National Institute for Health and Care Excellence

Consultation

Perioperative care in adults

[E] Evidence review for preoperative management of anaemia

NICE guideline

Intervention evidence review

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Draft for consultation

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1 Preoperative management of anaemia

1.1 Review question: What is the most clinically and cost effective oral iron supplementation strategy for the preoperative management of iron deficiency anaemia?

1.2 Review question: What is the most clinically and cost effective management strategy for the preoperative management of iron deficiency anaemia?

1.3 Introduction

Anaemia is a recognised predictor of adverse postoperative outcome. It is associated with an increased rate of perioperative blood transfusion and increased postoperative morbidity and mortality. Furthermore anaemia is common in the surgical population, particularly in the high risk group undergoing intermediate or major surgery. These data have led to an establishment of rapid access anaemia clinics employing patient blood management strategies including the administration of preoperative oral and intravenous iron. However, the question of whether these preoperative interventions, such as oral or intravenous iron therapy, can improve preoperative haemoglobin levels, reduce the need for postoperative blood transfusions and improve clinician and patient reported outcomes are unanswered. This section of the guideline aims to review the evidence for clinical and cost effectiveness of such strategies to inform clinical practice.

1.4 PICO table

For full details see the review protocol in Appendix A:.

Table 1: PICO characteristics of oral iron

Population	Adults 18 years and over having surgery who have been identified during preoperative assessment as having iron deficiency anaemia (haemoglobin <130 g/L (13 g/dL) in men older than age 15 years, <120 g/L (12 g/dL) in non-pregnant women older than age 15 years, and <110 g/L (11 g/dL) in pregnant women) undergoing surgery).
Intervention	Alternate day oral iron therapy
Comparison	Daily oral iron therapy
Outcomes	Critical outcomes: • all-cause mortality • health-related quality of life • preoperative Hb level • transfusion (pre-, intra- and post-surgery) • postoperative morbidity score (POMS) • change in healthcare management (for example, delayed surgery or surgery cancellation) Important outcomes: • length of hospital stay • unplanned ICU admission • ICU length of stay (planned and unplanned) • adherence • adverse events from iron tablets (e.g. constipation, nausea)

Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.

Table 2: PICO characteristics of IV iron

Population	Adults 18 years and over having elective surgery who have been identified during preoperative assessment as having iron deficiency anaemia.
Intervention	Preoperative intravenous iron therapy
Comparison	Preoperative oral iron therapy
Outcomes	Critical outcomes: • all-cause mortality • health-related quality of life • preoperative Hb level • blood transfusion (pre-, intra- and post-surgery) • postoperative morbidity score (POMS) • change in healthcare management (for example, delayed surgery or surgery cancellation) Important outcomes: • length of hospital stay • unplanned ICU admission • ICU length of stay (planned and unplanned) • adverse events from iron infusion(e.g. constipation, nausea) • adverse events from transfusion (e.g. infections, reactions (compatibility), hypersensitivity to)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs. Prospective cohort studies if no RCT evidence is identified.

1.5 Clinical evidence

1.5.1 Included studies for oral iron

No relevant clinical studies comparing alternate day oral iron therapy with daily oral iron therapy were identified.

See also the study selection flow chart in appendix C.

1.5.2 Included studies for IV iron

Three randomised controlled trials were included in the review comparing IV iron to oral iron;[29, 31, 47] these are summarised in Table 3 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 4).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

1.5.3 Excluded studies

See the excluded studies list in Appendix I:.

1.5.4 Summary of clinical studies included

Table 3: Summary of clinical studies included

Study	Intervention and comparison	Population	Outcomes	Comments
Keeler 2017[29]	**IV iron:** Ferric carboxymaltose diluted in 250 ml 0.9% saline. Dose calculated using body weight and Hb level. Maximum dose of 1000mg per week and 2000mg during the trial. Treatment for at least 2 weeks before surgery, median 3 weeks. (n=55) **Oral iron:** Ferous sulphate 200mg twice daily until surgery. Treatment for at least 2 weeks before surgery, median 3 weeks. (n=61)	Patients diagnosed with colorectal cancer with haemoglobin <11 g/dl for women and <12 g/dl for men, scheduled to undergo surgery. Median age (range): 74 (67-81) UK	• Perioperative Hb level • Blood transfusion • Length of hospital stay • Adverse events	
Kim 2009[31]	**IV iron:** Iron sucrose calculated following formula: weight (kg) x [10 Hb (g/dl) - actual Hb (g/dl) x 2.4 = 500 mg, rounded to the nearest multiple of 100 mg. Most patients received iron sucrose infusion at a rate of 200 mg every other day, 3 times a week, beginning 3 weeks before surgery. (n=39) **Oral iron:** 2 ampoules of oral protein succinylate (total of 80 mg of elementary iron) per day,	Menorrhagic patients with established IDA who had haemoglobin levels <9 g/dl and were scheduled to undergo surgical treatment. Mean age (SD): 42 (7.5) South Korea	• Perioperative Hb level • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	3 weeks before surgery until time of surgery. (n=37)			
Padmanabhan 2019[47]	IV oral therapy: Patients received FCM (Ferinject) treatment in accordance with the manufacturer's instructions (maximum dose 1000 mg). FCM was diluted in 250 ml of 0.9% sodium chloride using an aseptic technique and administered over 30 min during the preoperative clinic. The dose of FCM was calculated using a fixed FCM dosing regimen. A second dose was offered when required. (n=22) Oral iron therapy: Patients received 200mg of ferrous sulphate twice daily for 3-8 weeks until surgery. (n=22)	Patients scheduled for elective cardiac surgery, defined as coronary artery bypass graft and/or open valve surgery, were included if they were also anaemic according to the World Health Organization criteria (haemoglobin <120 g/l for women and <130 g/ l for men). Mean age (SD): 74 (11) UK	• Quality of life • Perioperative Hb level • Transfusions • Adverse events • Length of hospital stay • Length of ICU stay	

See appendix D for full evidence tables.

1.5.5 Quality assessment of clinical studies included in the evidence review

Table 4: Clinical evidence summary: IV iron compared to oral iron for preoperative management of anaemia

Outcomes	No of	Quality of the	Relati	Anticipated absolute effects

	Participants (studies) Follow up	evidence (GRADE)	ve effect (95% CI)	Risk with Oral iron	Risk difference with IV iron (95% CI)
Change in Hb levels from preoperative to postoperative	56 (1 study) 3 weeks	⨁⨁⨁⨀ MODERATE1 due to risk of bias		The mean change in Hb levels from preoperative to postoperative in the oral group was 0.8 g/dl	The mean change in Hb levels from preoperative to postoperative in the IV group was 2.2 higher (1.46 to 2.94 higher)
Preoperative Hb levels	44 (1 study) postoperatively	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision		The mean preoperative Hb levels in the control groups was 118.3 g/L	The mean preoperative Hb levels in the intervention groups was 1.80 higher (4.67 lower to 8.27 higher)
Patients transfused	40 (1 study) postoperatively	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision	RR 1.33 (0.88 to 2.02)	Moderate	
				600 per 1000	198 more per 1000 (from 72 fewer to 612 more)
Pre-operative blood transfusion	105 (1 study) 3 weeks	⨁⨁⨀⨀ LOW2 due to imprecision	Peto OR 0.15 (0.01 to 2.36)	Moderate	
				91 per 1000	80 fewer per 1000 (from 90 fewer to 100 more)
Blood transfusion on the day of surgery	105 (1 study) 3 weeks	⨁⨁⨀⨀ LOW2 due to imprecision	RR 1.10 (0.38 to 3.19)	Moderate	
				109 per 1000	11 more per 1000 (from 68 fewer to 234 more)
Post-operative blood transfusion	105 (1 study) 3 weeks	⨁⨁⨀⨀ LOW2 due to imprecision	RR 0.73 (0.22 to	Moderate	
				109 per 1000	29 fewer per 1000 (from 85 fewer to 158 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral iron	Risk difference with IV iron (95% CI)
			2.45)		
Perioperative blood transfusion volume	105 (1 study) 3 weeks	⨁⨁⨀⨀ LOW2 due to imprecision		The mean volume of transfusion from preoperative to postoperative in the oral group was 0.63 units	The mean volume of transfusion from preoperative to postoperative in the IV group was 0.07 units higher (0.58 lower to 0.71 higher)
Complications	96 (2 studies) 3 weeks	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	RR 0.93 (0.65 to 1.32)	Moderate	
				413 per 1000	29 fewer per 1000 (from 145 fewer to 132 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

See appendix F for full GRADE tables.

Table 5: Clinical evidence summary: Evidence not suitable for GRADE analysis

Study	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Risk of bias
Padmanabhan 2019[47]	Quality of life	No statistically significant differences in any subset of the EQ-5D or SF-36 were identified when considering the effects of treatment during the 3 study visits.				Very high
Keeler 2017[29]	Hb level change from baseline to surgery (g/dl)	Median (IQR): 1.55 (0.93-2.58)	50	Median (IQR): 0.5 (-0.13-1.33)	55	Low
		Change score of intervention vs control was statistically significant. P<0.001				
Padmanabhan 2019[47]	Transfusion requirements	Median (IQR): 2.0 units (1.0–4.8)	22	Median (IQR): 1.5 units (0–2.0)	22	High

Study	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Risk of bias
Keeler 2017[29]	Complications	Post-infusion headache was the most frequent complication (reported by three people). One significant adverse event was reported, a rash that required intervention of oral antihistamine medication. (n=55)		Two people reduced their dose because of complication (dyspepsia and constipation). (n=61)		High
Keeler 2017[29]	Post-operative length of stay (days)	Median (IQR): 6 (5-10)	50	Median (IQR): 6 (4-9)	55	Low
		Change score of intervention vs control was not statistically significant. P=0.950				
Padmanabhan 2019[47]	Length of hospital stay	Median (IQR): 7days (3–49)	20	Median (IQR): 9 days (3–30)	20	High
Padmanabhan 2019[47]	Length of ICU stay	Median: 88.0 hours	20	Median (IQR): 69 (12–190)	20	High

1.6 Economic evidence

1.6.1 Included studies

No health economic studies were included.

1.6.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G:.

