9% sodium chloride; solution and administered over 5-60 minutes; administered after an haemodialysis treatment. The duration of IV push/infusion was determined by local institutional protocol.

Loss to follow-up	12.8%
% Female	47
Mean age (SD)	13.1 (4.62)
Condition specific characteristics	Type of dialysis Haemodialysis (64%); peritoneal dialysis (25%) Mean baseline Hb (SD) 12.19 g/dL (0.85) Mean baseline ferritin (SD) 308 ng/mL (267) Mean baseline transferrin saturation (SD)

	33.2% (9.4)	
	IV iron sucrose (2.0 mg/kg) (N = 49)	
	2.0 mg/kg of iron sucrose; once every other week for 6 doses; undiluted over 5 minutes by IV push or diluted in 25 mL of 0.9% sodium chloride; solution and administered over 5-60 minutes; administered after an haemodialysis treatment. The duration of IV push/infusion was determined by local institutional protocol.	
	Loss to follow-up	22.4%
	% Female	37
	Mean age (SD)	13.1 (4.87)
	Condition specific characteristics	Type of dialysis Haemodialysis (61%); peritoneal dialysis (25%) Mean baseline Hb (SD) 12.03 g/dL (0.78) Mean baseline ferritin (SD) 326 ng/mL (293) Mean baseline transferrin saturation (SD) 31.9% (9.5)

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable

Section	Question	Answer
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns *(unclear randomisation method and allocation concealment; open-label trial)*
	Overall Directness	Directly applicable

Hsiao, 2016

Bibliographic Reference	Hsiao P.-J.; Chan J.-S.; Wu K.-L.; Chiang W.-F.; Huang J.-S.; Wu C.-C.; Chu P.; Chen J.-S. ; Comparison of short-term efficacy of iron sucrose with those of ferric chloride in hemodialysis patients: An open-label study; Journal of Research in Medical Sciences; 2016; vol. 21 (no. 7); 102

Study details

Study type	Randomised controlled trial (RCT)
Study location	Taiwan
Study setting	Hospital
Study dates	April to July 2013
Duration of follow-up	Post-treatment (after the 10-week treatment period)
Sources of funding	Nil
Inclusion criteria	Age ≥18 years Haematocrit

	between 22% and 32% Ferritin <200 µg/L Transferrin saturation <40% Other parameters regular haemodialysis for at least 3 months; normal serum Vitamin B12 and folic acid concentrations; no blood transfusion in the last 3 months
Exclusion criteria	Other conditions Hemoglobinopathies, malignancy, pregnancy, acute infectious state, gastrointestinal bleeding, mental incapacity Other exclusion criteria inability to abide to the study requirements
Sample size	56
Condition specific characteristics	Type of dialysis Haemodialysis ESA dose All patients received identical doses of rHuEPO (RECORMON 5000 IU/week).
Outcome measures	Other markers of anaemia Serum ferritin, haematocrit

Study arms

	IV iron sucrose (1000mg) (N = 26) 100 mg once weekly; administered as an infusion in 100 mL of normal saline in the last ½ h of dialysis through the venous bubble trap port of the dialysis circuit (time of infusion was 30 min). Iron supplementation was stopped to avoid iron overload and toxicity when serum ferritin values increased >800 µg/L.

Loss to follow-up	15%
% Female	34.7
Mean age (SD)	57.8 (13.2)

Condition specific characteristics	Mean baseline ferritin (SD) 172 µg/L (176) Mean baseline transferrin saturation (SD) 23.7% (8.5) Mean baseline haematocrit (SD) 28% (3.6) Mean baseline C-reactive protein (SD) 0.08 mg/dL (0.02) Diabetes 42.3%

IV ferric chloride hexahydrate (1000mg) (N = 30)

100 mg once weekly; administered as an infusion in 100 mL of normal saline in the last ½ h of dialysis through the venous bubble trap port of the dialysis circuit (time of infusion was 30 min). Iron supplementation was stopped to avoid iron overload and toxicity when serum ferritin values increased >800 µg/L.

Loss to follow-up	17%
% Female	30.0
Mean age (SD)	60.5 (14.6)
Condition specific characteristics	Mean baseline ferritin (SD) 137 µg/L (102) Mean baseline transferrin saturation (SD) 24.8% (8.1) Mean baseline haematocrit (SD) 29% (2.4) Mean baseline C-reactive protein (SD) 0.06 mg/dL (0.03) Diabetes 56.7%

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns *(unclear randomisation method and allocation concealment; clinical physicians were not blinded; protocol not reported)*
	Overall Directness	Directly applicable

Macdougall, 2019

Bibliographic Reference Macdougall, Iain C; White, Claire; Anker, Stefan D; Bhandari, Sunil; Farrington, Kenneth; Kalra, Philip A; McMurray, John J V; Murray, Heather; Tomson, Charles R V; Wheeler, David C; Winearls, Christopher G; Ford, Ian; PIVOTAL Investigators and Committees; Intravenous Iron in Patients Undergoing Maintenance Hemodialysis.; The New England journal of medicine; 2019; vol. 380 (no. 5); 447-458

Study details

Study location	UK
Study setting	Hospital
Study dates	2013 to 2018
Duration of follow-up	The median follow-up was 2.1 years, with a maximum follow-up of 4.4 years.
Sources of funding	The trial was funded by Kidney Research UK, which was supported by an unrestricted grant from Vifor Fresenius Medical Care Renal Pharma (which also provided iron sucrose for the trial, free of charge).
Inclusion criteria	Age >18 years Ferritin <400 µg/L Transferrin saturation <30% Erythropoietic stimulating agent On ESA therapy Other parameters Patients established on a chronic haemodialysis program for end-stage renal failure; Clinically stable per the judgment of the investigator; 0–12 months since commencing haemodialysis; Patients who have switched to haemodialysis from peritoneal dialysis or have received previous haemodialysis or renal transplants are eligible to enter the study. Consent Written informed consent
Exclusion criteria	Parameters CRP >50 mg/L Other conditions Active infection; Current active malignancy; Known HIV, active hepatitis B or active hepatitis C; Chronic liver disease and/or screening ALT or AST >3 × ULN; Advanced heart failure; Pregnancy or breast feeding Other exclusion criteria Clinically stable per the judgment of the investigator; 0–12 months since commencing haemodialysis; Patients who have switched to haemodialysis from peritoneal dialysis or have received previous haemodialysis or renal transplants are eligible to enter the study; Life expectancy <12 months per the judgement of the investigator; Living-donor transplant scheduled within 12 months; Scheduled to switch to peritoneal dialysis or home haemodialysis; History of acquired iron overload; Previous severe hypersensitivity reactions to IV iron sucrose; Compromised ability to give written informed consent and/or to comply with study procedures

Sample size	2141
Condition specific characteristics	Type of dialysis Haemodialysis
Outcome measures	Hb level Hb was only reported in graphs in the supplementary appendix (data could not be extracted) Other markers of anaemia Serum ferritin was only reported in graphs in the supplementary appendix (data could not be extracted) All-cause mortality CV specific mortality Adverse events Blood transfusion Quality of life Only reported as Least-squares mean change in EQ-5D quality-of-life health index score & KDQOL overall score averaged over time (data could not be extracted) Subgroup analysis

Study arms

	IV iron sucrose (high dose-proactive) (N = 1093)	
	Month 1: 600 mg divided equally over 3 haemodialysis sessions. Month 2 through the end of treatment: • If ferritin ≤700 µg/l: 200 mg during each of the first 2 dialysis sessions • If ferritin >700 µg/l and/or transferrin saturation ≥40%: the iron dose was withheld.	
	Loss to follow-up	6%
	% Female	35.0
	Mean age (SD)	62.7 (14.9)
	Condition specific characteristics	Duration of dialysis treatment Median duration (25th to 75th percentile): 4.9 months (2.8–8.4) Type of access (catheter or fistula) Dialysis catheter (41.1%); Arteriovenous fistula or graft (58.9%) Mean baseline Hb (SD)

		10.6 g/dL (1.4) Mean baseline ferritin (SD) Median (25th to 75th percentile): 214 µg/l (132–305) Mean baseline transferrin saturation (SD) Median (25th to 75th percentile): 20% (16–24) Mean baseline C-reactive protein (SD) Median (25th to 75th percentile): 6.0 mg/l (3.3–13.9) Diabetes 45.2% ESA dose Median dose (25th to 75th percentile): 8000 IU/wk (5000–10,000)
	IV iron sucrose (low dose-reactive) (N = 1048) • If ferritin <100 µg/l and transferrin saturation <40%: 200 mg during each of the first 2 dialysis sessions • If ferritin 100 to 200 µg/l and transferrin saturation <40%: 200 mg during the first dialysis session • If ferritin 201 to 700 µg/l and transferrin saturation ≤20%: 100 mg during the first dialysis session • If ferritin >200 µg/l and transferrin saturation >20%: no iron • If ferritin >700 µg/l and/or transferrin saturation ≥40%: no iron	
	Loss to follow-up	7%
	% Female	34.4%
	Mean age (SD)	62.9 (15.1)
	Condition specific characteristics	Duration of dialysis treatment Mean (25th to 75th percentile): 4.8 months (2.8-8.1) Type of access (catheter or fistula) Dialysis catheter (40.8%); Arteriovenous fistula or graft (59.2%) Mean baseline Hb (SD) Median (25th to 75th percentile): 10.5 g/dl (1.4) Mean baseline ferritin (SD) Median (25th to 75th percentile): 217 µg/l (137–301) Mean baseline transferrin saturation (SD) Median (25th to 75th percentile): 20% (16–24)

	Mean baseline C-reactive protein (SD)
	Median (25th to 75th percentile): 7.0 mg/l (4.0–15.0)
	Diabetes
	43.5%
	ESA dose
	Median (25th to 75th percentile): 8000 IU/wk (5000–12,000)

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low *(participants and researchers were not blinded but this was unlikely to affect outcomes)*
	Overall Directness	Directly applicable

Nissenson, 1999

Bibliographic Reference	Nissenson, A R; Lindsay, R M; Swan, S; Seligman, P; Strobos, J; Sodium ferric gluconate complex in sucrose is safe and effective in hemodialysis patients: North American Clinical Trial.; American journal of kidney diseases : the official journal of the National Kidney Foundation; 1999; vol. 33 (no. 3); 471-82

Study details

Study type	Randomised controlled trial (RCT)
Study location	US
Study setting	Not reported
Study dates	Not reported
Duration of follow-up	Day 2, 14 and 30 after treatment
Sources of funding	Supported by R&D Laboratories, Inc. Clinical supplies in the form of Ferrlecit Injection (sodium ferric gluconate complex in sucrose) were provided by the manufacturer, Rhoˆne-Poulenc Rorer GmBH, Dagenham, United Kingdom.
Inclusion criteria	Age Adults Haemoglobin <10 g/dL Haematocrit ≤32% Ferritin <100 ng/m Transferrin saturation <18%
Exclusion criteria	Medications if they had received parenteral iron products or any investigational drug that might interfere with iron metabolism in the 2 months preceding enrollment Other conditions significant comorbid conditions

	Other exclusion criteria baseline rHuEPO requirements greater than 10,000 units three times weekly
Sample size	88
Loss to follow-up	6%
Condition specific characteristics	Type of dialysis Haemodialysis ESA dose The study design required that starting rHuEPO doses remain unchanged throughout the study.
Outcome measures	Hb level Other markers of anaemia Serum ferritin; haematocrit All-cause mortality There were no deaths CV specific mortality There were no deaths Adverse events Events were not specified by arm. Blood transfusion The protocol precluded blood transfusion.