1.6.3 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Oral iron:

Table 6: UK costs of oral iron drugs

Drug	Formulation	Dose	Unit cost	Cost – 3 weeks	Cost – 3 months	Source of dosage
Ferrous sulfate	Tablets	210mg 3 times daily	Pack of 28 = £1.06	£2.39	£10.36	GC member
Ferrous sulfate	Tablets	210mg 3 times a day, on alternate days	Pack of 28 = £1.06	£1.19	£5.18	Stoffel 2017[56]

Source: British National Formulary, September 2019[27]

IV iron:

Table 7 shows the drug costs associated with IV iron, and Table 8 shows the additional resource use associated with this approach.

Table 7: UK costs of intravenous iron

Drug	Iron mg/ vial	No. of vials per vist	No. of visits	Cost/vial	Total drug cost	Source of dosage
Ferric carboxymaltose	500mg	2	2	£81	**£325**	Keeler 2017[29]
Iron sucrose	100mg	2	3	£9	**£52**	GC opinion
Iron dextran	500mg	2	1	£40	**£80**	Blood transfusion guideline[42]
Iron isomaltoside 1000	500mg	2	1	£85	**£170**	
Unweighted average					**£134**	

Sources: British National Formulary, May 2018[27]

Table 8: Costs of administering intravenous iron

Drug	Preparation (minutes)[a]	Infusion time (minutes) [a]	Observation (minutes)[a]	Nurse costs[b]	Consumables [b]	Transport[b]	Admin time[b]	Clinic space[b]	Total costs (inc. drug)
Ferric carboxymaltose	15	15	30	£98	£11	£9	£3	£11	**£456**
Iron sucrose	15	30	30	£122	£16	£14	£3	£20	**£227**
Iron dextran	15	300	30	£562	£5	£5	£3	£30	**£685**
Iron isomaltoside 1000	15	30	30	£122	£5	£5	£3	£7	**£312**
Unweighted average				£226	£9	£8	£3	£17	**£420**

(a) Source: Blood Transfusion, NICE guideline, NG24, Appendix N, costs used in the guideline were inflated to 2017[42]
(b) Source: Curtis, L. & Burns, A. (2018) Unit Costs of Health and Social Care 2018, Personal Social Services Research Unit, University of Kent, Canterbury[13]*, cost of nurse time includes the ratio of direct to indirect time with patients and qualification costs from the PSSRU*
(c) Transport cost is based on committee assumption that 10% of patients would require transport

Potential downstream costs

As well as drug costs, the downstream costs which may arise from a series of different outcomes in the interventions being compared are of importance, and some costs are illustrated below.

Table 9: Potential downstream costs

HRG code	Description	Cost per unit	Source, Assumptions
Blood transfusion cost			
n/a	Standard red cells (BC001)	£133.44	NHSBT Price list 2019[45]
n/a	Red blood cell transfusion on a day unit	£57.19 (first unit) £36.13 (subsequent units)	Stokes 2018[57]
Cost of hospital stay			
ED22A – ED23C	Cost of elective excess bed days in high risk of bleeding (Complex, coronary artery bypass graft with single heart valve replacement or repair)	£260	NHS reference costs, 2017/18[14] This was based on the costs used in the blood transfusion guideline NG24)[42] , cost-effectiveness analysis of tranexamic acid and cell salvage (The blood transfusion GDG considered these surgeries to be reflective of surgeries used in the clinical evidence of the guideline)[(a)] Weighted average was

HRG code	Description	Cost per unit	Source, Assumptions
			calculated
HN12A – HN24C and HT12D – HT24C[(b)]	Cost of elective excess bed days in moderate risk of bleeding (Hip and knee procedures, trauma and non-trauma	£415	NHS reference costs 2017/18[14] Assumptions as above Weighted average was calculated

(a) Taken from NICE Blood Transfusion guideline (NG24), Appendix M[42], Costs used in the guideline were updated to NHS reference costs 2017/18[14].

(b) HN13G, HN13H, HN14F, HN14G, HN14H, HN23D, HN23E and HT23E excluded as based on people 18 years and under.

1.6.4 Other calculations

Simple costing was conducted to estimate the impact of people requiring blood transfusions and is in Table 10. This showed that the costs associated with IV iron were much higher than oral iron when considering blood transfusion.

Table 10: Costs including blood transfusion

	Oral iron		IV iron	
	Number of people requiring blood transfusions	N	Number of people requiring blood transfusions	N
Data from study				
Total	14	55	10	50
Calculations				
% of people having transfusion	25%		20%	
Costs of blood transfusion	£33.97[(a)]		£26.69[(a)]	
Costs of iron	£2.39		£420	
Cost including blood transfusion	**£36[(a)]**		**£447[(a)]**	

(a) Blood transfusion costs were taken from the NHS Blood transfusion price list (£133.44)[45]

1.7 Evidence statements

1.7.1 Clinical evidence statements

No relevant published evidence was identified for oral iron strategies .

IV iron versus oral iron

No evidence was found for all-cause mortality, health-related quality of life, POMS, change in healthcare management as the critical outcomes, unplanned ICU admission, ICU length of stay, and adverse events from transfusion (for example, infections, reactions (compatibility), hypersensitivity).

Haemoglobin levels

One study found a clinically important benefit of IV iron on haemoglobin levels at 3 weeks compared to oral iron (1 study, n=56, moderate quality evidence).

One study found no clinically important difference between IV iron and oral iron on pre-operative haemoglobin levels (1 study, n=44, very low quality evidence).

Blood transfusions

One study showed a clinically important harm of IV iron on number of patients transfused compared to oral iron (1 study, n=40, low quality evidence). A single study demonstrated a clinical important benefit of IV iron for pre-operative blood transfusions, but no clinically important difference with IV iron of intra-operative or postoperative blood transfusions, or perioperative transfusion volume compared to oral iron (1 study, n=105, low quality evidence).

Adverse events

Two studies showed no clinically important difference between IV and oral iron for rate of complications (2 studies, n=96, very low quality evidence).

Outcomes not suitable for GRADE analysis

One study showed no notable difference of IV iron compared to oral iron on quality of life (1 study, n=44, very high risk of bias).

One study showed no notable difference of IV iron compared to oral iron on volume of blood transfusion requirement (1 study, n=44, high risk of bias).

One study found a trend to benefit of IV iron on haemoglobin levels at 3 weeks compared to oral iron (1 study, n=105, low risk of bias).

Two studies showed no notable difference for IV iron on post-operative length of stay when compared to oral iron (2 studies, n=105 & 44, low & high risk of bias).

One study showed no notable difference for IV iron on post-operative length of ICU stay when compared to oral iron (n=44, high risk of bias).

One study showed no notable difference between IV and oral iron for rate of complications (1 study, n=105, high risk of bias).

1.7.2 Health economic evidence statements

- No relevant economic evaluations were identified for either review.

1.8 The committee's discussion of the evidence

1.8.1 Interpreting the evidence

Please see recommendation 1.3.3 in the guideline.

1.8.1.1 The outcomes that matter most

Oral iron

Anaemia is a recognised predictor of adverse postoperative outcome and associated with an increased rate of perioperative blood transfusion and increased postoperative morbidity and mortality. As such, the committee identified all-cause mortality, health-related quality of life, preoperative Hb level, transfusion (pre-, intra- and post-surgery), postoperative morbidity score (POMS), and change in healthcare management (for example, delayed surgery or surgery cancellation) as the critical outcomes for decision making on strategies of oral iron therapy. The following outcomes were identified as important for the preoperative management of iron-deficiency anaemia: length of hospital stay, unplanned ICU admission, ICU length of stay (planned and unplanned), adherence, adverse events from iron tablets (for example, constipation, nausea).

No relevant clinical studies were identified; therefore, no evidence was available for any of these outcomes.

IV iron

The committee also identified all-cause mortality, health-related quality of life, preoperative Hb level, blood transfusion (pre-, intra- and post-surgery), postoperative morbidity score (POMS), and change in healthcare management (for example, delayed surgery or surgery cancellation) as the critical outcomes for decision making on oral or IV iron therapy. The following outcomes were identified as important for the preoperative management of iron-deficiency anaemia: length of hospital stay, unplanned ICU admission, ICU length of stay (planned and unplanned), adverse events from transfusion (for example, infections, reactions (compatibility), hypersensitivity), and adverse events from iron supplementation (for example, constipation, nausea).

1.8.1.2 The quality of the evidence

Oral iron

No relevant clinical studies were identified for this review.

IV iron

The quality of evidence that was suitable for GRADE analysis ranged from very low to moderate. The majority of the evidence was graded at low quality. This was mostly due to outcome reporting bias and imprecision. The committee also noted that the studies were relatively small, limiting the confidence with which they could draw conclusions from the evidence.

Outcomes which were not suitable for GRADE analysis were considered to be a low and high risk of bias.

1.8.1.3 Benefits and harms

Oral iron

No relevant clinical studies were identified for this review. However, the committee felt that a research recommendation in this area was warranted.

The committee acknowledged the possible side-effects of oral iron supplementation including constipation or diarrhoea, nausea and vomiting. It was considered that an understanding of varying oral iron therapy regimes may elucidate potential benefits with regards to managing the side effects of supplementation as well as patient compliance with therapy. The committee agreed that alternate day iron regimens can be considered if the side effects of daily dosing cannot be tolerated.

IV iron

The committee discussed the evidence on the preoperative management of iron deficiency anaemia.

The committee discussed evidence from three studies showing IV iron had an improved capacity to increase preoperative haemoglobin levels compared with oral iron. This benefit was considered by the committee to be clinically important.

Evidence from one study showed a clinical benefit of IV iron for the number of preoperative transfusions. However, the committee noted that there was no clinically important difference between oral iron and IV iron on the number of patients transfused on the day of surgery, after surgery or the total blood transfusion volume. A second study showed an increased risk of patients requiring blood transfusion with IV iron compared to oral iron. Given that blood transfusion was recognised as a critically important outcome, the committee felt that the overall lack of difference between oral and IV iron therapy to an extent negated the potential benefits of the aforementioned increase in haemoglobin levels.

Evidence reviewed by the committee also showed no significant difference in health-related quality of life, length of hospital stay or rate of complications between those receiving oral or IV iron. The committee also noted that there was no data reported on any complications from blood transfusion.

No evidence was found for all-cause mortality, POMS, change in healthcare management as the critical outcomes, or unplanned ICU admission, and adverse events from transfusion (for example, infections, reactions (compatibility), hypersensitivity).

The committee referenced a general acceptance that increased haemoglobin levels in anaemic patients reduces the risk of morbidity associated with surgery and recognised this as a noteworthy benefit of IV iron therapy. However, the committee noted that a reduction in morbidity was not reflected in the reported rates of transfusions in people receiving IV iron therapy compare to oral iron therapy..

The committee highlighted that preoperative anaemia is associated with adverse post-operative outcomes. However, there is uncertainty that treating anaemia in the preoperative period reduces these risks.

1.8.2 Cost effectiveness and resource use

Oral iron

No economic evidence was identified.

The committee were presented with some examples of unit costs for the different oral iron administrations, as well as excess bed day costs and blood transfusion costs. Ferrous sulfate is a common type of oral iron that is prescribed in the NHS, and requires adults taking 200mg tablets three times a day. For the daily oral iron regime, the total cost is £10.36. For the

alternate day regime the total cost is £5.18. Costs were based on taking the tablets for three months, as this is the time it usually takes to get iron and haemoglobin levels back to normal. The committee discussed that oral iron results in unpleasant side effects such as constipation and nausea, which can lead to adherence issues particularly if people have to take it on a daily basis. No clinical evidence was identified. However, the committee noted that there may be emerging evidence in non-surgical populations that taking oral iron on alternate days results in the same effectiveness on haemoglobin levels, but fewer side effects which can also resolve the issue around adherence. A higher adherence rate could reduce the chances of adults having their surgery delayed, which can have a negative impact on the adult's quality of life and their condition. Also, a more effective intervention, in terms of increasing an adult's haemoglobin level, could reduce the chances of needing a blood transfusion and of having an adverse event, which can lead to extra days in hospital

Current practice is to administer daily oral iron, which is the more expensive option. As there was no relevant clinical evidence in the surgical population, there is uncertainty about which intervention is more effective and therefore on the impact of downstream costs and effects. If further research could demonstrate that the alternate day option is as, or more, effective than the daily option, it could lead to future savings for the NHS. Therefore the committee made a research recommendation.

<u>IV iron</u>

No economic evaluations were identified.

The committee were presented with some examples of unit costs for oral iron and IV iron, as well as excess bed day and blood transfusion costs.

The committee felt the clinical data demonstrated that oral and IV iron had similar effectiveness. Oral iron is a very cheap drug to administer, costing only £1.19 for three weeks. On the other hand, IV iron can cost an average of £134 for three weeks. IV iron results in much higher costs, as the drug is more expensive and requires staff time in hospital and clinic space and some adults may require NHS transport. Other downstream costs were considered, such as the cost of a blood transfusion, which can cost around £133 and the cost of excess bed days, which ranges from £260 to £415.

The IV iron group had a larger increase in haemoglobin levels in all three studies. This can prevent other complications, such as wound infections, which were not measured in the studies. Wound infections can have a negative impact on the patient's quality of life and incur downstream costs to the NHS in order to manage and treat them. Also, if an adult has not reached an optimum haemoglobin level their surgery might be delayed, which is another outcome that was not measured. This can have a negative impact on their condition and quality of life. However, the committee felt that although there is evidence to support the increase in haemoglobin levels in IV iron, it is an area that requires more evidence to indicate whether this increase in haemoglobin levels leads to less surgeries being delayed and a reduction in complications. The committee also highlighted that although the haemoglobin levels increased, the magnitude of benefit is dependent on the baseline haemoglobin level. For example, if an adult's haemoglobin level increases from 8 to 10, this is an important clinical difference. But if their haemoglobin level increases from 10 to 12, this is likely to be less significant.

A simple costing example was calculated to see what the estimated cost per patient would be if we were to include the number of blood transfusions reported in the clinical review, as well as the intervention costs. The intervention cost for oral iron was based on a cost of £1.19 for taking ferrous sulfate for 3 weeks, and the unweighted average cost of intravenous iron was £420. One study reported blood transfusions on the day of surgery as well as pre and post-operatively. This showed that 20% of people in the IV iron group had a blood transfusion and 25% in the oral iron group. Using the cost of blood transfusion and adding it to the cost of the drug (as well as administration costs) resulted in IV iron costing £447 per

person and oral iron costing £35 per person, a difference of £412. This is a large difference and the committee felt that this cost magnitude of IV iron was too high to justify. The committee discussed that there were risks associated with blood transfusions, and felt that there would be an additional cost associated with these. They felt that the quality of clinical evidence was too weak to make any judgment on the number of transfusions in total, based on the wide confidence intervals.

The blood transfusion guideline indicated that IV iron should be considered when the interval between diagnosis of anaemia and surgery was too short for oral iron to work. This question aimed to clarify what constitutes 'too short', as there is uncertainty and variation in current practice. As the committee discussed that the quality and quantity of the evidence was insufficient, and therefore considered the costs associated with IV iron and agreed that the magnitude of benefit that IV iron produced was not great enough to result in it being cost-effective. Therefore they recommended offering oral iron and considering IV iron in circumstances where oral iron was not tolerated or sufficient. All studies had a similar time frame so there was no information to help inform the issue around timing, and a research recommendation was made around this.

This recommendation could result in some changes to current practice and could lead to some cost-savings as clinicians might stop using IV iron and prescribe oral iron during a 'short' time frame.

1.8.3 Other factors the committee took into account

Oral iron

The committee reviewed recommendations made in [NG24] the blood transfusion guideline and agreed that these were relevant to the perioperative care population.

The committee commented that alternate day therapy may address an issue of non-adherence in patients undergoing surgery; however, this needs to be balanced against the possibility that alternate-day therapy might be complicated for patients who are required to take multiple tablets otherwise taken daily. As a large proportion of adults presenting with iron-deficiency anaemia may be elderly, the committee expressed some concern around introducing the alternate day regime as it can be confusing. However, this could be rectified by adherence strategies like adults using compliance devices (for example, pill boxes). The committee also made consideration for the side effects associated with oral iron treatment which may be affected with alternate day therapy.

IV iron

The committee also noted that the evidence from one of the three included studies was taken from a specific population of menorrhagic women scheduled to undergo gynaecologic surgery. While this group of people were identified as having iron deficiency anaemia, the committee questioned whether it would be possible to generalise the findings from this study for all people with iron deficiency anaemia.

The committee noted that IV iron is indicated in people with FID who have normal iron levels but are unable to use it efficiently.

The committee was aware of a large ongoing trial (PREVENTT) which may add insight into the efficacy of IV iron in major abdominal/pelvic surgery.

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Appendices

Appendix A: Review protocols

Table 11: Review protocol: Preoperative management of anaemia (oral iron)

ID	Field	Content
0.	PROSPERO registration number	Not registered on PROSPERO
1.	Review title	What is the most clinically and cost effective oral iron supplementation strategy for the preoperative management of iron deficiency anaemia?
2.	Review question	What is the most clinically and cost effective oral iron supplementation strategy for the preoperative management of iron deficiency anaemia?
3.	Objective	To determine the most clinically and cost effective oral iron supplementation strategy for people with iron deficiency anaemia (haemoglobin <130 g/L (13 g/dL) in men older than age 15 years, <120 g/L (12 g/dL) in non-pregnant women older than age 15 years, and <110 g/L (11 g/dL) in pregnant women) undergoing surgery.
4.	Searches	• Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Perioperative care
6.	Population	Inclusion: Adults 18 years and over having surgery who have been identified during preoperative assessment as having iron deficiency anaemia. Exclusion: • children and young people aged 17 years and younger

		• surgery for burns, traumatic brain injury or neurosurgery
7.	Intervention/Exposure/Test	• alternate day oral iron therapy
8.	Comparator/Reference standard/Confounding factors	• daily oral iron therapy
9.	Types of study to be included	Randomised controlled trials (RCTs), systematic reviews of RCTs. Observational studies if no RCT evidence is identified.
10.	Other exclusion criteria	Exclusions: • non-English language studies • studies published before 2000
11.	Context	One of the main issues with management of anaemia is thought to be adherence to daily oral iron therapy. The concept that alternate day therapy may improve compliance may lead to improvements in people with iron deficiency anaemia.
12.	Primary outcomes (critical outcomes)	• all-cause mortality • health-related quality of life • preoperative Hb level • transfusion (pre-, intra- and post-surgery) • postoperative morbidity score (POMS) • change in healthcare management (for example, delayed surgery or surgery cancellation) The committee did not agree to on any established minimal clinically important differences, therefore the default MIDs will be used and any difference in mortality will be considered clinically important.
13.	Secondary outcomes (important outcomes)	• length of hospital stay • unplanned ICU admission • ICU length of stay (planned and unplanned) • adherence • adverse events from iron tablets (e.g. constipation, nausea) The committee did not agree to on any established minimal clinically important differences, therefore the default MIDs will be used and any difference in mortality will be considered clinically important.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 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. Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I • Case control study: CASP case control checklist • Controlled before-and-after study or Interrupted time series: Effective Practice and Organisation of Care (EPOC) RoB Tool • Cross sectional study: JBI checklist for cross sectional study • Case series: Institute of Health Economics (IHE) checklist for case series 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of

		Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • CERQual will be used to synthesise data from qualitative studies. • WinBUGS will be used for network meta-analysis, if possible given the data identified. • List any other software planned to be used. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects.		
17.	Analysis of sub-groups	Subgroups: • Time between initiation of oral iron therapy and surgery (≤6 weeks, >6 weeks) • Older people (over 75) • American Society of Anesthesiologists (ASA) Physical Status grade • surgery grade based on NICE preoperative tests for elective surgery guideline categorisation		
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	[To be added.]		
22.	Anticipated completion date	[To be added.]		
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 National Guideline Centre 5b Named contact e-mail perioperativecare@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Ms Kate Ashmore Ms Kate Kelley Ms Sharon Swaine Mr Ben Mayer Ms Maria Smyth Mr Vimal Bedia Mr Audrius Stonkus Ms Madelaine Zucker Ms Annabelle Davis Ms Lina Gulhane		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from 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.	
29.	Other registration details	n/a	
30.	Reference/URL for published protocol	n/a	
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	Perioperative care, preoperative, iron, anaemia	
33.	Details of existing review of same topic by same authors	n/a	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	n/a	
36.	Details of final publication	www.nice.org.uk	