Study arms

	IV sodium ferric gluconate complex in sucrose (1000mg) (N = 47) administered intravenously as 125 mg in 100 mL saline over 30 or 60 minutes in 8 divided doses over 8 sequential dialysis sessions.	
	% Female	50.2
	Mean age (SD)	57.1 (17.7)
	Condition specific characteristics	Mean baseline Hb (SD) 9.6 d/dL (0.9) Mean baseline ferritin (SD)

	88.4 mg/mL (143.2) Mean baseline transferrin saturation (SD) 15.6% (7.5) Mean baseline haematocrit (SD) 28.8% (2.6)	
	IV sodium ferric gluconate complex in sucrose (500mg) (N = 41) administered intravenously as 62.5 mg in 50 mL saline over 30 or 60 minutes in 8 divided doses over 8 sequential dialysis sessions.	
	% Female	56.1
	Mean age (SD)	55.0 (17.7)
	Condition specific characteristics	Mean baseline Hb (SD) 9.8 g/dL (0.8) Mean baseline ferritin (SD) 105.6 mg/mL (116.3) Mean baseline transferrin saturation (SD) 20.1% (11.9) Mean baseline haematocrit (SD) 29.4% (2.3)

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns *(unclear randomisation method and allocation concealment; open-label trial; protocol not reported)*
	Overall Directness	Directly applicable

Roe, 1996

Bibliographic Reference	Roe, D J; Harford, A M; Zager, P G; Wiltbank, T B; Kirlin, L; Della Valle, A M; Van Wyck, D B; Iron utilization after iron dextran administration for iron deficiency in patients with dialysis-associated anemia: a prospective analysis and comparison of two agents.; American journal of kidney diseases : the official journal of the National Kidney Foundation; 1996; vol. 28 (no. 6); 855-60

Study details

Study type	Randomised controlled trial (RCT)
Study location	US
Study setting	Not reported
Study dates	Not reported
Duration of follow-up	week 1, week 2, week 3, and day 30 after treatment
Sources of funding	Supported by an award from Luitpold Pharmaceuticals, Inc.

Inclusion criteria	Age 18 years or older Ferritin <100 µg/L Transferrin saturation <20% Other parameters life expectancy greater than 60 days, were receiving erythropoietin therapy for dialysisassociated anemia (hemoglobin 9 to 12 g/dL)
Exclusion criteria	Iron oral iron supplementation within 48 hours of study entry Other conditions active inflammatory disease (including positive serum RA or ANA titers), infection, carcinoma, active gastrointestinal bleeding, transfusion dependency, or transfusion or intravenous iron within 1 month of study entry Other exclusion criteria elective surgery planned prior to study completion, previous sensitivity to iron dextran
Sample size	20
Condition specific characteristics	Type of dialysis Haemodialysis ESA dose Erythropoietin doses were held constant throughout the study and were similar between the two treatment groups.
Outcome measures	Hb level Other markers of anaemia Serum ferritin

Study arms

	IV iron dextran MW 267,000 (N = 9) single 100 mg dose within the first 30 minutes of the dialysis session, on study day 1, by a 5-minute intravenous infusion, undiluted via the venous port of the dialysis tubing. Four subsequent doses over the next 4 consecutive dialysis sessions, for a total dose of 500 mg.	
	% Female	44

	Mean age (SD)	54.4 (17.6)
	Condition specific characteristics	Duration of dialysis treatment Mean 1.2 (SD 1.4) Mean baseline Hb (SD) 10.29 g/dL (0.68) Mean baseline ferritin (SD) 128.6 µg/L (91.3) Mean baseline transferrin saturation (SD) 14.3% (2.8)

IV iron dextran MW 96,000 (N = 11)

single 100 mg dose within the first 30 minutes of the dialysis session, on study day 1, by a 5-minute intravenous infusion, undiluted via the venous port of the dialysis tubing. Four subsequent doses over the next 4 consecutive dialysis sessions, for a total dose of 500 mg.

	% Female	55
	Mean age (SD)	57.6 (13.5)
	Condition specific characteristics	Duration of dialysis treatment Mean 1.9 (SD 1.5) Mean baseline Hb (SD) 10.72 g/dL (0.62) Mean baseline ferritin (SD) 105.8 µg/L (76.7) Mean baseline transferrin saturation (SD) 17.5% (6.7)

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High *(unclear randomisation method and allocation concealment; analysis used to estimate the effect of assignment to intervention was not reported; protocol not reported)*
	Overall Directness	Directly applicable

Ruiz-Jaramillo, 2004

Bibliographic Reference	Ruiz-Jaramillo, Ma de la Cruz; Guizar-Mendoza, Juan Manuel; Gutierrez-Navarro, Maria de Jesus; Dubey-Ortega, Luis Antonio; Amador-Licona, Norma; Intermittent versus maintenance iron therapy in children on hemodialysis: a randomized study.; Pediatric nephrology (Berlin, Germany); 2004; vol. 19 (no. 1); 77-81

Study details

Study type	Randomised controlled trial (RCT)

Study location	Mexico
Study setting	Department of Pediatric Nephrology
Study dates	August 2000 to December 2001
Duration of follow-up	after 3, 4 and 6 months of treatment
Sources of funding	The Research was supported by CONACYT-SIHGO and Fondo para el Fomento a la Investigacion (FOFOI) del Instituto Mexicano del Seguro Social.
Inclusion criteria	Age <16 years Other parameters Anaemia and absolute iron deficiency (ferritin <100 µg/l and transferrin saturation <20%) or functional iron deficiency (ferritin >100 µg/l and transferrin saturation <20% or haematocrit <33%)
Exclusion criteria	Iron iron overload (ferritin >800 µg/l or transferrin saturation >50%, medium corpuscular volume >100 fl) Other conditions coagulation abnormalities, abnormal hepatic function Other exclusion criteria hypersensitive to iron, or had been transfused a month previously; a documented allergy to iron dextran, infection, if they were transfused with red blood cells, when they changed dialysis therapy, if they developed iron overload, or when they decided not to continue with the study
Sample size	40
Loss to follow-up	Unclear
% Female	30
Condition specific characteristics	Type of dialysis Haemodialysis
Outcome measures	Hb level Other markers of anaemia Ferritin Blood transfusion

Study arms

IV Iron dextran (dose depended on ferritin levels) (N = 20)	
Iron dextran was administered intravenously in 20 ml normal saline over 30 min. Iron reserves were calculated, iron needs, and net projected iron stores as follows: iron reserves (mg)=400x(log ferritin-log 30), iron needs for new hemoglobin synthesis: Fe (mg)=150x(11.55-Hb1), net projected iron stores=iron reserves-iron needs. The net projected iron stores were administered as weekly doses according to the body weight (<10 kg 25 mg/dose, 10–20 kg 50 mg/dose, >20 kg 100 mg/dose). After this loading dose, each patient received weekly maintenance doses of 1 mg/kg per week. Iron was discontinued if ferritin was >800 µg/l and/or TSAT >50%.	
Mean age (SD)	11.7 €2.6
Condition specific characteristics	Duration of dialysis treatment Mean 16 months (SD 14) Mean baseline Hb (SD) 8.4 g/dl (1.4) Mean baseline ferritin (SD) 260 µg/l (181) Mean baseline transferrin saturation (SD) 25.3% (11) ESA dose Mean dose 216 IU/kg per week (SD 93)
IV Iron dextran (10-dose courses on body weight) (N = 20)	
Iron dextran was administered intravenously in 20 ml normal saline over 30 min. Ten-dose courses according to body weight: <10 kg 25 mg/dose, 10–20 kg 50 mg/dose, and >20 kg 100 mg/dose. If the haematocrit was <33%, ferritin <100 µg/l, and/or TSAT <20%, we repeated another ten-dose course.	
Mean age (SD)	9.7 (3.7)
Condition specific characteristics	Duration of dialysis treatment Mean 9 months (SD 8) Mean baseline Hb (SD) 7.7 g/dl (1.5) Mean baseline ferritin (SD) 264 µg/l (256)

	Mean baseline transferrin saturation (SD) 19.8% (10) ESA dose Mean dose 226 IU/kg per week (SD 26)

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	No information
	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns *(unclear randomisation method and allocation concealment; unclear if blinding; unclear if there was outcome data for all randomised participants; protocol not reported)*
	Overall Directness	Directly applicable

Wan, 2018

Bibliographic Reference	Wan, Li; Zhang, Dongliang; Effect of frequency of intravenous iron administration on hemoglobin variability in maintenance hemodialysis patients.; International urology and nephrology; 2018; vol. 50 (no. 8); 1511-1518

Study details

Study type	Randomised controlled trial (RCT) The trial was cross-over but the committee did not consider the washout period to be appropriate for patients receiving ESA. Therefore, this trial is regarded as a parallel trial. Data was only extracted from the first period.
Study location	China
Study setting	Hospital
Study dates	August 2016–April 2017
Duration of follow-up	3 months
Sources of funding	Not reported
Inclusion criteria	Age Adults Haemoglobin maintained at 100–130 (g/l) Ferritin 100–500 (ng/ml) Erythropoietic stimulating agent Treated with recombinant human erythropoietin Other parameters Regular haemodialysis patients (4 h per session and three times a week) with duration of stable haemodialysis more than 6 months; intact parathyroid hormone < 800 (pg/ml); Kt/V of each haemodialysis session >1.2 during the screening period
Exclusion criteria	Medications allergy to intravenous iron Other conditions malignant tumors, new or chronic infectious diseases, peptic ulcer, active rheumatism, malnutrition, and cachexia

	Other exclusion criteria Incomplete clinical records; recombinant human erythropoietin low response
Sample size	47
Condition specific characteristics	Type of dialysis Haemodialysis
Outcome measures	Hb level Other markers of anaemia Serum ferritin reported as median (25th, 75th range); haematocrit Adverse events no adverse events during follow-up

Study arms

IV iron sucrose (continuous administration) (N = 23) 100 mg in each dialysis session and completed within 1 month when sum doses reached 1000 mg.	
Loss to follow-up	26%
% Female	41
Mean age (SD)	64.8 (8.5)
Condition specific characteristics	Duration of dialysis treatment Mean 85.2 months (SD 33.6) Mean baseline Hb (SD) 112.03 g/l (9.48) Mean baseline ferritin (SD) 251.5 ng/ml (25th to 75th range: 215.4, 274.1) Mean baseline transferrin saturation (SD) 35.49% (20.62) Mean baseline haematocrit (SD) 34.79% (3.08) Mean baseline C-reactive protein (SD)

		high sensitive C reaction protein 6.99 mg/l (5.26) ESA dose Mean dose 134.31 U×kg−1×W−1 (SD 64.34)
	IV iron sucrose (intermittent administration) (N = 24) 100 mg per week and completed total 1000 mg doses within 3 months.	
	Loss to follow-up	29%
	% Female	53
	Mean age (SD)	62.5 (6.9)
	Condition specific characteristics	Duration of dialysis treatment Mean 67.2 months (SD 26.4) Mean baseline Hb (SD) 111.30 g/l (10.40) Mean baseline ferritin (SD) 259.5 ng/ml (25th and 75th range: 220.8, 280.1) Mean baseline transferrin saturation (SD) 40.98% (16.99) Mean baseline haematocrit (SD) 34.23% (3.19) Mean baseline C-reactive protein (SD) high sensitive C reaction protein 7.07 mg/l (5.14) ESA dose Mean dose 132.35 U×kg−1×W− 1 (SD 76.54)

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns *(unclear randomisation method and allocation concealment; unclear if blinding; protocol not reported)*
	Overall Directness	Directly applicable

Warady, 2005		
Bibliographic Reference	**Warady, Bradley A; Zobrist, R Howard; Wu, Jingyang; Finan, Eileen; Ferrlecit Pediatric Study Group; Sodium ferric gluconate complex therapy in anemic children on hemodialysis.; Pediatric nephrology (Berlin, Germany); 2005; vol. 20 (no. 9); 1320-7**	
Study details		
Study type	Randomised controlled trial (RCT)	
Study location	21 sites in five countries (Mexico [five patients at one site], Poland [17 patients at eight sites], Russia [20 patients at six sites], Serbia [eight patients at one site], and the United States [17 patients at five sites]) enrolled 67 patients in the study.	