1 **Table 12: Review protocol: Preoperative management of anaemia (IV iron)**

ID	Field	Content
0.	PROSPERO registration number	Not registered on PROSPERO
1.	Review title	What is the most clinically and cost effective management strategy for the preoperative

		management of iron deficiency anaemia?
2.	Review question	What is the most clinically and cost effective management strategy for the preoperative management of iron deficiency anaemia?
3.	Objective	To determine the most clinically and cost effective oral iron supplementation strategy for people with iron deficiency anaemia (haemoglobin <130 g/L (13 g/dL) in men older than age 15 years, <120 g/L (12 g/dL) in non-pregnant women older than age 15 years, and <110 g/L (11 g/dL) in pregnant women) undergoing surgery.
4.	Searches	• Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Perioperative care
6.	Population	Inclusion: Adults 18 years and over having surgery who have been identified during preoperative assessment as having iron deficiency anaemia. Exclusion: • children and young people aged 17 years and younger • surgery for burns, traumatic brain injury or neurosurgery
7.	Intervention/Exposure/Test	• preoperative intravenous iron therapy
8.	Comparator/Reference standard/Confounding factors	• preoperative oral iron therapy
9.	Types of study to be included	Randomised controlled trials (RCTs), systematic reviews of RCTs. Observational studies if no RCT evidence is identified.
10.	Other exclusion criteria	Exclusions: • non-English language studies • studies published before 2000

11.	Context	Preoperative anaemia is considered to be associated with an increased risk of perioperative complications.
12.	Primary outcomes (critical outcomes)	• all-cause mortality • health-related quality of life • preoperative Hb level • transfusion (pre-, intra- and post-surgery) • postoperative morbidity score (POMS) • change in healthcare management (for example, delayed surgery or surgery cancellation) The committee did not agree to on any established minimal clinically important differences, therefore the default MIDs will be used and any difference in mortality will be considered clinically important.
13.	Secondary outcomes (important outcomes)	• length of hospital stay • unplanned ICU admission • ICU length of stay (planned and unplanned) • adverse events from iron infusion(e.g. constipation, nausea) • adverse events from transfusion (e.g. infections, reactions (compatibility), hypersensitivity) The committee did not agree to on any established minimal clinically important differences, therefore the default MIDs will be used and any difference in mortality will be considered clinically important.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 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. Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort

		studies: Cochrane ROBINS-I • Case control study: CASP case control checklist • Controlled before-and-after study or Interrupted time series: Effective Practice and Organisation of Care (EPOC) RoB Tool • Cross sectional study: JBI checklist for cross sectional study • Case series: Institute of Health Economics (IHE) checklist for case series 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • CERQual will be used to synthesise data from qualitative studies. • WinBUGS will be used for network meta-analysis, if possible given the data identified. • List any other software planned to be used. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial

<table>
<tr><td></td><td></td><td colspan="3">heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects.</td></tr>
<tr><td>17.</td><td>Analysis of sub-groups</td><td colspan="3">Subgroups:
older people (over 60 years)
surgery grade based on NICE preoperative tests for elective surgery guideline categorisation
American Society of Anesthesiologists (ASA) Physical Status grade
Time to surgery
2-6 weeks
6-12 weeks
12-18 weeks
>18 weeks</td></tr>
<tr><td rowspan="8">18.</td><td rowspan="8">Type and method of review</td><td>☒</td><td colspan="2">Intervention</td></tr>
<tr><td>☐</td><td colspan="2">Diagnostic</td></tr>
<tr><td>☐</td><td colspan="2">Prognostic</td></tr>
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<tr><td>☐</td><td colspan="2">Other (please specify)</td></tr>
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<tr><td>21.</td><td>Anticipated or actual start date</td><td colspan="3">[To be added.]</td></tr>
<tr><td>22.</td><td>Anticipated completion date</td><td colspan="3">[To be added.]</td></tr>
<tr><td rowspan="8">23.</td><td rowspan="8">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☐</td><td>☐</td></tr>
<tr><td>Piloting of the study selection process</td><td>☐</td><td>☐</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☐</td><td>☐</td></tr>
<tr><td>Data extraction</td><td>☐</td><td>☐</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☐</td><td>☐</td></tr>
<tr><td>Data analysis</td><td>☐</td><td>☐</td></tr>
<tr><td></td></tr>
<tr><td>24.</td><td>Named contact</td><td colspan="3">5a. Named contact</td></tr>
</table>

		National Guideline Centre 5b Named contact e-mail perioperativecare@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre: Ms Kate Ashmore Ms Kate Kelley Ms Sharon Swaine Mr Ben Mayer Ms Maria Smyth Mr Vimal Bedia Mr Audrius Stonkus Ms Madelaine Zucker Ms Margaret Constanti Ms Annabelle Davis Ms Lina Gulhane
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from 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:	
29.	Other registration details	n/a	
30.	Reference/URL for published protocol	n/a	
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	Perioperative care, preoperative, iron, anaemia	
33.	Details of existing review of same topic by same authors	n/a	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	n/a	
36.	Details of final publication	www.nice.org.uk	

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2 **Table 13: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review	Studies not meeting any of the search criteria above will be excluded. Studies

strategy

published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded.

Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[43] [43]

Inclusion and exclusion criteria

- If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.
- If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.
- If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'.
- Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the

	more useful the analysis will be for decision-making in the guideline. For example, economic evaluations based on observational studies will be excluded, when the clinical review is only looking for RCTs,

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Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2018.[43]

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 14: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 30 May 2019	Exclusions
Embase (OVID)	1974 – 30 May 2019	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 5 of 12 CENTRAL to 2019 Issue 5 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

Medline (Ovid) search terms

1.	exp Preoperative Care/ or Preoperative Period/
2.	(pre-operat* or preoperat* or pre-surg* or presurg*).ti,ab.
3.	((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
4.	or/1-3
5.	limit 4 to English language
6.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
7.	5 not 6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/

21.	exp Preoperative Care/ or Preoperative Period/
22.	(pre-operat* or preoperat* or pre-surg* or presurg*).ti,ab.
23.	((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
24.	or/1-3
25.	limit 4 to English language
26.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
27.	5 not 6
28.	letter/
29.	editorial/
30.	news/
31.	exp historical article/
32.	Anecdotes as Topic/
33.	comment/
34.	case report/
35.	(letter or comment*).ti.
36.	or/8-15
37.	randomized controlled trial/ or random*.ti,ab.
38.	16 not 17
39.	animals/ not humans/
40.	exp Animals, Laboratory/
41.	exp Animal Experimentation/
42.	exp Models, Animal/
43.	exp Rodentia/
44.	(rat or rats or mouse or mice).ti.
45.	or/18-24
46.	7 not 25
47.	exp Anemia/
48.	(anemi* or anaemi*).ti,ab.
49.	27 or 28
50.	26 and 29

1 **Embase (Ovid) search terms**

1.	*preoperative care/ or *preoperative period/
2.	(pre-operat* or preoperat* or pre-surg* or presurg*).ti,ab.
3.	((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
4.	or/1-3
5.	limit 4 to English language
6.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
7.	5 not 6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/

12.	(letter or comment*).ti.
13.	or/8-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animal/ not human/
17.	nonhuman/
18.	exp Animal Experiment/
19.	exp Experimental Animal/
20.	animal model/
21.	exp Rodent/
22.	(rat or rats or mouse or mice).ti.
23.	or/15-22
24.	7 not 23
25.	exp Anemia/
26.	(anemi* or anaemi*).ti,ab.
27.	25 or 26
28.	24 and 27

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Preoperative Care] this term only
#2.	MeSH descriptor: [Preoperative Period] this term only
#3.	MeSH descriptor: [Perioperative Nursing] this term only
#4.	(pre-operat* or preoperati*or pre-surg* or presurg*):ti,ab
#5.	(before or prior or advance or pre or prepar*) near/3 (surg* or operat* or anaesthes* or anesthes*):ti,ab
#6.	(or #1-#5)
#7.	MeSH descriptor: [Anemia] explode all trees
#8.	(anemi* or anaemi*):ti,ab
#9.	#7 or #8
#10.	#6 and #9

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the perioperative care population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional health economics searches were run on Medline and Embase.

Table 15: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 30 May 2019	Exclusions Health economics studies
Embase	2014 – 30 May 2019	Exclusions Health economics studies
Centre for Research and	HTA - Inception – 02 May	None

Database	Dates searched	Search filter used
Dissemination (CRD)	2019 NHSEED - Inception to 02 May 2019	

1 **Medline (Ovid) search terms**

1.	exp Preoperative Care/ or exp Perioperative Care/ or exp Perioperative Period/ or exp Perioperative Nursing/
2.	((pre-operative* or preoperative* or preop* or pre-op* or pre-surg* or presurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
3.	((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
4.	((postoperative* or postop* or post-op* or post-surg* or postsurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
5.	((care* or caring or treat* or nurs* or recover* or monitor*) adj3 (before or prior or advance or during or after) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
6.	1 or 2 or 3 or 4 or 5
7.	(intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*).ti,ab.
8.	((during or duration) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
9.	7 or 8
10.	postoperative care/ or exp Postoperative Period/ or exp Perioperative nursing/
11.	(postop* or post-op* or post-surg* or postsurg* or perioperat* or peri-operat*).ti,ab.
12.	(after adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
13.	(post adj3 (operat* or anaesthes* or anesthes*)).ti,ab.
14.	10 or 11 or 12 or 13
15.	exp Preoperative Care/ or Preoperative Period/
16.	(pre-operat* or preoperat* or pre-surg* or presurg*).ti,ab.
17.	((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
18.	15 or 16 or 17
19.	6 or 9 or 14 or 18
20.	letter/
21.	editorial/
22.	news/
23.	exp historical article/
24.	Anecdotes as Topic/
25.	comment/
26.	case report/
27.	(letter or comment*).ti.
28.	or/20-27
29.	randomized controlled trial/ or random*.ti,ab.
30.	28 not 29
31.	animals/ not humans/
32.	exp Animals, Laboratory/
33.	exp Animal Experimentation/
34.	exp Models, Animal/

35.	exp Rodentia/
36.	(rat or rats or mouse or mice).ti.
37.	or/30-36
38.	19 not 37
39.	limit 38 to English language
40.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
41.	39 not 40
42.	economics/
43.	value of life/
44.	exp "costs and cost analysis"/
45.	exp Economics, Hospital/
46.	exp Economics, medical/
47.	Economics, nursing/
48.	economics, pharmaceutical/
49.	exp "Fees and Charges"/
50.	exp budgets/
51.	budget*.ti,ab.
52.	cost*.ti.
53.	(economic* or pharmaco?economic*).ti.
54.	(price* or pricing*).ti,ab.
55.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
56.	(financ* or fee or fees).ti,ab.
57.	(value adj2 (money or monetary)).ti,ab.
58.	or/42-57
59.	41 and 58

1 **Embase (Ovid) search terms**

1.	*preoperative period/ or *intraoperative period/ or *postoperative period/ or *perioperative nursing/ or *surgical patient/
2.	((pre-operative* or preoperative* or preop* or pre-op* or pre-surg* or presurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
3.	((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
4.	((care* or caring or treat* or nurs* or recover* or monitor*) adj3 (before or prior or advance or during or after) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
5.	1 or 2 or 3 or 4
6.	peroperative care/ or exp peroperative care/ or exp perioperative nursing/
7.	(intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*).ti,ab.
8.	((during or duration) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
9.	6 or 7 or 8
10.	postoperative care/ or exp postoperative period/ or perioperative nursing/
11.	(postop* or post-op* or post-surg* or postsurg* or perioperat* or peri-operat*).ti,ab.
12.	(after adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
13.	(post adj3 (operat* or anaesthes* or anesthes*)).ti,ab.

14.	10 or 11 or 12 or 13
15.	exp preoperative care/ or preoperative period/
16.	(pre-operat* or preoperat* or pre-surg* or presurg*).ti,ab.
17.	((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
18.	15 or 16 or 17
19.	5 or 9 or 14 or 18
20.	letter.pt. or letter/
21.	note.pt.
22.	editorial.pt.
23.	case report/ or case study/
24.	(letter or comment*).ti.
25.	or/20-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animal/ not human/
29.	nonhuman/
30.	exp Animal Experiment/
31.	exp Experimental Animal/
32.	animal model/
33.	exp Rodent/
34.	(rat or rats or mouse or mice).ti.
35.	or/27-34
36.	19 not 35
37.	limit 36 to English language
38.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
39.	37 not 38
40.	health economics/
41.	exp economic evaluation/
42.	exp health care cost/
43.	exp fee/
44.	budget/
45.	funding/
46.	budget*.ti,ab.
47.	cost*.ti.
48.	(economic* or pharmaco?economic*).ti.
49.	(price* or pricing*).ti,ab.
50.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
51.	(financ* or fee or fees).ti,ab.
52.	(value adj2 (money or monetary)).ti,ab.
53.	or/40-52

54.	39 and 53

1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Preoperative Care EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Perioperative Care EXPLODE ALL TREES
#3.	MeSH DESCRIPTOR Perioperative Period EXPLODE ALL TREES
#4.	MeSH DESCRIPTOR Perioperative Nursing EXPLODE ALL TREES
#5.	(((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)))
#6.	(((care* or caring or treat* or nurs* or recover* or monitor*) adj3 (before or prior or advance or during or after) adj3 (surg* or operat* or anaesthes* or anesthes*)))
#7.	(((pre-operative* or preoperative* or preop* or pre-op* or pre-surg* or presurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)))
#8.	(((postoperative* or postop* or post-op* or post-surg* or postsurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)))
#9.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10.	(* IN HTA)
#11.	(* IN NHSEED)
#12.	#9 AND #10
#13.	#9 AND #11
#14.	MeSH DESCRIPTOR Intraoperative Care EXPLODE ALL TREES
#15.	#1 OR #2 OR #3 OR #4 OR #14
#16.	((intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*))
#17.	(((during or duration) adj3 (surg* or operat* or anaesthes* or anesthes*)))
#18.	((postop* or post-op* or post-surg* or postsurg* or perioperat* or peri-operat*))
#19.	((after adj3 (surg* or operat* or anaesthes* or anesthes*)))
#20.	((post adj3 (operat* or anaesthes* or anesthes*)))
#21.	((pre-operat* or preoperat* or pre-surg* or presurg*))
#22.	(((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)))
#23.	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#24.	#10 AND #23
#25.	#11 AND #23
#26.	#12 OR #13 OR #24 OR #25

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Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of preoperative management of anaemia (oral iron).

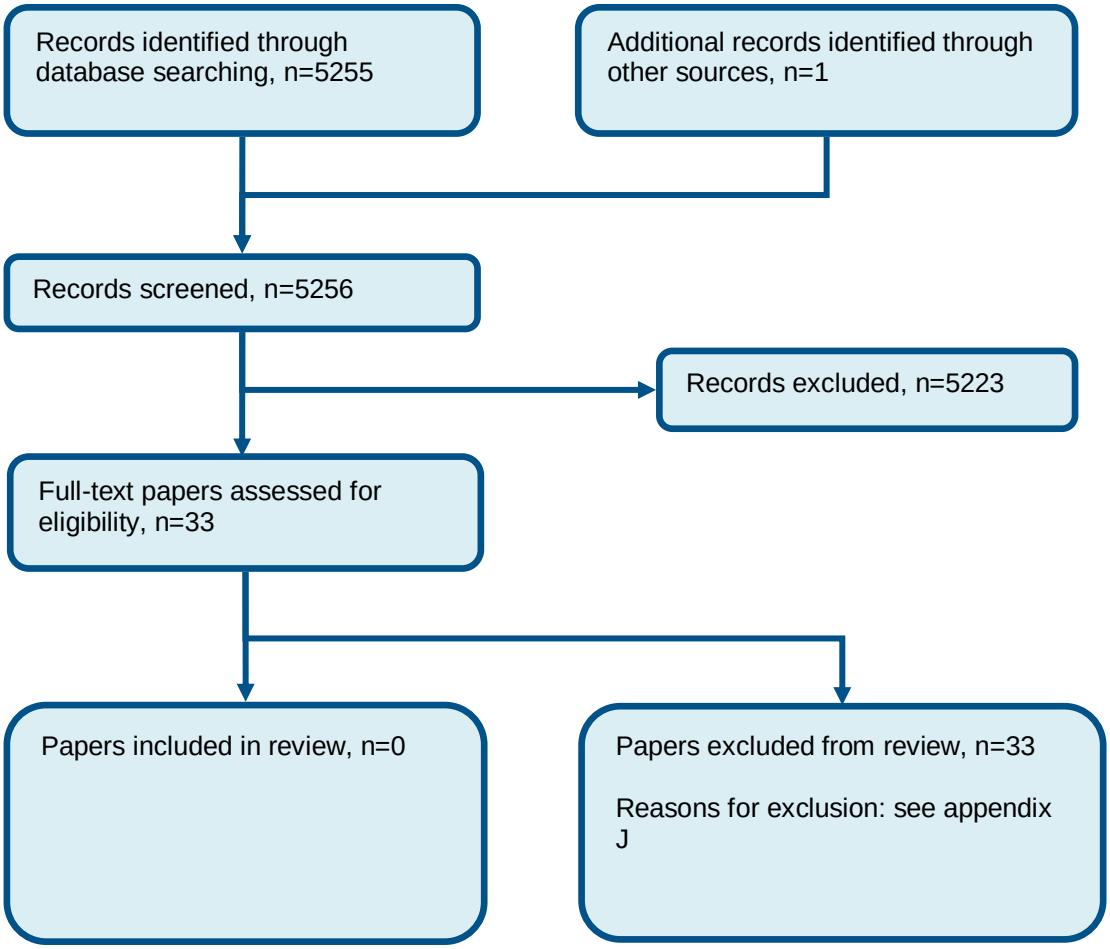
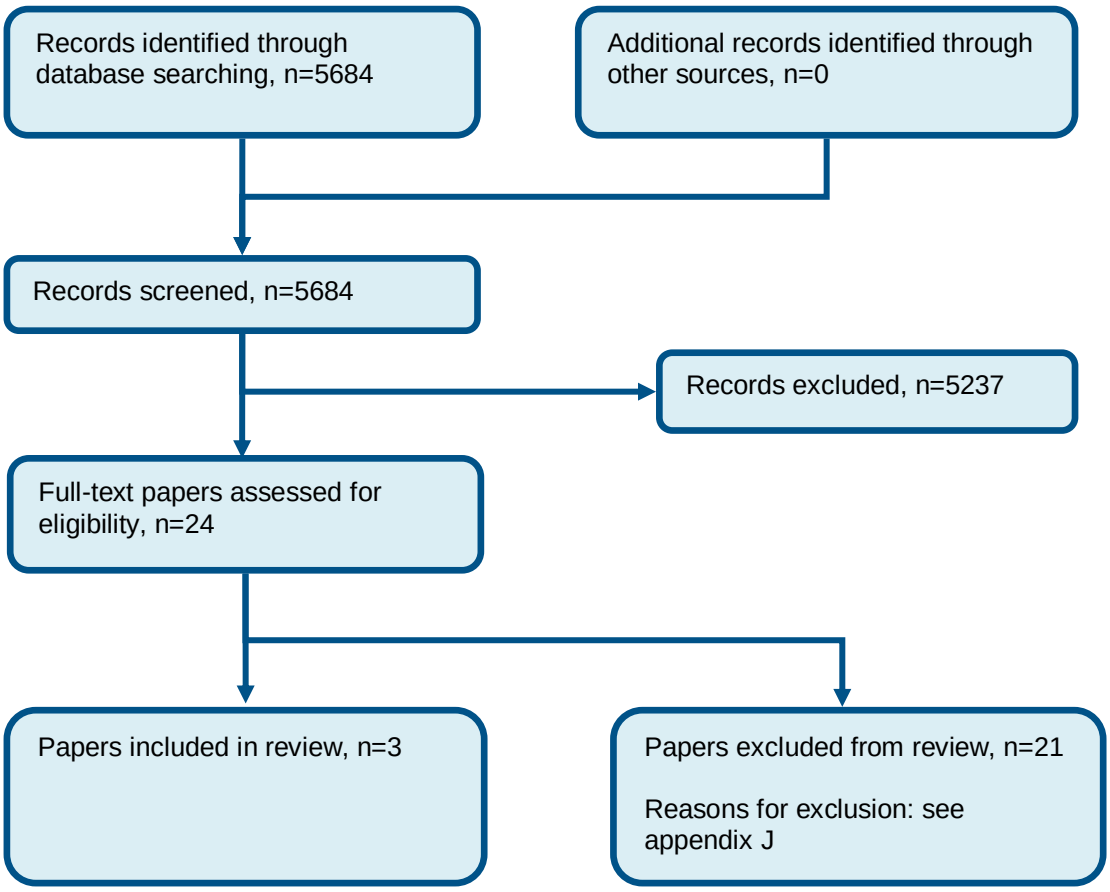


Figure 2: Flow chart of clinical study selection for the review of preoperative management of anaemia (IV iron versus oral iron).