Study setting	Not reported
Study dates	Not reported
Duration of follow-up	2 and 4 weeks after treatment
Sources of funding	This trial was supported by a grant from Watson Pharmaceuticals, to each of the participating centers.
Inclusion criteria	Age 2 to 15 years Erythropoietic stimulating agent receiving concomitant recombinant human erythropoietin therapy with stable dosing regimen (defined as ≤25% change in the dose during the 4 weeks before treatment assignment) Other parameters need for iron-repletion therapy as reflected by a transferrin saturation of <20% and/or a serum ferritin of <100 ng mL-1
Exclusion criteria	Other exclusion criteria blood transfusions or any form (oral and IV) of iron supplementation in the 4 weeks before administration of the first dose of sodium ferric gluconate complex; clinically unstable
Sample size	66
Condition specific characteristics	Type of dialysis Haemodialysis ESA dose dose was held constant throughout the treatment period and during the 2 weeks between the last treatment dose and the 2-week evaluation time point. The investigators were permitted to adjust the ESA dose as needed between the 2- and 4-week evaluation time points.
Outcome measures	Hb level Other markers of anaemia Serum ferritin All-cause mortality There were no deaths CV specific mortality There were no deaths Adverse events

	Blood transfusion
	2 patients had blood transfusions but were not included in the efficacy analyses and it was not specified from which group

Study arms

	IV sodium ferric gluconate complex (1.5 mg kg-1) (N = 32)
	8 doses of 1.5 mg kg-1. Patients received each single dose beginning 1 to 2 h after initiation of the dialysis session. Sodium ferric gluconate complex was diluted in normal saline and infused in a total volume of 25 mL by syringe pump over 1 h, not to exceed 125 mg per dose during each of 8 consecutive haemodialysis sessions.

Loss to follow-up	25%
% Female	53.1
Mean age (SD)	12.3 (2.5)
Condition specific characteristics	Mean baseline Hb (SD) 9.9 g/dL (2.1) Mean baseline ferritin (SD) 90.7 ng/mL (121.8) Mean baseline transferrin saturation (SD) 19.5% (10.4)

	IV sodium ferric gluconate complex (3.0 mg kg-1) (N = 34)
	8 doses of 3.0 mg kg-1. Patients received each single dose beginning 1 to 2 h after initiation of the dialysis session. Sodium ferric gluconate complex was diluted in normal saline and infused in a total volume of 25 mL by syringe pump over 1 h, not to exceed 125 mg per dose during each of 8 consecutive haemodialysis sessions.

Loss to follow-up	6%
% Female	44.1
Mean age (SD)	12.0 (2.6)
Condition specific characteristics	Mean baseline Hb (SD) 9.4 g/dL (2.3) Mean baseline ferritin (SD)

161.8 ng/mL (223.5)
Mean baseline transferrin saturation (SD)
16.2% (10.6)

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns *(unclear randomisation method and allocation concealment; the effect to assignment to intervention was not analysed; protocol not reported)*
	Overall Directness	Directly applicable

Appendix F – Forest plots

Children and young people

IV iron high dose vs low dose in children and young people with GFR category G5 who are on dialysis:

Figure 1: Outcome: Hb g/dL; higher values are better

Study or Subgroup	High dose Mean	SD	Total	Low dose Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
14.1.1 Week 2							
Warady 2005 (1)	0.9	1.1	32	0.9	1.3	24	0.00 [-0.64, 0.64]
14.1.2 Week 4							
Warady 2005 (2)	1	1.6	32	0.9	1.7	24	0.10 [-0.78, 0.98]

Mean Difference IV, Fixed, 95% CI
-1 -0.5 0 0.5 1
Favours Low dose Favours High dose
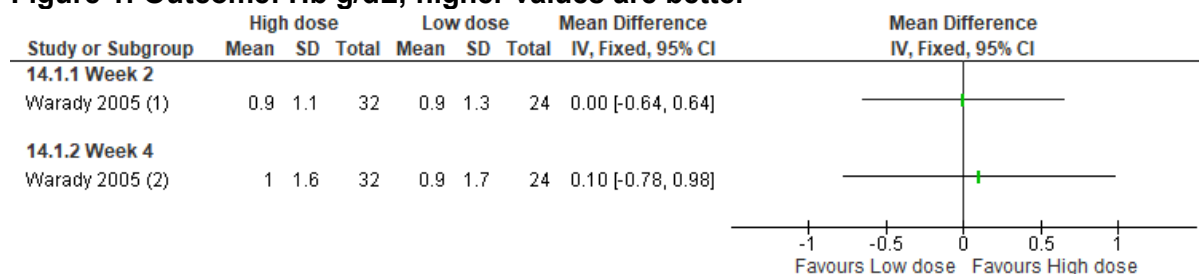
Footnotes
(1) SFGC (high=3.0 mg/kg) vs SFGC (low=1.5 mg/kg)
(2) SFGC (high=3.0 mg/kg) vs SFGC (low=1.5 mg/kg)

Figure 2: Outcome: Hb 10.5-14.0 g/dL; higher values are better

Study or Subgroup	High dose Events	Total	Low or very low dose Events	Total	Risk Ratio M-H, Fixed, 95% CI
14.2.1 High dose vs low dose					
Goldstein 2013 (1)	10	24	16	29	0.76 [0.42, 1.34]
14.2.2 High dose vs very low dose					
Goldstein 2013 (2)	10	24	17	29	0.71 [0.40, 1.25]
14.2.3 Low dose vs very low dose					
Goldstein 2013 (3)	16	29	17	29	0.94 [0.60, 1.47]

Risk Ratio M-H, Fixed, 95% CI
0.5 0.7 1 1.5 2
Favours low/very low dose Favours high/low dose

Footnotes
(1) IV iron sucrose (high=2.0 mg/kg) vs IV iron sucrose (low=1.0 mg/kg)
(2) IV iron sucrose (high=2.0 mg/kg) vs IV iron sucrose (very low=0.5 mg/kg)
(3) IV iron sucrose (low=1.0 mg/kg) vs IV iron sucrose (very low=0.5 mg/kg)

Figure 3: Outcome: Serum ferritin μg/L or ng mL; higher values are better

Study or Subgroup	High dose Mean	SD	Total	Low dose Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
14.3.1 Week 2							
Warady 2005 (1)	314	187.7	32	196.8	227.4	24	117.20 [5.37, 229.03]
14.3.2 Week 4							
Warady 2005 (2)	257.6	159.7	32	192.3	287.1	24	65.30 [-62.19, 192.79]
14.3.3 4 months							
Ruiz-Jaramillo 2004 (3)	334	401.697	20	66	286.316	20	268.00 [51.81, 484.19]

Mean Difference IV, Fixed, 95% CI
-500 -250 0 250 500
Favours Low dose Favours High dose

Footnotes
(1) IV SFGC (high=3.0 mg/kg) vs IV SFGC (low=1.5 mg/kg)
(2) IV SFGC (high=3.0 mg/kg) vs IV SFGC (low=1.5 mg/kg)
(3) IV iron dextran (low=6mg/kg per month) vs IV iron dextran (high=14.4mg/kg per month)

Adults

IV iron high dose vs low dose in adults with GFR category G5 who are on dialysis:
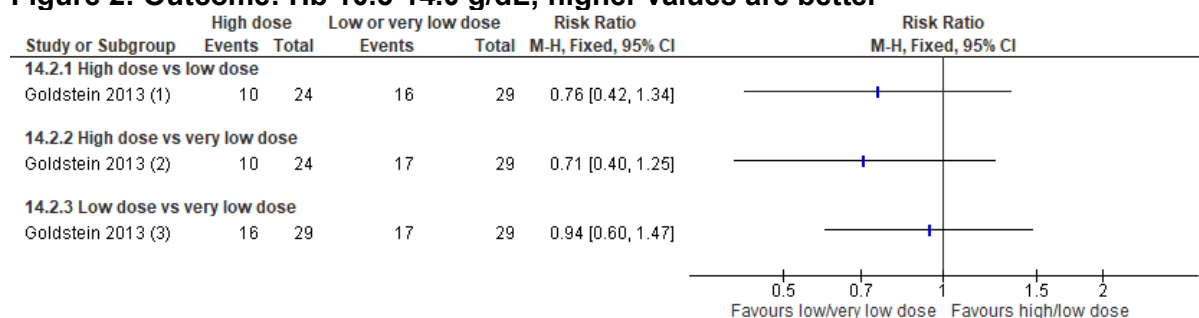
Figure 4: Outcome: Hb g/dL; higher values are better

Figure 5: Outcome: Ferritin ng/mL; higher values are better

Chronic kidney disease: evidence reviews for managing anaemia with IV iron DRAFT (Jan 2021)

Figure 6: Outcome: Haematocrit %; higher values are better

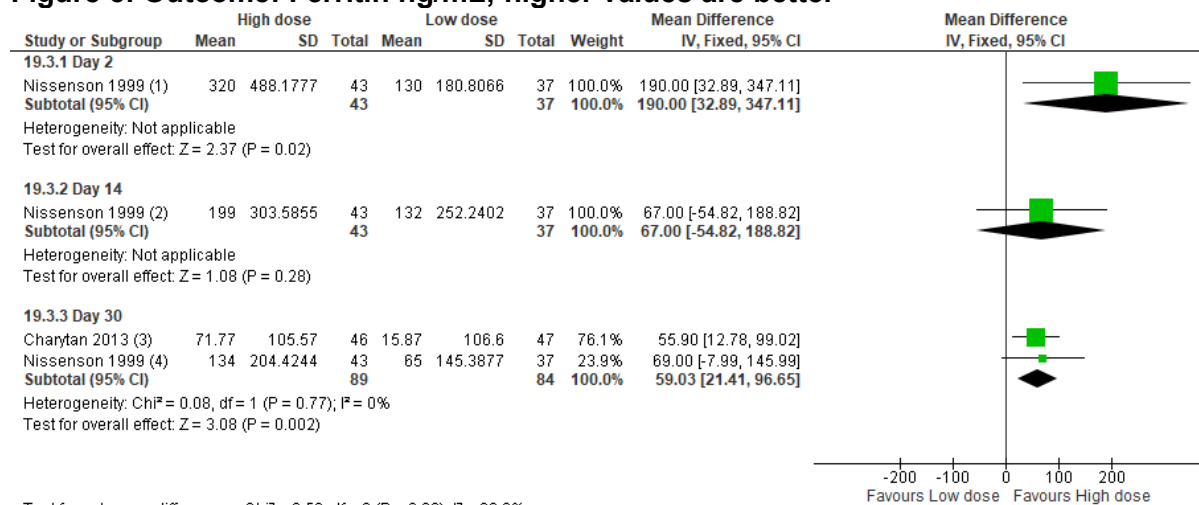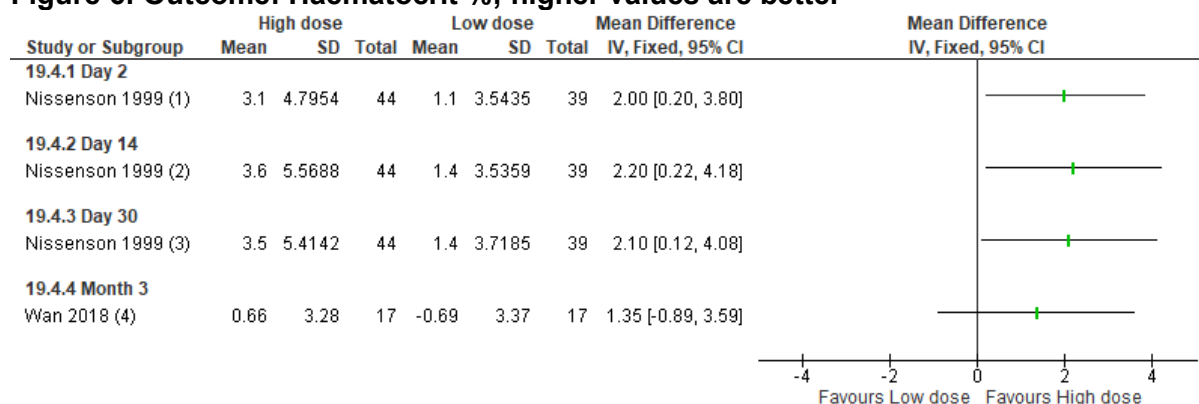| Study or Subgroup	High dose Mean	SD	Total	Low dose Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
19.4.1 Day 2							
Nissenson 1999 (1)	3.1	4.7954	44	1.1	3.5435	39	2.00 [0.20, 3.80]
19.4.2 Day 14							
Nissenson 1999 (2)	3.6	5.5688	44	1.4	3.5359	39	2.20 [0.22, 4.18]
19.4.3 Day 30							
Nissenson 1999 (3)	3.5	5.4142	44	1.4	3.7185	39	2.10 [0.12, 4.08]
19.4.4 Month 3							
Wan 2018 (4)	0.66	3.28	17	-0.69	3.37	17	1.35 [-0.89, 3.59]