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Appendix D: Clinical evidence tables

1.8.4 Oral iron

No clinical evidence identified.

1.8.5 IV iron

Study	Keeler 2017[29]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=116)
Countries and setting	Conducted in United Kingdom; Setting: Secondary care. Across 7 sites in the UK.
Line of therapy	Not applicable
Duration of study	Intervention time: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable:
Inclusion criteria	Patients diagnosed with colorectal cancer with haemoglobin <11 g/dl for women and <12 g/dl for men.
Exclusion criteria	Patients with metastatic disease, pre-existing haemotological disease, renal failure and those currently undergoing chemotherapy were excluded to minimise the risk of inclusion of people with non-iron deficiency anaemia.
Recruitment/selection of patients	Patients with colorectal cancers screened for eligibility.
Age, gender and ethnicity	Age - Median (range): 74 (67-81). Gender (M:F): 72/44. Ethnicity: Not reported
Further population details	1. American Society of Anesthesiologists (ASA) Physical Status grade: N/A 2. Older people (over 60): Yes 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: Major
Indirectness of population	No indirectness
Interventions	(n=55) Intervention 1: intravenous iron therapy. Ferric carboxymaltose diluted in 250 ml 0.9% saline. Dose calculated using body weight and Hb level. Maximum dose of 1000mg per week and 2000mg during the trial. . Duration 3 weeks. Concurrent medication/care: NA . Indirectness: No indirectness Further details: 1. Time to surgery: Median 3 weeks

Study	Keeler 2017[29]
	Comments: treatment for at least 2 weeks (n=61) Intervention 2: oral iron therapy. Ferous sulphate 200mg twice daily until surgery. Duration 3 weeks. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Time to surgery: Median 3 weeks Comments: treatment at least 2 weeks
Funding	Study funded by industry (Grant received from Syner-Med and Vifor Pharma and Pharmacosmos)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRAVENOUS IRON THERAPY versus ORAL IRON THERAPY

Protocol outcome 1: Perioperative Hb level
- Actual outcome: Hb levels at surgery at 3 weeks (median); IV iron: Median (IQR): 1.55 (0.93-2.58) (n=50); oral iron: Median (IQR): 0.5 (-0.13-1.33)(n=55). Change score of intervention vs control was statistically significant. P<0.001
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: failed to meet 14 day treatment period prior to surgery; Group 2 Number missing: 6, Reason: failed to meet 14 day treatment period prior to surgery

Protocol outcome 2: Blood transfusion (pre, intra and post surgery)
- Actual outcome: Pre-operative blood transfusion at (median)3 weeks; Group 1: 0/50, Group 2: 5/55
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: failed to meet 14 day treatment period prior to surgery; Group 2 Number missing: 6, Reason: failed to meet 14 day treatment period prior to surgery

Protocol outcome 3: Blood transfusion (pre, intra and post surgery)
- Actual outcome: Blood transfusion on the day of surgery at (median)3 weeks; Group 1: 6/50, Group 2: 6/55
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: failed to meet 14 day treatment period prior to surgery; Group 2 Number missing: 6, Reason: failed to meet 14 day treatment period prior to surgery

Protocol outcome 4: Blood transfusion (pre, intra and post surgery)
- Actual outcome: Post-operative blood transfusion at (median)3 weeks; Group 1: 4/50, Group 2: 6/55
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: failed to meet 14 day treatment period prior to surgery; Group 2 Number missing: 6, Reason: failed to meet 14 day treatment period prior to surgery. Comments: Study reports total number of transfusions, subtracted no. of pre and intra-transfusions to ascertain post-op figures.

Study	Keeler 2017[29]
	Protocol outcome 5: Blood transfusion (pre, intra and post surgery) - Actual outcome: Perioperative blood transfusion volume at 3 weeks (median); Group 1 mean 0.632 units (SD 1.3835); n=55, Group 2: mean 0.698 units (SD 1.9247); n=50. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: failed to meet 14 day treatment period prior to surgery; Group 2 Number missing: 6, Reason: failed to meet 14 day treatment period prior to surgery. Protocol outcome 5: Length of hospital stay - Actual outcome: Post operative length of stay at 3 weeks (median); IV iron: Median (IQR): 6 (5-10) (n=50); oral iron: Median (IQR): 6 (4-9) (n=55). Change score of intervention vs control was not statistically significant. P=0.950 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: failed to meet 14 day treatment period prior to surgery; Group 2 Number missing: 6, Reason: failed to meet 14 day treatment period prior to surgery Protocol outcome 6: Adverse events from iron infusion(e.g. constipation, nausea) - Actual outcome: Complications at 3 weeks (median); Oral iron: two people reduced their dose because of complication (dyspepsia and constipation) IV iron: Postinfusion headache was the most frequent complication (reported by three people). One significant adverse event was reported, a rash that required intervention of oral antihistamine medication. ; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: failed to meet 14 day treatment period prior to surgery; Group 2 Number missing: 6, Reason: failed to meet 14 day treatment period prior to surgery
Protocol outcomes not reported by the study	Mortality ; Quality of life ; Postoperative morbidity score ; Unplanned ICU admission ; ICU length of stay (planned and unplanned) ; Adverse events from transfusion (e.g. infections, reactions (compatibility), hypersensitivity)

Study	Kim 2009[31]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=76)
Countries and setting	Conducted in South Korea; Setting: Women's clinic of three hospitals in South Korea
Line of therapy	Not applicable
Duration of study	Intervention time: 3 weeks

Study	Kim 2009[31]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Menorrhagic patients with established IDA who had haemoglobin levels <9 g/dl and were scheduled to undergo surgical treatment.
Exclusion criteria	Anaemia from causes other than IDA, current administration of iron, previous iron therapy or transfusion within 3 months, a history of hematologic disease, and chronic disease not appropriate for clinical trial.
Recruitment/selection of patients	Recruited from the women's clinic of three hospitals
Age, gender and ethnicity	Age - Mean (SD): 42 (7.5). Gender (M:F): Not reported. Ethnicity:
Further population details	1. American Society of Anesthesiologists (ASA) Physical Status grade: N/A 2. Older people (over 60): No 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: Major
Indirectness of population	No indirectness
Interventions	(n=39) Intervention 1: intravenous iron therapy. Iron sucrose calculated following formula: weight (kg) x [10 Hb (g/dl) - actual Hb (g/dl) x 2.4 = 500 mg, rounded to the nearest multiple of 100 mg. Most patients received iron sucrose infusion at a rate of 200 mg every other day, 3 times a week, beginning 3 weeks before surgery. . Duration 3 weeks. Concurrent medication/care: Additional oral iron was not administered. . Indirectness: No indirectness Further details: 1. Time to surgery: 3 weeks (n=37) Intervention 2: oral iron therapy. 2 ampoules of oral protein succinylate (total of 80 mg of elementary iron) per day, 3 weeks before surgery until time of surgery.. Duration 3 weeks. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Time to surgery: 3 weeks
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRAVENOUS IRON THERAPY versus ORAL IRON THERAPY

Protocol outcome 1: Perioperative Hb level
- Actual outcome: Difference in Hb from preoperative Hb to postoperative Hb (g/dl) at 3 weeks; Group 1: mean 3 g/dl (SD 1.6); n=30, Group 2: mean 0.8 g/dl (SD 1.2); n=26; Comments: preoperative Hb: IV iron 7.5 (1.2), oral iron 7.8 (1.1)
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low,

Study	Kim 2009[31]
Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7, Reason: non-compliance; Group 2 Number missing: 11, Reason: non-compliance Protocol outcome 2: Adverse events from iron infusion(e.g. constipation, nausea) - Actual outcome: Adverse events at 3 weeks; Group 1: 3/30, Group 2: 2/26; Comments: IV: two cases of myalgia, one case of injection pain. Oral: one event of nausea, one event of dyspepsia. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7, Reason: non-compliance; Group 2 Number missing: 11, Reason: non-compliance	
Protocol outcomes not reported by the study	Mortality ; Quality of life ; Blood transfusion (pre, intra and post surgery) ; Postoperative morbidity score ; Change in healthcare management (e.g. delayed surgery, surgery cancellation) ; Length of hospital stay ; Unplanned ICU admission ; ICU length of stay (planned and unplanned) ; Adverse events from transfusion (e.g. infections, reactions (compatibility), hypersensitivity)

Study	Padmanabhan 2019[47]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in the UK; Setting: the Heart & Lung Centre at Royal Wolverhampton Hospitals NHS Trust.
Line of therapy	Not applicable
Duration of study	Intervention time: 3-8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled for elective cardiac surgery, defined as coronary artery bypass graft and/or open valve surgery, were included if they were also anaemic according to the World Health Organization criteria (haemoglobin <120 g/l for women and <130 g/ l for men).
Exclusion criteria	Patients were excluded if they had deficiencies in B12 or folic acid. Other exclusion criteria were low haemoglobin attributable to haemoglobinopathy, participating in another trial, inability to provide written consent, recognized allergy or other contraindications to intravenous iron or related products, already receiving intravenous iron treatment, evidence of significant symptomatic anaemia that would normally

Study	Padmanabhan 2019[47]
	require urgent transfusion at the time of assessment, haemoglobin less than 90 g/l (9.0 g/dl), blood transfusion between enrolment and admission and pregnancy and/or breastfeeding.
Recruitment/selection of patients	Recruited from participating hospital
Age, gender and ethnicity	Age - Mean (SD): 74 (11). Gender (M:F): 27:17
Further population details	1. American Society of Anesthesiologists (ASA) Physical Status grade: N/A 2. Older people (over 60): No 3. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: Major
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: IV oral therapy: Patients randomized to intravenous iron (FCM; Ferinject) received treatment in accordance with the manufacturer's instructions (maximum dose 1000 mg). FCM was diluted in 250 ml of 0.9% sodium chloride using an aseptic technique and administered over 30 min during the preoperative clinic. Standard observations including pulse rate, blood pressure, temperature and oxygenation saturation were monitored before and after infusion and as indicated by their clinical status. The dose of FCM was calculated using a fixed FCM dosing regimen. A second dose was offered when required. Duration unclear. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Time to surgery: 3-8 weeks (n=22) Intervention 2: oral iron therapy. Patients allocated to oral iron received 200mg of ferrous sulphate twice daily. Compliance with medication use was checked by asking patients to return the empty blister packs and to complete a medication log. Duration 3-8 weeks. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Time to surgery: 3-8 weeks
Funding	Supported by a Tripartite charitable award (hospital based) and Vifor Pharma (UK).

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRAVENOUS IRON THERAPY versus ORAL IRON THERAPY

Protocol outcome 1: Perioperative Hb level
- Actual outcome: Difference in Hb from enrolment Hb to surgical admission Hb (g/dl) at 3 weeks; Group 1: mean haemoglobin increased from 118.8 (8.9) g/l to 120.1 (9.8) g/l in the intravenous group (P = 0.44)n=22, Group 2: mean haemoglobin increased from 113.9 (11.1) g/l to 118.3 (12.0) g/l in the oral group (P = 0.06); n=22; Comments: difference in baseline Hb levels
Risk of bias: All domain – Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Blood transfusion

Study	Padmanabhan 2019[47]
- Actual outcome: patients transfused. Group 1: 16/20, Group 2: 12/20 For transfusion requirements, there were no differences in median postoperative packed red cell use between groups [intravenous 2.0 units (IQR 1.0–4.8), oral 1.5 units (interquartile range 0–2.0); P = 0.16]. However, the intravenous group was associated with larger volume of blood loss during the first 12h (median 655ml; interquartile range 162–1540 ml) compared to the oral iron group (median 313 ml; interquartile range 150–1750 ml; P < 0.007). Protocol outcome 3: Adverse events from iron infusion (e.g. constipation, nausea) - Actual outcome: Adverse events at postoperative period; Group 1: 15/20 (infection (4), AF (10), RRT (1)); Group 2: 17/20, (infection (5), AF (11), RRT (1)) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 4: Length of hospital stay -Actual outcome: Length of stay (days), median (IQR). Group 1: 7 (3–49) ; Group 2; 9 (3–30) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 5: Length of ICU stay -Actual outcome: Length of ICU stay (hours), median (IQR). Group 1: 88.0 (?-106.) ; Group 2; 69 (12–190) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness. Comments: IQR incompletely reported in paper. Protocol outcome 6: Quality of life -Actual outcome: Quality of life: No statistically significant differences in any subset of the EQ-5D or SF-36 were identified when considering the effects of treatment during the 3 study visits. Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality ; Quality of life ; Postoperative morbidity score ; Change in healthcare management (e.g. delayed surgery, surgery cancellation) Unplanned ICU admission ; Adverse events from transfusion (e.g. infections, reactions (compatibility), hypersensitivity)

Appendix E: Forest plots

E.1 IV iron versus oral iron

Figure 3: Change in Hb levels from preoperative to postoperative

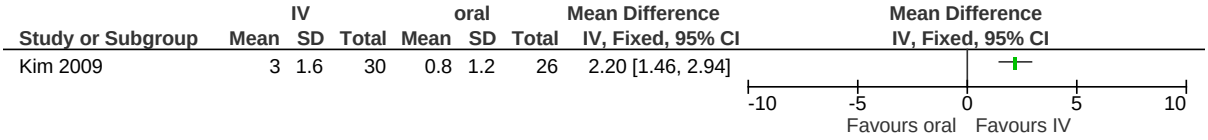

Figure 4: Preoperative Hb levels

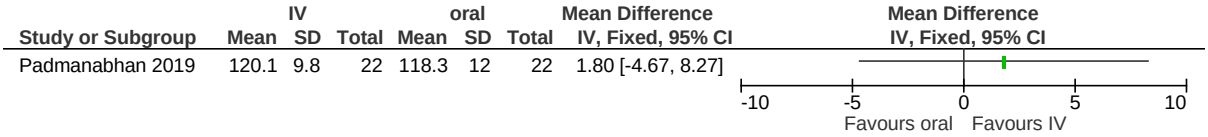

Figure 5: Preoperative blood transfusion

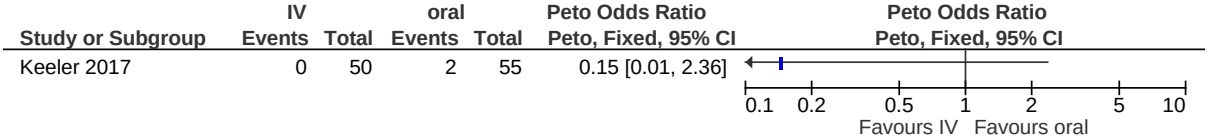

Figure 6: Blood transfusion on the day of surgery

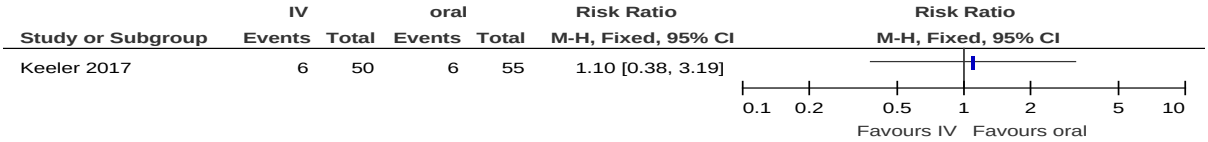

Figure 7: Postoperative blood transfusion

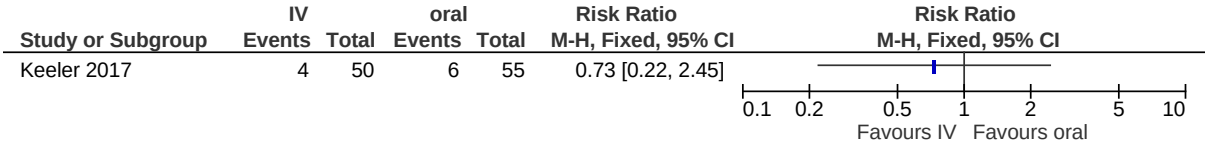

Figure 8: Perioperative blood transfusion volume

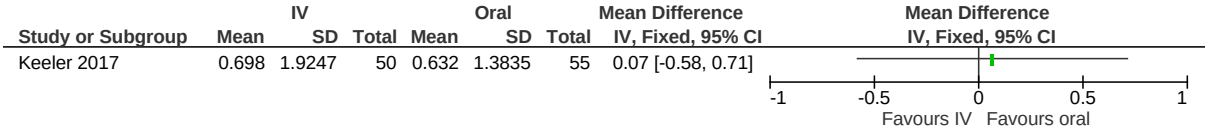

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Figure 9: Patients transfused

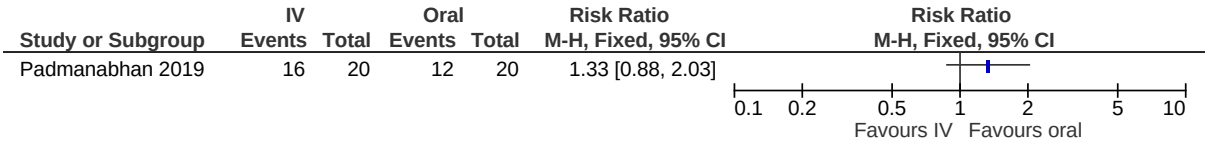

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Figure 10: Complications

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Appendix F: GRADE tables

Table 16: Clinical evidence profile: IV iron compared to oral iron for preoperative management of anaemia