Favours Low dose   Favours High dose

Footnotes
(1) IV SFGC in sucrose (high=1000mg) vs IV SFGC in sucrose (low=500mg)
(2) IV SFGC in sucrose (high=1000mg) vs IV SFGC in sucrose (low=500mg)
(3) IV SFGC in sucrose (high=1000mg) vs IV SFGC in sucrose (low=500mg)
(4) IV sucrose (high=continuous administration [1000mg within 1m]) vs IV sucrose (low=intermittent administration [1000mg within 3m])

Figure 7: Outcome: All-cause mortality; lower values are better
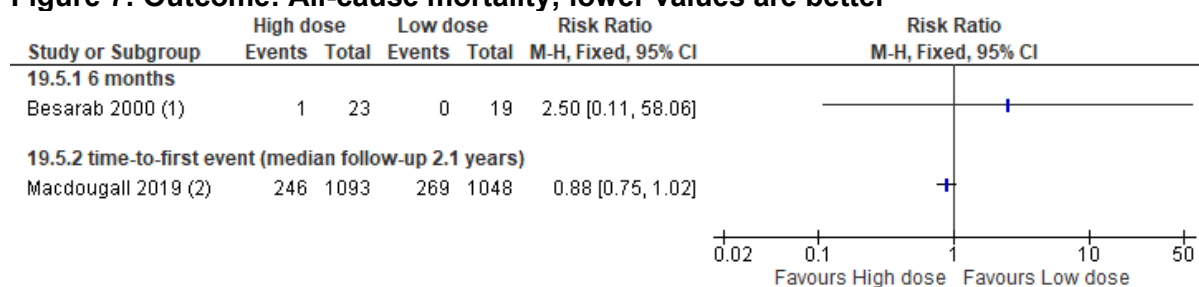
Study or Subgroup	High dose Events	Total	Low dose Events	Total	Risk Ratio M-H, Fixed, 95% CI
19.5.1 6 months					
Besarab 2000 (1)	1	23	0	19	2.50 [0.11, 58.06]
19.5.2 time-to-first event (median follow-up 2.1 years)					
Macdougall 2019 (2)	246	1093	269	1048	0.88 [0.75, 1.02]

Favours High dose   Favours Low dose

Footnotes
(1) IV dextran (high= to maintain TSAT 30 to 50%) vs IV dextran (low= to maintain TSAT 20 to 30%)
(2) IV sucrose (high= proactive [400mg monthly]) vs IV sucrose (low= reactive [0 to 400mg monthly])

Figure 8: Outcome: CV mortality; lower values are better
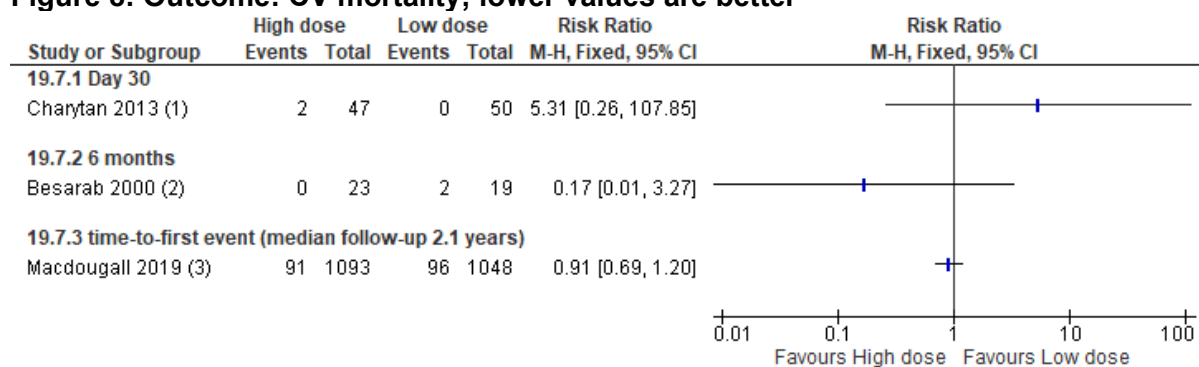
Study or Subgroup	High dose Events	Total	Low dose Events	Total	Risk Ratio M-H, Fixed, 95% CI
19.7.1 Day 30					
Charytan 2013 (1)	2	47	0	50	5.31 [0.26, 107.85]
19.7.2 6 months					
Besarab 2000 (2)	0	23	2	19	0.17 [0.01, 3.27]
19.7.3 time-to-first event (median follow-up 2.1 years)					
Macdougall 2019 (3)	91	1093	96	1048	0.91 [0.69, 1.20]

Favours High dose   Favours Low dose

Footnotes
(1) Standard medical care (high=mean 561 [SD 327.0]) vs IV ferric carboxymaltose (low=mean 200 [SD 0])
(2) IV dextran (high= to maintain TSAT at 30 to 50%) vs IV dextran (low= to maintain TSAT at 20 to 30%)
(3) IV sucrose (high= proactive [400mg monthly]) vs IV sucrose (low= reactive [0 to 400mg monthly])

Figure 9: Outcome: Adverse events; lower values are better
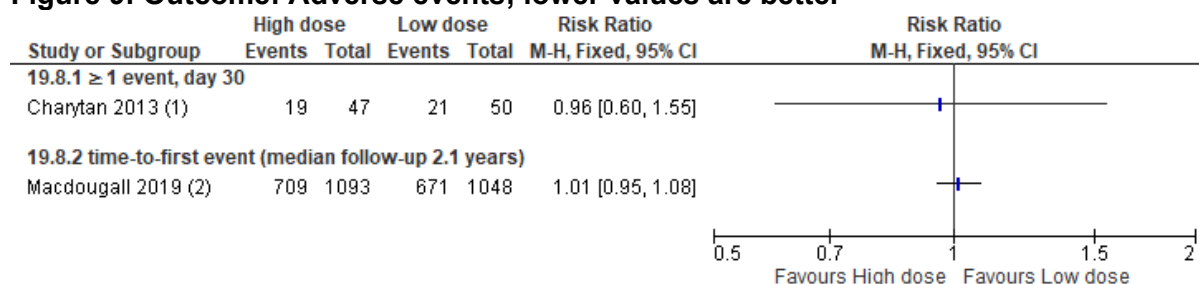
Footnotes
(1) Standard medical care (high=mean 561 [SD 327.0]) vs IV ferric carboxymaltose (low=mean 200 [SD 0])
(2) IV sucrose (high=proactive [400mg monthly]) vs IV sucrose (low=reactive [0 to 400mg monthly])

Figure 10:   Outcome: Adverse events (infection); lower values are better
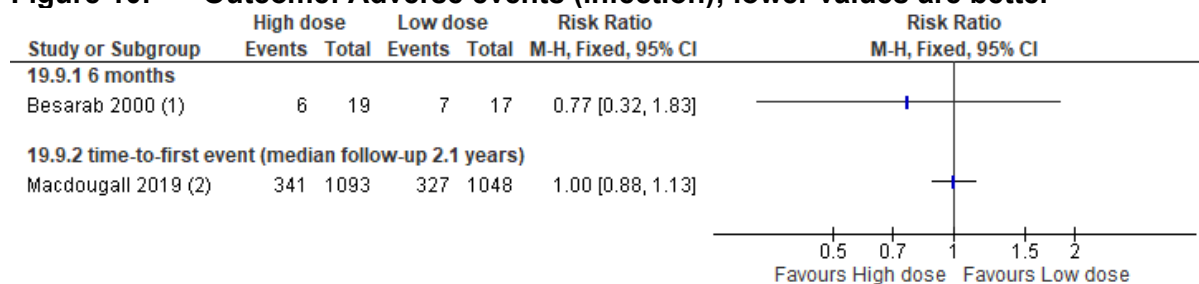
Footnotes
(1) IV dextran (high=to maintain TSAT at 30 to 50%) vs IV dextran (low=to maintain TSAT at 20 to 30%)
(2) IV sucrose (high=proactive [400mg monthly]) vs IV sucrose (low=reactive [0 to 400mg monthly])

Figure 11:   Outcome: Adverse events (hospitalisations); lower values are better

Footnotes
(1) IV dextran (high=to maintain TSAT at 30 to 50%) vs IV dextran (low=to maintain TSAT at 20 to 30%)
(2) IV sucrose (high=proactive [400mg monthly]) vs IV sucrose (low=reactive [0 to 400mg monthly])

Appendix G – GRADE tables

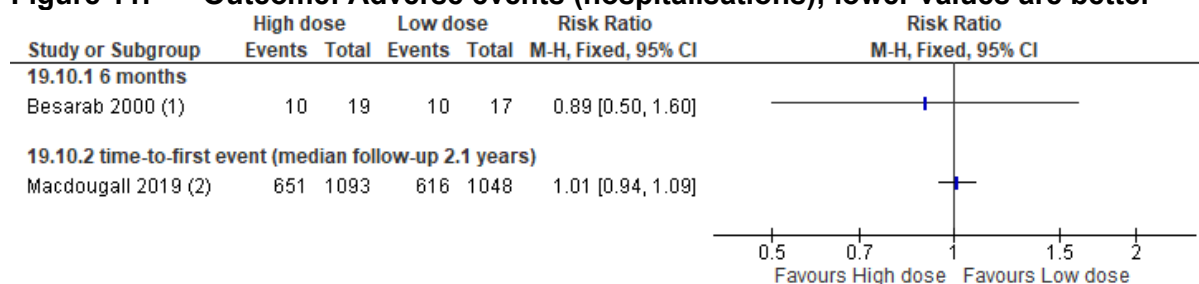## IV iron high dose vs low dose in children and young people

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron high dose	IV iron low dose	Relative (95% CI)	Absolute	MID for MDs*	Quality
			Quality assessment				No of patients		Effect		Estimated	
Hb g/dL - Week 2 (Better indicated by higher values)												
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	32	24	-	MD 0 higher (0.64 lower to 0.64 higher)	0.65	MODERATE
Hb g/dL - Week 4 (Better indicated by higher values)												
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	32	24	-	MD 0.1 higher (0.78 lower to 0.98 higher)	0.85	LOW
Hb 10.5-14.0 g/dL - High dose vs low dose												
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	very serious[5]	none	10/24 (41.7%)	16/29 (55.2%)	RR 0.76 (0.42 to 1.34)	13 fewer per 100 (from 32 fewer to 19 more)	-	VERY LOW
Hb 10.5-14.0 g/dL - High dose vs very low dose												
1	randomised trials[6]	serious[2]	no serious inconsistency	no serious indirectness	very serious[5]	none	10/24 (41.7%)	17/29 (58.6%)	RR 0.71 (0.4 to 1.25)	17 fewer per 100 (from 35 fewer to 15 more)	-	VERY LOW
Hb 10.5-14.0 g/dL - Low dose vs very low dose												
1	randomised trials[7]	serious[2]	no serious inconsistency	no serious indirectness	very serious[5]	none	16/29 (55.2%)	17/29 (58.6%)	RR 0.94 (0.6 to 1.47)	4 fewer per 100 (from 23 fewer to 28 more)	-	VERY LOW
Serum ferritin µg/L or ng mL - Week 2 (Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	32	24	-	MD 117.2 higher (5.37 to 229.03 higher)	113.7	LOW
Serum ferritin µg/L or ng mL - Week 4 (Better indicated by higher values)												

| 1 | randomised trials[1] | serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 32 | 24 | - | MD 65.3 higher (62.19 lower to 192.79 higher) | 143.55 | LOW |

Serum ferritin µg/L or ng mL - 4 months (Better indicated by higher values)

| 1 | randomised trials[8] | serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 20 | 20 | - | MD 268 higher (51.81 to 484.19 higher) | 143.15 | LOW |

Blood transfusions, 6 months

| 1 | randomised trials[8] | serious[2] | no serious inconsistency | no serious indirectness | very serious[3] | none | 3/20 (15%) | 0/20 (0%) | RR 7 (0.38 to 127.32) | - | - | VERY LOW |

Adverse events, week 4

| 1 | randomised trials[1] | serious[2] | no serious inconsistency | no serious indirectness | very serious[5] | none | 1/34 (2.9%) | 1/32 (3.1%) | RR 0.94 (0.06 to 14.42) | 0 fewer per 100 (from 3 fewer to 42 more) | - | VERY LOW |

[*] Calculated using the SD of the control group for individual studies or the median SD of the control group for pooled estimates
[1] Warady 2005; IV SFGC (high=3.0 mg/kg) vs SFGC (low=1.5 mg/kg)
[2] Study at moderate risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval
[4] Goldstein 2013; IV iron sucrose (high=2.0 mg/kg) vs IV iron sucrose (low=1.0 mg/kg)
[5] 95% confidence interval crosses both ends of a defined MID interval
[6] Goldstein 2013; IV iron sucrose (high=2.0 mg/kg) vs IV iron sucrose (very low=0.5 mg/kg)
[7] Goldstein 2013; IV iron sucrose (low=1.0 mg/kg) vs IV iron sucrose (very low=0.5 mg/kg)
[8] Ruiz-Jaramillo 2004; IV iron dextran (low=6mg/kg per month) vs IV iron dextran (high=14.4mg/kg per month)

IV iron high dose vs low dose in adults

| | Quality assessment | | | | | | No of patients | | Effect | | Estimated | |
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron high dose	IV iron low dose	Relative (95% CI)	Absolute	MID for MDs*	Importance
Hb level ≤12.5 g/dL - Day 30												
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	18/46 (39.1%)	16/47 (34%)	RR 1.15 (0.67 to 1.97)	5 more per 100 (from 11 fewer to 33 more)	-	VERY LOW
Hb g/l - Day 2 (Better indicated by higher values)												

1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	44	39	-	MD 0.7 higher (0.14 to 1.26 higher)	0.50	LOW
Hb g/l - Day 14 (Better indicated by higher values)												
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	44	39	-	MD 0.8 higher (0.21 to 1.39 higher)	0.50	LOW
Hb g/l - Day 30 (Better indicated by higher values)												
2	randomised trials[6]	serious[2]	serious[7]	no serious indirectness	serious[5]	none	89	86	-	MD 0.43 higher (0.14 lower to 1.0 higher)	0.51	VERY LOW
Hb g/l - Month 3 (Better indicated by higher values)												
1	randomised trials[8]	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	17	17	-	MD 0.38 higher (0.41 lower to 1.17 higher)	0.62	LOW
Ferritin ng/mL - Day 2 (Better indicated by higher values)												
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	43	37	-	MD 190 higher (32.89 to 347.11 higher)	90.40	LOW
Ferritin ng/mL - Day 14 (Better indicated by higher values)												
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	43	37	-	MD 67 higher (54.82 lower to 188.82 higher)	126.12	LOW
Ferritin ng/mL - Day 30 (Better indicated by higher values)												
2	randomised trials[9]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	89	84	-	MD 59.03 higher (21.41 to 96.65 higher)	125.99	MODERATE
Haematocrit % - Day 2 (Better indicated by higher values)												
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	44	39	-	MD 2.0 higher (0.2 to 3.8 higher)	1.77	LOW
Haematocrit % - Day 14 (Better indicated by higher values)												

1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	44	39	-	MD 2.2 higher (0.22 to 4.18 higher)	1.76	LOW

Haematocrit % - Day 30 (Better indicated by higher values)

1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	44	39	-	MD 2.1 higher (0.12 to 4.08 higher)	1.85	LOW

Haematocrit % - Month 3 (Better indicated by higher values)

1	randomised trials[8]	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	17	17	-	MD 1.35 higher (0.89 lower to 3.59 higher)	1.68	LOW

All-cause mortality - 6 months

1	randomised trials[10]	serious[2]	no serious inconsistency	no serious indirectness	serious[11]	none	1/23 (4.3%)	0/19 (0%)	RR 2.5 (0.11 to 58.06)	-	-	LOW

All-cause mortality - time-to-first event (median follow-up 2.1 years)

1	randomised trials[12]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[11]	none	246/1093 (22.5%)	269/1048 (25.7%)	RR 0.88 (0.75 to 1.02)	3 fewer per 100 (from 6 fewer to 1 more)	-	MODERATE

All-cause mortality: subgroups - Catheter access

1	randomised trials[12]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	102/452 (22.6%)	127/432 (29.4%)	RR 0.77 (0.61 to 0.96)	7 fewer per 100 (from 1 fewer to 11 fewer)	-	HIGH

All-cause mortality: subgroups - Fistula access

1	randomised trials[12]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[11]	none	144/641 (22.5%)	142/616 (23.1%)	RR 0.97 (0.79 to 1.19)	1 fewer per 100 (from 5 fewer to 4 more)	-	MODERATE

All-cause mortality: subgroups - Diabetes

1	randomised trials[12]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[11]	none	138/490 (28.2%)	149/453 (32.9%)	RR 0.86 (0.71 to 1.04)	5 fewer per 100 (from 10 fewer to 1 more)	-	MODERATE

All-cause mortality: subgroups - Non-diabetes

1	randomised trials[12]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[11]	none	108/603 (17.9%)	120/595 (20.2%)	RR 0.89 (0.7 to 1.12)	2 fewer per 100 (from 6 fewer to 2 more)	-	MODERATE

All-cause mortality: subgroups - Duration of dialysis <5 months

1	randomised trials[12]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[11]	none	103/499 (20.6%)	116/487 (23.8%)	RR 0.87 (0.69 to 1.1)	3 fewer per 100 (from 7 fewer to 2 more)	-	MODERATE

All-cause mortality: subgroups - Duration of dialysis ≥5 months

1	randomised trials[12]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[11]	none	143/594 (24.1%)	153/561 (27.3%)	RR 0.88 (0.73 to 1.07)	3 fewer per 100 (from 7 fewer to 2 more)	-	MODERATE

CV mortality - Day 30

1	randomised trials[6]	serious[2]	no serious inconsistency	no serious indirectness	serious[11]	none	2/47 (4.3%)	0/50 (0%)	RR 5.31 (0.26 to 107.85)	-	-	LOW

CV mortality - 6 months

1	randomised trials[10]	serious[2]	no serious inconsistency	no serious indirectness	serious[11]	none	0/23 (0%)	2/19 (10.5%)	RR 0.17 (0.01 to 3.27)	9 fewer per 100 (from 10 fewer to 24 more)	-	LOW

CV mortality - time-to-first event (median follow-up 2.1 years)

1	randomised trials[12]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[11]	none	91/1093 (8.3%)	96/1048 (9.2%)	RR 0.91 (0.69 to 1.2)	1 fewer per 100 (from 3 fewer to 2 more)	-	MODERATE

Adverse events - ≥1 event, day 30

1	randomised trials[6]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	19/47 (40.4%)	21/50 (42%)	RR 0.96 (0.6 to 1.55)	2 fewer per 100 (from 17 fewer to 23 more)	-	VERY LOW

Adverse events - time-to-first event (median follow-up 2.1 years)

1	randomised trials[12]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	709/1093 (64.9%)	671/1048 (64%)	RR 1.01 (0.95 to 1.08)	1 more per 100 (from 3 fewer to 5 more)	-	HIGH

Adverse events: infection - 6 months

1	randomised trials[10]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/19 (31.6%)	7/17 (41.2%)	RR 0.77 (0.32 to 1.83)	9 fewer per 100 (from 28 fewer to 34 more)	-	VERY LOW

Adverse events: infection - time-to-first event (median follow-up 2.1 years)

1	randomised trials[12]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	341/1093 (31.2%)	327/1048 (31.2%)	RR 1 (0.88 to 1.13)	0 fewer per 100 (from 4 fewer to 4 more)		HIGH
Adverse events: hospitalisations - 6 months												
1	randomised trials[10]	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	10/19 (52.6%)	10/17 (58.8%)	RR 0.89 (0.5 to 1.6)	6 fewer per 100 (from 29 fewer to 35 more)	-	VERY LOW
Adverse events: hospitalisations - time-to-first event (median follow-up 2.1 years)												
1	randomised trials[12]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	651/1093 (59.6%)	616/1048 (58.8%)	RR 1.01 (0.94 to 1.09)	1 more per 100 (from 4 fewer to 5 more)	-	HIGH
Adverse events: vascular access thrombosis - time-to-first event (median follow-up 2.1 years)												
1	randomised trials[12]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	262/1093 (24%)	218/1048 (20.8%)	RR 1.15 (0.98 to 1.35)	3 more per 100 (from 0 fewer to 7 more)	-	MODERATE
Blood transfusion - time-to-first event (median follow-up 2.1 years)												
1	randomised trials[12]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	198/1093 (18.1%)	226/1048 (21.6%)	RR 0.84 (0.71 to 1.0)	3 fewer per 100 (from 6 fewer to 0 more)	-	MODERATE

[*] Calculated using the SD of the control group for individual studies or the median SD of the control group for pooled estimates
[1] Charytan 2013; Standard medical care (high=mean 561 [SD 327.0]) vs IV Ferric carboxymaltose (low=mean 200 [SD 0])
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval
[4] Nissenson 1999; IV SFGC in sucrose (high=1000mg) vs IV SFGC in sucrose (low=500mg)
[5] 95% confidence interval crosses one end of a defined MID interval
[6] Charytan 2013; Standard medical care (high=mean 561 [SD 327.0]) vs IV ferric carboxymaltose (low=mean 200 [SD 0]). Nissenson 1999; IV SFGC in sucrose (high=1000mg) vs IV SFGC in sucrose (low=500mg)
[7] i-squared >33.3%; RE model was used for this subgroup (i-squared 54%)
[8] Wan 2018; IV sucrose (high=continuous administration [1000mg within 1m]) vs IV sucrose (low=intermittent administration [1000mg within 3m])
[9] Nissenson 1999; Charytan 2013
[10] Besarab 2000; IV dextran (high= to maintain TSAT 30 to 50%) vs IV dextran (low= to maintain TSAT 20 to 30%)
[11] 95% confidence interval crosses line of no effect
[12] Macdougall 2019; IV sucrose (high= proactive [400mg monthly]) vs IV sucrose (low= reactive [0 to 400mg monthly])

IV iron dextran MW 267,000 vs IV iron dextran MW 96,000, adults

Quality assessment	No of patients	Effect	Estimated MID for MDs*	Quality

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron dextran MW 267,000	IV iron dextran MW 96,000	Relative (95% CI)	Absolute		
Hb g/dL - week 1 (Better indicated by higher values)												
1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	9	11	-	MD 0.59 higher (0.16 lower to 1.34 higher)	0.43	VERY LOW
Hb g/dL - week 2 (Better indicated by higher values)												
1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	9	11	-	MD 0.3 higher (0.49 lower to 1.09 higher)	0.49	VERY LOW
Hb g/dL - week 3 (Better indicated by higher values)												
1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	9	11	-	MD 0.77 higher (0.08 to 1.46 higher)	0.42	VERY LOW
Hb g/dL - week 4 (Better indicated by higher values)												
1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	9	11	-	MD 0.77 higher (0.06 to 1.48 higher)	0.46	VERY LOW
Serum ferritin µg/L - week 1 (Better indicated by higher values)												
1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	9	11	-	MD 341.5 higher (386.54 lower to 1069.54 higher)[5]	70.84	VERY LOW
Serum ferritin µg/L - week 2 (Better indicated by higher values)												
1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	9	11	-	MD 5.2 higher (85.87 lower to 96.27 higher)	45.75	VERY LOW
Serum ferritin µg/L - week 3 (Better indicated by higher values)												
1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	9	11	-	MD 3.7 higher (84.66 lower to 92.06 higher)	45.89	VERY LOW
Serum ferritin µg/L - week 4 (Better indicated by higher values)												
1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	9	11	-	MD 24.1 lower (113.35 lower to 65.15 higher)	48.15	VERY LOW

* Calculated using the SD of the control group for individual studies or the median SD of the control group for pooled estimates
[1] Roe 1996
[2] Study at high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval
[4] 95% confidence interval crosses both ends of a defined MID interval
[5] IV iron dextran MW 267,000 includes an extreme value of 3,670 µg/L for a single patient

IV iron sucrose (500mg) vs IV iron isomaltoside 1000 (500mg), adults, week 6

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron sucrose (500mg)	IV iron isomaltoside 1000 (500mg)	Relative (95% CI)	Absolute	

Hb >12.5 g/dL											
1	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	11/115 (9.6%)	22/226 (9.7%)	RR 0.98 (0.49 to 1.96)	0 fewer per 100 (from 5 fewer to 9 more)	LOW
All-cause mortality											
1	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	0/117 (0%)	3/234 (1.3%)	RR 0.28 (0.01 to 5.46)	1 fewer per 100 (from 1 fewer to 6 more)	MODERATE
Adverse events											
1	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	59/116 (50.9%)	110/230 (47.8%)	RR 1.06 (0.85 to 1.33)	3 more per 100 (from 7 fewer to 16 more)	MODERATE

[1] Bhandari 2015
[2] 95% confidence interval crosses both ends of a defined MID interval
[3] 95% confidence interval crosses line of no effect
[4] 95% confidence interval crosses one end of a defined MID interval

IV iron sucrose (1000mg) vs IV ferric chloride hexahydrate (1000mg), adults, week 10

Quality assessment							No of patients		Effect		Estimated MID for MDs*	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron sucrose (1000mg)	IV ferric chloride hexahydrate (1000mg)	Relative (95% CI)	Absolute		
Serum ferritin µg/L (Better indicated by higher values)												
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	26	30	-	MD 129 higher (34.41 lower to 292.41 higher)	179.51	LOW
Haematocrit (%) (Better indicated by higher values)												
1	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	26	30	-	MD 1 higher (0.83 lower to 2.83 higher)	1.34	LOW

* Calculated using the SD of the control group for individual studies or the median SD of the control group for pooled estimates
[1] Hsiao 2016
[2] Study at moderate risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval

IV ferric saccharate (100mg/week) vs IV ferric saccharate (2 x 50mg/week), adults, 2 months

Quality assessment							No of patients		Effect		Estimated MID for MDs*	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV ferric saccharate (100mg/week)	IV ferric saccharate (2 x 50mg/week)	Relative (95% CI)	Absolute		
Serum ferritin µg/L (Better indicated by higher values)												

1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	10	7	-	MD 9 higher (49.9 lower to 67.9 higher)	15	VERY LOW
Haematocrit % (Better indicated by higher values)												
1	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	10	7	-	MD 2.8 lower (6.2 lower to 0.6 higher)	2.1	VERY LOW

* Calculated using the SD of the control group for individual studies or the median SD of the control group for pooled estimates
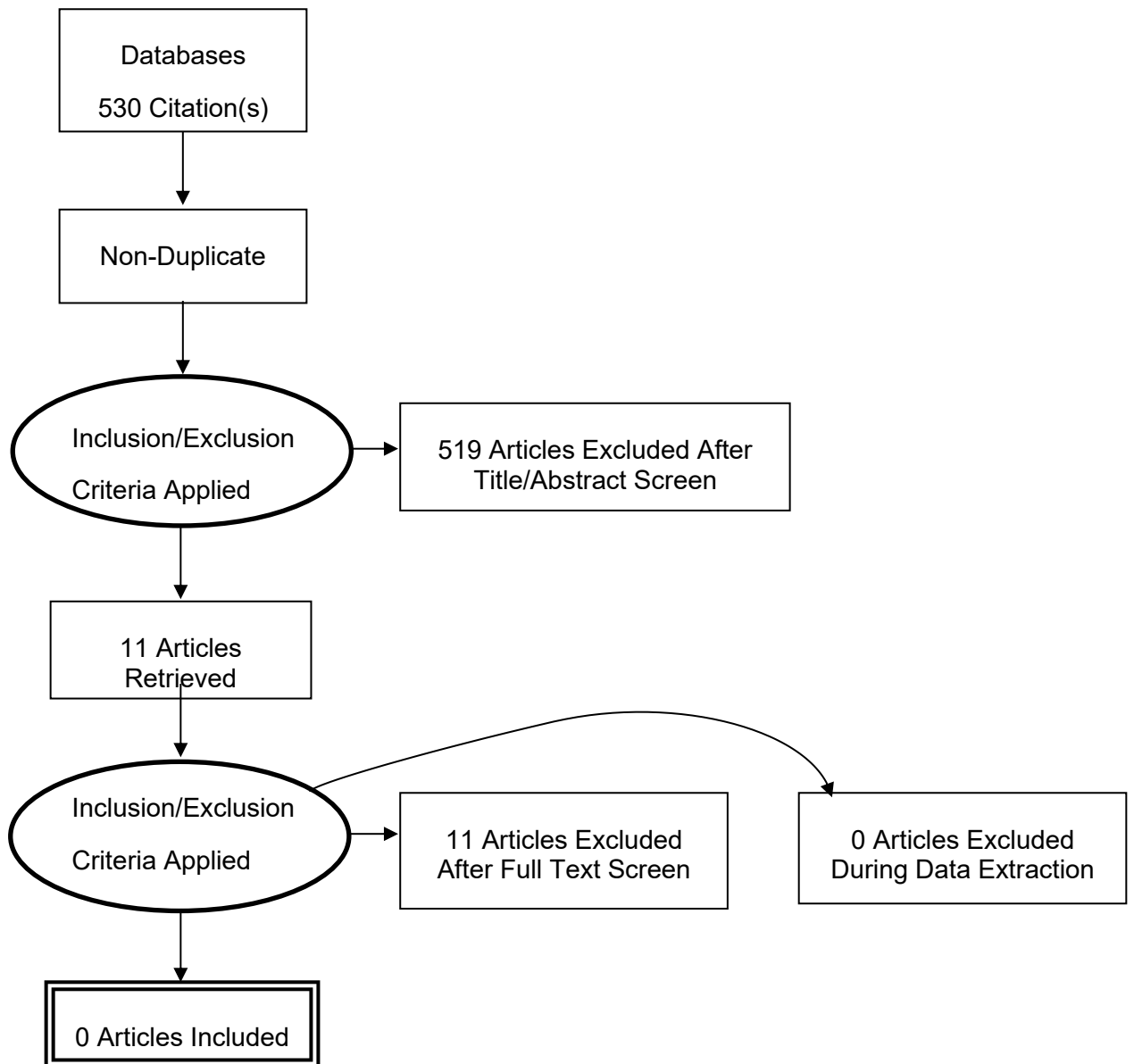[1] Akcicek 1997
[2] Study at high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval
[4] 95% confidence interval crosses one end of a defined MID interval

Appendix H – Economic evidence study selection

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┌─────────────────────┐
│     Databases       │
│                     │
│  530 Citation(s)    │
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│   Non-Duplicate     │
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   ╱ Inclusion/    ╲───────▶│  519 Articles Excluded   │
  │  Exclusion      │       │  After Title/Abstract    │
   ╲ Criteria       ╱       │  Screen                  │
    ╲ Applied      ╱        └──────────────────────────┘
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│   11 Articles       │
│   Retrieved         │
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   ╱ Inclusion/    ╲───▶│ 11 Articles Excluded │     │ 0 Articles Excluded  │
  │  Exclusion      │    │ After Full Text      │     │ During Data          │
   ╲ Criteria       ╱    │ Screen               │     │ Extraction           │
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Chronic kidney disease: evidence reviews for managing anaemia with IV iron DRAFT (Jan 2021)

Appendix I – Economic evidence tables

None – no economic evaluations relevant to the review question were found.

Appendix J – Health economic model

None – no economic evaluations relevant to the review question were found.

Appendix K – Excluded studies

Clinical studies

Study	Reason for exclusion
Adhikary, L and Acharya, S (2011) Efficacy of IV iron compared to oral iron for increment of haemoglobin level in anemic chronic kidney disease patients on erythropoietin therapy. JNMA; journal of the nepal medical association 51(183): 133-136	- Not a relevant study design
Agarwal, Rajiv; Kusek, John W; Pappas, Maria K (2015) A randomized trial of intravenous and oral iron in chronic kidney disease. Kidney international 88(4): 905-14	- Does not contain a population of people on dialysis
Agarwal, Rajiv, Leehey, David J, Olsen, Scott M et al. (2011) Proteinuria induced by parenteral iron in chronic kidney disease--a comparative randomized controlled trial. Clinical journal of the American Society of Nephrology : CJASN 6(1): 114-21	- Does not contain a population of people on dialysis
Ahsan, N (2000) Infusion of total dose iron versus oral iron supplementation in ambulatory peritoneal dialysis patients: a prospective, cross-over trial. Advances in peritoneal dialysis. Conference on peritoneal dialysis 16: 80-84	- Comparator in study does not match that specified in protocol
Albaramki Jumana, Hodson Elisabeth M, Craig Jonathan C, Webster Angela C (2012) Parenteral versus oral iron therapy for adults and children with chronic kidney disease. Cochrane Database of Systematic Reviews: Reviews issue1	- Comparator in study does not match that specified in protocol
Albaramki Jumana, Hodson Elisabeth M, Craig Jonathan C, Webster Angela C (2012) Parenteral versus oral iron therapy for adults and children with chronic kidney disease. Cochrane Database of Systematic Reviews: Reviews issue1	- Duplicate reference
Allegra, V; Mengozzi, G; Vasile, A (1991) Iron deficiency in maintenance hemodialysis patients: assessment of diagnosis criteria and of three different iron treatments. Nephron 57(2): 175-182	- Not a relevant study design
Anirban, Ganguli, Kohli, H S, Jha, Vivekanand et al. (2008) The comparative safety of various intravenous iron preparations in chronic kidney disease patients. Renal failure 30(6): 629-38	- Does not contain a population of people on dialysis Mixed conservative management and RRT
Auerbach, M, Winchester, J, Wahab, A et al. (1998) A randomized trial of three iron dextran infusion methods for anemia in EPO-treated dialysis patients. American journal of kidney diseases : the official journal of the National Kidney Foundation 31(1): 81-6	- Data not reported in an extractable format
Bregman D.B. and Goodnough L.T. (2014) Experience with intravenous ferric carboxymaltose in patients with iron deficiency	- Review article but not a systematic review

Study	Reason for exclusion
anemia. Therapeutic Advances in Hematology 5(2): 48-60	
Broumand, B, Ghods, A, Taheri, FM et al. (1998) Intravenous versus oral iron supplementation in the management of anemia in end stage renal disease. 35th congress. European renal association. European dialysis and transplantation association; 1998 jun 6-9; rimini, italy: 330	- Full text paper not available
Chertow, Glenn M, Mason, Phillip D, Vaage-Nilsen, Odd et al. (2004) On the relative safety of parenteral iron formulations. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 19(6): 1571-5	- Not a relevant study design
DeVita, M V, Frumkin, D, Mittal, S et al. (2003) Targeting higher ferritin concentrations with intravenous iron dextran lowers erythropoietin requirement in hemodialysis patients. Clinical nephrology 60(5): 335-40	- Study does not contain a relevant intervention RCT using single formulation but with different target levels for Hb
Dull, R B and Davis, E (2015) Heme iron polypeptide for the management of anaemia of chronic kidney disease. Journal of clinical pharmacy and therapeutics 40(4): 386-90	- Study does not contain a relevant intervention
Fishbane S., Shapiro W., Dutka P. et al. (2001) A randomized trial of iron deficiency testing strategies in hemodialysis patients. Kidney International 60(6): 2406-2411	- Study does not contain a relevant intervention
Fishbane, S; Frei, G L; Maesaka, J (1995) Reduction in recombinant human erythropoietin doses by the use of chronic intravenous iron supplementation. American journal of kidney diseases : the official journal of the National Kidney Foundation 26(1): 41-6	- Comparator in study does not match that specified in protocol iv vs oral
Fudin, R, Jaichenko, J, Shostak, A et al. (1998) Correction of uremic iron deficiency anemia in hemodialyzed patients: a prospective study. Nephron 79(3): 299-305	- Comparator in study does not match that specified in protocol no vs iv vs oral
Fukao, Wataru, Hasuike, Yukiko, Yamakawa, Tomo et al. (2018) Oral Versus Intravenous Iron Supplementation for the Treatment of Iron Deficiency Anemia in Patients on Maintenance Hemodialysis-Effect on Fibroblast Growth Factor-23 Metabolism. Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation 28(4): 270-277	- Comparator in study does not match that specified in protocol
Gillespie, Robert S and Wolf, Fredric M (2004) Intravenous iron therapy in pediatric hemodialysis patients: a meta-analysis. Pediatric nephrology (Berlin, Germany) 19(6): 662-6	- Systematic review used as source of primary studies
Gupta, A, Amin, NB, Besarab, A et al. (1999) Dialysate iron therapy: infusion of soluble ferric pyrophosphate via the dialysate during	- Not a relevant study design

Study	Reason for exclusion
hemodialysis. Kidney international 55(5): 1891-1898	
Hougen I., Collister D., Bourrier M. et al. (2018) Safety of intravenous iron in dialysis: A systematic review and meta-analysis. Clinical Journal of the American Society of Nephrology 13(3): 457-467	- Systematic review used as source of primary studies
Jacobs, Claude; Frei, Dieter; Perkins, Alan C (2005) Results of the European Survey on Anaemia Management 2003 (ESAM 2003): current status of anaemia management in dialysis patients, factors affecting epoetin dosage and changes in anaemia management over the last 5 years. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 20suppl3: iii3-24	- Not a relevant study design - Study does not contain a relevant intervention
Johnson, DW, Herzig, KA, Gissane, R et al. (2001) A prospective crossover trial comparing intermittent intravenous and continuous oral iron supplements in peritoneal dialysis patients. Nephrology, dialysis, transplantation 16(9): 1879-1884	- Comparator in study does not match that specified in protocol
Kao, H H, Chen, K S, Tsai, C J et al. (2000) Clinical characteristic of parenteral iron supplementation in hemodialysis patients receiving erythropoietin therapy. Chang Gung medical journal 23(10): 608-13	- Full text paper not available
Kato, A, Hamada, M, Suzuki, T et al. (2001) Effect of weekly or successive iron supplementation on erythropoietin doses in patients receiving hemodialysis. Nephron 89(1): 110-112	- Comparator in study does not match that specified in protocol
Kotaki, M, Uday, K, Henriquez, M et al. (1997) Maintenance therapy with intravenous iron in hemodialysis patients receiving erythropoietin. Clinical nephrology 48(1): 63-4	- Letter to editor
Kuji T., Toya Y., Fujikawa T. et al. (2015) Acceleration of iron utilization after intravenous iron administration during activated erythropoiesis in hemodialysis patients: A randomized study. Therapeutic Apheresis and Dialysis 19(2): 131-137	- Aim of study does not match protocol to evaluate the effect of different timings of iron administration during erythropoiesis activated by continuous erythropoietin receptor activator (CERA) on reticulocyte iron uptake
Kuragano, T, Yahiro, M, Kida, A et al. (2014) Effect of protoconized therapy for renal anemia on adverse events of patients with maintenance hemodialysis. International journal of artificial organs 37(12): 865-874	- Study does not contain a relevant intervention mixture of oral and sometimes IV iron
Leehey, David J, Palubiak, David J, Chebrolu, Srivasa et al. (2005) Sodium ferric gluconate causes oxidative stress but not acute renal injury in patients with chronic kidney disease: a pilot study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 20(1): 135-40	- NAC was given prior to each iron infusion to prevent oxidative stress

Study	Reason for exclusion
Li, H and Wang, SX (2009) Intravenous iron sucrose in maintenance dialysis patients with renal anemia: a clinical study. Zhonghua yi xue za zhi 89(7): 457-462	- Study not reported in English
Li, Han and Wang, Shi-xiang (2008) Intravenous iron sucrose in Chinese hemodialysis patients with renal anemia. Blood purification 26(2): 151-6	- Comparator in study does not match that specified in protocol
Li, Han and Wang, Shi-Xiang (2008) Intravenous iron sucrose in peritoneal dialysis patients with renal anemia. Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis 28(2): 149-54	- Comparator in study does not match that specified in protocol
Macdougall I.C., Tucker B., Thompson J. et al. (1996) A randomized controlled study of iron supplementation in patients treated with erythropoietin. Kidney International 50(5): 1694-1699	- Comparator in study does not match that specified in protocol
Macdougall, IC, Bock, A, Carrera, F et al. (2013) FIND-CKD: a 56-week randomized trial of intravenous ferric carboxymaltose versus oral iron in anemic patients with chronic kidney disease and iron defi ciency. Journal of the american society of nephrology : JASN 24(abstracts): 3b	- Conference abstract
McMahon, Lawrence P, Kent, Annette B, Kerr, Peter G et al. (2010) Maintenance of elevated versus physiological iron indices in non-anaemic patients with chronic kidney disease: a randomized controlled trial. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 25(3): 920-6	- Comparator in study does not match that specified in protocol
McMahon, LP, Kent, AB, Roger, SD et al. (2007) IV iron sucrose versus oral iron for the anemia of chronic kidney disease (CKD) - a randomized controlled trial. Journal of the american society of nephrology : JASN 18(abstractsue): 813a	- Conference abstract
Michael, Beckie, Coyne, Daniel W, Fishbane, Steven et al. (2002) Sodium ferric gluconate complex in hemodialysis patients: adverse reactions compared to placebo and iron dextran. Kidney international 61(5): 1830-9	- Comparator in study does not match that specified in protocol historical control vs placebo vs iv
Michelis R.; Sela S.; Kristal B. (2005) Intravenous iron-gluconate during haemodialysis modifies plasma beta2-microglobulin properties and levels. Nephrology Dialysis Transplantation 20(9): 1963-1969	- Not a relevant study design
O'Lone, Emma L, Hodson, Elisabeth M, Nistor, Ionut et al. (2019) Parenteral versus oral iron therapy for adults and children with chronic kidney disease. The Cochrane database of systematic reviews 2: cd007857	- Study does not contain a relevant intervention
Park, Jongha, Chang, Jai Won, Lee, Jong Soo et al. (2009) Efficacy of low-dose i.v. iron	- Comparator in study does not match that specified in protocol

Study	Reason for exclusion
therapy in haemodialysis patients. Nephrology (Carlton, Vic.) 14(8): 716-21	
Pollock, R.F. and Muduma, G. (2020) A patient-level cost-effectiveness analysis of iron isomaltoside versus ferric carboxymaltose for the treatment of iron deficiency anemia in the United Kingdom. Journal of Medical Economics 23(7): 751-759	- Does not contain a population of people on dialysis
Ragab M.; Mahmoud K.; Ragab A. (2007) Maintenance intravenous iron sucrose therapy in children under regular hemodialysis. Journal of Medical Sciences 7(7): 1112-1116	- Comparator in study does not match that specified in protocol
Rath, Thomas, Florschutz, Kai, Kalb, Klaus et al. (2010) Low-molecular-weight iron dextran in the management of renal anaemia in patients on haemodialysis--the IDIRA Study. Nephron. Clinical practice 114(1): c81-8	- Not a relevant study design
Roger, Simon D, Tio, Martin, Park, Hyeong-Cheon et al. (2017) Intravenous iron and erythropoiesis-stimulating agents in haemodialysis: A systematic review and meta-analysis. Nephrology (Carlton, Vic.) 22(12): 969-976	- Systematic review used as source of primary studies
Rozen-Zvi, Benaya, Gafter-Gvili, Anat, Paul, Mical et al. (2008) Intravenous versus oral iron supplementation for the treatment of anemia in CKD: systematic review and meta-analysis. American journal of kidney diseases : the official journal of the National Kidney Foundation 52(5): 897-906	- Comparator in study does not match that specified in protocol
Saltissi, D; Sauvage, D; Westhuyzen, J (1998) Comparative response to single or divided doses of parenteral iron for functional iron deficiency in hemodialysis patients receiving erythropoietin (EPO). Clinical nephrology 49(1): 45-48	- Data not reported in an extractable format
Sav, Tansu, Tokgoz, Bulent, Sipahioglu, Murat Hayri et al. (2007) Is there a difference between the allergic potencies of the iron sucrose and low molecular weight iron dextran?. Renal failure 29(4): 423-6	- Does not contain a population of people on dialysis Mixed pop with 35% not on dialysis
Shepshelovich, Daniel, Rozen-Zvi, Benaya, Avni, Tomer et al. (2016) Intravenous Versus Oral Iron Supplementation for the Treatment of Anemia in CKD: An Updated Systematic Review and Meta-analysis. American journal of kidney diseases : the official journal of the National Kidney Foundation 68(5): 677-690	- Comparator in study does not match that specified in protocol
Sirken, G; Raja, R; Rizkala, A R (2006) Association of different intravenous iron preparations with risk of bacteremia in maintenance hemodialysis patients. Clinical nephrology 66(5): 348-56	- Not a relevant study design
St. Peter W.L.; Lambrecht L.J.; Macres M. (1996) Randomized cross-over study of adverse	- Data not reported in an extractable format

Study	Reason for exclusion
reactions and cost implications of intravenous push compared with infusion of iron dextran in hemodialysis patients. American Journal of Kidney Diseases 28(4): 523-528	
Sunder-Plassmann, G and Horl, W H (1995) Importance of iron supply for erythropoietin therapy. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 10(11): 2070-6	- Not a relevant study design
Susantitaphong, P., Siribumrungwong, M., Takkavatakarn, K. et al. (2020) Effect of Maintenance Intravenous Iron Treatment on Erythropoietin Dose in Chronic Hemodialysis Patients: A Multicenter Randomized Controlled Trial. Canadian Journal of Kidney Health and Disease 7	- Study does not contain a relevant intervention Unclear what iron supplement was used
Svára, F, Sulková, S, Kvasnićka, J et al. (1996) Iron supplementation during erythropoietin therapy in patients on hemodialysis. Vnitrni lekarstvi 42(12): 849-852	- Full text paper not available
Tsuchida A., Paudyal B., Paudyal P. et al. (2010) Effectiveness of oral iron to manage anemia in long-term hemodialysis patients with the use of ultrapure dialysate. Experimental and Therapeutic Medicine 1(5): 777-781	- Study does not contain a relevant intervention
Visciano, B, Nazzaro, P, Tarantino, G et al. (2013) Liposomial iron: a new proposal for the treatment of anaemia in chronic kidney disease. Giornale italiano di nefrologia 30(5)	- Study not reported in English
Warady B.A., Kausz A., Lerner G. et al. (2004) Iron therapy in the pediatric hemodialysis population. Pediatric Nephrology 19(6): 655-661	- Comparator in study does not match that specified in protocol
Weiss, Gunter and Kronenberg, Florian (2015) Intravenous iron administration: new observations and time for the next steps. Kidney international 87(1): 10-2	- Not a relevant study design Commentary
Wingard, R L, Parker, R A, Ismail, N et al. (1995) Efficacy of oral iron therapy in patients receiving recombinant human erythropoietin. American journal of kidney diseases : the official journal of the National Kidney Foundation 25(3): 433-9	- Study does not contain a relevant intervention
Wu, Chih-Jen, Lin, Hsin-Chang, Lee, Kun-Feng et al. (2010) Comparison of parenteral iron sucrose and ferric chloride during erythropoietin therapy of haemodialysis patients. Nephrology (Carlton, Vic.) 15(1): 42-7	- Data not reported in an extractable format Reported as medians
Yin, L, Chen, X, Chen, J et al. (2012) Multi-frequency low-dose intravenous iron on oxidative stress in maintenance hemodialysis patients. Zhong nan da xue xue bao. Yi xue ban [Journal of Central South University. Medical sciences] 37(8): 844-848	- Study not reported in English

Study	Reason for exclusion
Ziedan A. and Bhandari S. (2019) Protocol and baseline data for a prospective open-label explorative randomized single-center comparative study to determine the effects of various intravenous iron preparations on markers of oxidative stress and kidney injury in chronic kidney disease (IRON-CKD). Trials 20(1): 194	- Not a relevant study design Protocol
Zitt E., Sturm G., Kronenberg F. et al. (2014) Iron supplementation and mortality in incident dialysis patients: An observational study. PLoS ONE 9(12): e114144	- Not a relevant study design

Economic studies

Study	Reason
Aiello, Andrea, Berto, Patrizia, Conti, Paolo et al. (2020) Economic impact of ferric carboxymaltose in haemodialysis patients. Giornale italiano di nefrologia : organo ufficiale della Societa italiana di nefrologia 37(suppl75)	Study not reported in English
Besarab, A, Amin, N, Ahsan, M et al. (2000) Optimization of epoetin therapy with intravenous iron therapy in hemodialysis patients. Journal of the American Society of Nephrology: JASN 11(3): 530-8	Does not include quality of life data.
Bhandari, Sunil (2011) A hospital-based cost minimization study of the potential financial impact on the UK health care system of introduction of iron isomaltoside 1000. Therapeutics and clinical risk management 7: 103-13	Does not include quality of life data.
Dahl N.V., Kaper R.F., Strauss W.E. et al. (2017) Cost-effectiveness analysis of intravenous ferumoxytol for the treatment of iron deficiency anemia in adult patients with non-dialysis-dependent chronic kidney disease in the USA. ClinicoEconomics and Outcomes Research 9: 557-567	Does not include quality of life data.
Darba, Josep and Ascanio, Meritxell (2018) Budget Impact Analysis of Oral Fisiogen Ferro Forte versus Intravenous Iron for the Management of Iron Deficiency in Chronic Kidney Disease in Spain. Clinical drug investigation 38(9): 801-811	Does not include quality of life data.
Fragoulakis V., Kourlaba G., Goumenos D. et al. (2012) Economic evaluation of intravenous iron treatments in the management of anemia patients in Greece. ClinicoEconomics and Outcomes Research 4(1): 127-134	Does not include quality of life data.
Pollock, R.F. and Muduma, G. (2020) A patient-level cost-effectiveness analysis of iron	Does not contain a population of people with CKD

Study	Reason
isomaltoside versus ferric carboxymaltose for the treatment of iron deficiency anemia in the United Kingdom. Journal of Medical Economics 23(7): 751-759	
Rognoni, Carla, Ortalda, Vittorio, Biasi, Caterina et al. (2019) Economic Evaluation of Ferric Carboxymaltose for the Management of Hemodialysis Patients with Iron Deficiency Anemia in Italy. Advances in therapy 36(11): 3253-3264	Does not include quality of life data
Sepandj, F, Jindal, K, West, M et al. (1996) Economic appraisal of maintenance parenteral iron administration in treatment of anaemia in chronic haemodialysis patients. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association 11(2): 319-22	Does not include quality of life data.
Wilson, Paul D, Hutchings, Adam, Jeans, Aruna et al. (2013) An analysis of the health service efficiency and patient experience with two different intravenous iron preparations in a UK anaemia clinic. Journal of medical economics 16(1): 108-14	Does not include quality of life data.
Wong, Germaine, Howard, Kirsten, Hodson, Elisabeth et al. (2013) An economic evaluation of intravenous versus oral iron supplementation in people on haemodialysis. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association 28(2): 413-20	Compares oral versus IV rather than IV versus IV iron.

Appendix L – Research recommendations – full details

L.1.1 Research recommendation

For people with GFR category G5 who are on dialysis but not on ESA, what amount of intravenous iron is most clinically and cost effective in managing anaemia and its associated outcomes?

L.1.2 Why this is important

All the evidence for intravenous iron in managing anaemia was derived from RCTs that recruited adults, children and young people with GFR category G5 who were on dialysis and ESA.

Further research needs to explore the clinical and cost-effectiveness of intravenous iron in managing anaemia in adults, children and young people with GFR category G5 who are on dialysis but not on ESA.

L.1.3 Rationale for research recommendation

Importance to 'patients' or the population	Little is known about the clinical and cost-effectiveness of intravenous iron in managing anaemia in adults, children and young people with GFR category G5 who are on dialysis but not on ESA.
Relevance to NICE guidance	This guideline has considered evidence on intravenous iron in managing anaemia in adults, children and young people with GFR category G5 and there is a lack of data on those who are on dialysis but not on ESA.
Relevance to the NHS	The outcome would affect the types of treatment provided by the NHS for managing anaemia in adults, children and young people with GFR category G5 who are on dialysis but not on ESA and may also predict future healthcare needs for this population.
National priorities	High
Current evidence base	None
Equality considerations	None known

L.1.4 Modified PICO table

Population	Inclusion:
	Adults, children and young people with a clinical diagnosis of anaemia and CKD 5 and who are on dialysis but not on ESA.
	Exclusion:
	Management of anaemia in people whose anaemia is not principally caused by CKD.
	Ferumoxytol (withdrawn due to safety concerns)

Intervention	**IV iron**
	• Ferric carboxymaltose
	• Iron dextran
	• Iron isomaltoside 1000
	• Iron polymaltose
	• Iron sucrose
	• Sodium ferric gluconate complex (SFGC)
Comparator	Other doses/schedules/formulations of IV iron
Outcome	**Primary outcomes:**
	Hb level
	• Other markers of anaemia (for example serum ferritin)
	• All-cause mortality
	• CV specific mortality
	• Adverse events (infection, vascular access thrombosis, hypertension, hospitalization, anaphylaxis)
	Secondary outcomes:
	• Incidence of blood transfusions
	• QoL
Study design	RCT
Timeframe	Long term
Additional information	This RCT should be carried out within the UK.
	The study should be powered to detect the superiority of the interventions over the comparators.
	Subgroup analyses should include:
	• People on ESA vs not on ESA
	• Catheter vs fistula access
	• Diabetes vs non-diabetes
	• Duration of dialysis

L.1.5 Research recommendation

What are the long-term consequences of high ferritin levels (>800) in children and young people with CKD?

L.1.6 Why this is important

The committee agreed that for some children and young people where estimates of iron status (e.g. reticulocyte haemoglobin, hypochromic red blood cells) are out of range, iron would be given clinically even if serum ferritin levels were high. It therefore agreed that it was important to understand the long-term consequences of high serum ferritin.

L.1.7 Rationale for research recommendation

Importance to 'patients' or the population	Little is known about the long-term consequences of high serum ferritin in children and young people whose estimates of iron status (e.g. reticulocyte haemoglobin, hypochromic red blood cells) are out of range

	and iron is given clinically even if serum ferritin levels are high.
Relevance to NICE guidance	This guideline has considered evidence on intravenous iron in managing anaemia in children and young people with GFR category G5 and there is a lack of data on those who are given iron even if serum ferritin levels are high.
Relevance to the NHS	The outcome would affect the types of treatment provided by the NHS for managing anaemia in children and young people with GFR category G5 and with high serum ferritin levels and may also predict future healthcare needs for this population.
National priorities	High
Current evidence base	None
Equality considerations	None known

L.1.8   Modified PICO table

Population	**Inclusion:** Children and young people with a clinical diagnosis of anaemia secondary to CKD receiving iron therapy. **Exclusion:** • Children and young people receiving iron therapy for reasons other than anaemia of CKD • Raised CRP • Infection
Prognostic factors	• High ferritin levels (>800)
Outcome	• Liver damage • gastrointestinal problems • fatigue • joint pain • oxidative stress • endothelial dysfunction • inflammation • impaired immunity • renal injury
Confounders	Data must be adjusted for known confounders, including: • Age • ESA status • Concurrent medication
Study design	Prospective cohort studies (retrospective if no prospective studies are found)
Timeframe	Long term
Additional information	None