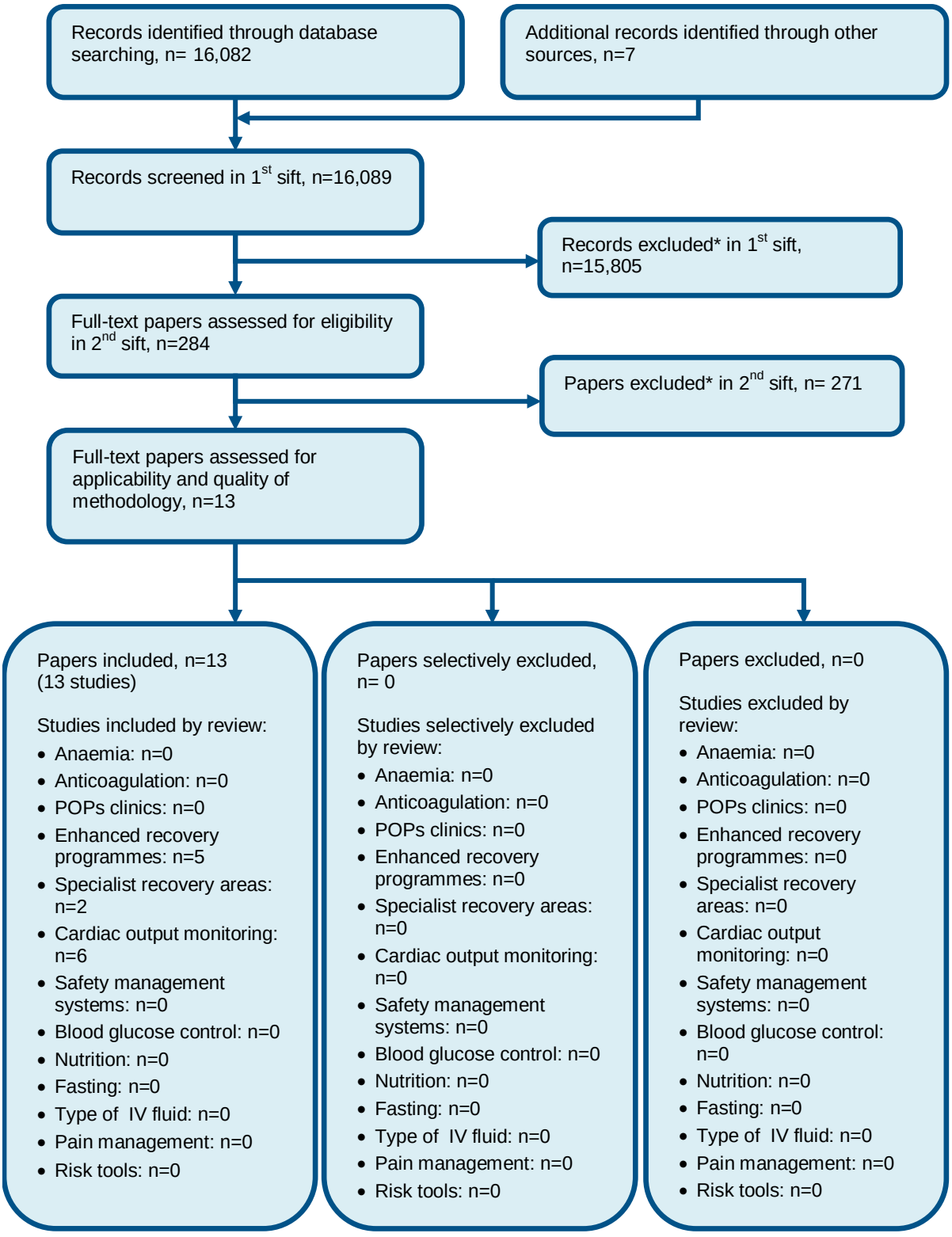
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron	Oral iron	Relative (95% CI)	Absolute		
Change in Hb levels from preoperative to postoperative (follow-up mean 3 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	26	-	MD 2.2 higher (1.46 to 2.94 higher)	ΘΘΘO MODERATE	CRITICAL
Pre-operative blood transfusion (follow-up median 3 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	0/50 (0%)	9.1%	Peto OR 0.15 (0.01 to 2.36)	80 fewer per 1000 (from 90 fewer to 100 more)	ΘΘΘO MODERATE	CRITICAL
Blood transfusion on the day of surgery (follow-up median 3 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	6/50 (12%)	10.9%	RR 1.1 (0.38 to 3.15)	11 more per 1000 (from 68 fewer to 234 more)	ΘΘOO LOW	CRITICAL
Complications (follow-up mean 3 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	18/50 (36%)	41.3%	RR 0.93 (0.65 to 1.32)	29 fewer per 1000 (from 145 fewer to 132 more)	ΘOOO VERY LOW	IMPORTANT
Post-operative blood transfusion (follow-up median 3 weeks)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	4/50 (8%)	10.9%	RR 0.73 (0.22 to 2.45)	29 fewer per 1000 (from 85 fewer to 158 more)	ΘΘOO LOW	CRITICAL
Postoperative Hb levels (follow-up post-operatively; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22	22	-	MD 1.80 higher (4.67 lower to 8.27 higher)	ΘOOO VERY LOW	CRITICAL
Patients transfused (follow-up postoperatively)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16/20 (80%)	60%	RR 1.33 (0.88 to 2.02)	198 more per 1000 (from 72 fewer to 612 more)	ΘΘOO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Appendix G: Health economic evidence selection

Figure 11: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 17: Studies excluded from the clinical review (oral iron)

Reference	Reason for exclusion
Abraham 2017[1]	Excluded due to inappropriate study comparison
Alexander 2017[2]	Systematic review not relevant to review PICO
Armas-Loughran 2003[4]	Excluded due to inappropriate study design
Ashby 1967[5]	Excluded due to inappropriate interventions
Baele 2002[6]	Excluded due to inappropriate study design
Bisbe 2012[7]	Excluded due to inappropriate study design
Borstlap 2015[9]	Systematic review not relevant to review PICO
Clevenger 2015[12]	Excluded due to inappropriate study design
Fischer 2015[17]	Excluded due to inappropriate comparison
Grant-Casey 2010[23]	Excluded due to inappropriate study design
Guinn 2016[24]	Excluded due to inappropriate study design
Hare 2011[25]	Excluded due to inappropriate study design
Jans 2018[26]	Excluded due to inappropriate population
Kansagra 2016[28]	Excluded due to inappropriate study design
Kotze 2012[32]	Excluded due to inappropriate study comparison
Kumar 2008[33]	Excluded due to inappropriate study design
Layton 2013[34]	Excluded due to inappropriate study design
Lidder 2007[36]	Excluded due to inappropriate interventions
Lilaramani 1974[37]	Excluded due to inappropriate interventions
Munoz 2012[39]	Excluded due to inappropriate study design; interventions
Munoz 2014[38]	Systematic review not relevant to review PICO
Najafi 2015[40]	Excluded due to inappropriate study design; interventions
Napolitano 2005[41]	Excluded due to inappropriate study design
Ng 2015[44]	Systematic review not relevant to review PICO
Okuyama 2005[46]	Excluded due to inappropriate interventions
Petis 2017[49]	Excluded due to inappropriate interventions
Quinn 2010[51]	Excluded due to inappropriate study comparison
Rineau 2017[53]	Excluded due to inappropriate study comparison
Sheth 2002[55]	Excluded due to inappropriate interventions
Stoffel 2017[56]	Excluded due to inappropriate review population
Stoneham 2007[58]	Excluded due to inappropriate study design
Taylor 2013[60]	Excluded due to inappropriate study design
Tseliou 2002[61]	Excluded due to inappropriate study comparison

Table 18: Studies excluded from the clinical review (IV iron)

Study	Exclusion reason
Alexander 2017[2]	Systematic review is not relevant to review question or unclear PICO

Study	Exclusion reason
Andrews 1997[3]	Incorrect study design. Incorrect interventions
Bisbe 2014[8]	Not review population
Borstlap 2015[10]	Incorrect study design - review protocol
Borstlap 2015[11]	Incorrect study design - abstract
Derzon 2019[15]	Systematic review: references screened
Edwards 2009[16]	Inappropriate comparison
Froessler 2012[20]	Incorrect study design - review protocol
Froessler 2013[19]	Systematic review is not relevant to review question or unclear PICO. Relevant study already included in review
Froessler 2016[18]	Incorrect interventions
Garrido 2010[22]	Incorrect interventions
Garrido-Martin 2012[21]	Incorrect interventions
Khalafallah 2015[30]	study design - structured abstract
Lee 2018[35]	Incorrect study design - review protocol
Ng 2015[44]	Relevant study already included in review
Peters 2018[48]	Systematic review is not relevant to review question or unclear PICO. Relevant study already included in review
Quinn 2017[50]	Incorrect study design. Inappropriate comparison
Richards 2015[52]	Incorrect study design - review protocol
Schack 2019[54]	Systematic review: references screened
Tang 2019[59]	Systematic review: references screened
Wilson 2018[62]	Incorrect interventions. Incorrect study design

I.2 Excluded health economic studies

Table 19: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

Appendix J: Research recommendations

J.1 Management of anaemia

Research question: For people with iron-deficiency anaemia, how long before surgery should oral iron supplementation be started, and what is the clinical and cost effectiveness of daily oral iron compared with oral iron given on alternative days?

Why this is important:

Iron deficiency anaemia is common in the surgical population. The time from identification of iron deficiency anaemia in a surgical patient, to the time of surgery is variable; it can be months for an elective procedure such as joint replacement or two weeks for cancer surgery. Treatment options include oral supplementation and/or intravenous preparations. There are limited randomised controlled clinical trials examining the clinical and cost effectiveness of oral versus intravenous iron for the treatment of iron deficiency anaemia prior to surgery. This has led variation in clinical practice in the treatment of iron deficiency prior to surgery and requires further research to inform development of guidelines and standardisation of routine care.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Adults 18 years and over having surgery who have been identified during preoperative assessment as having iron deficiency anaemia (haemoglobin <130 g/L (13 g/dL) in men older than age 15 years, <120 g/L (12 g/dL) in non-pregnant women older than age 15 years, and <110 g/L (11 g/dL) in pregnant women) undergoing surgery). Intervention(s): Preoperative alternate day oral iron therapy and daily oral iron therapy Comparison: Compared to each other, compared to different durations of therapy before surgery Outcome(s): All-cause mortality, health-related quality of life, preoperative Hb level, transfusion (pre-, intra- and post-surgery), postoperative morbidity score (POMS), change in healthcare management (for example, delayed surgery or surgery cancellation), length of hospital stay, unplanned ICU admission, ICU length of stay (planned and unplanned), adherence and adverse events from iron tablets (e.g. constipation, nausea)
Importance to patients or the population	Research in this field would help to define the most acceptable, clinically effective and cost effective treatment option for patients allowing them to make an informed choice on the best treatment option
Relevance to NICE guidance	There is current uncertainty concerning the optimal preoperative intervention for iron deficiency anaemia
Relevance to the NHS	Research in this area will inform NICE recommendations for service delivery (for example the need for rapid access anaemia clinics) and provide information about clinical and cost-effectiveness.
National priorities	None identified
Current evidence base	No studies were identified comparing daily oral iron therapy with alternate oral iron therapy. There were three RCTs comparing IV iron with oral iron however there is uncertainty which reduces the probability of adverse post- operative outcomes

Equality	Not applicable
Study design	RCT ideally, if not then a large non-randomised cohort study with adequate adjustment for key confounders including age, ethnicity, co-morbidities and some measure of baseline health (e.g. quality of life)
Feasibility	With the expansion of rapid access anaemia clinics administering intravenous iron it may be difficult for clinicians to accept equipoise and recruit patients to such a study
Other comments	None
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

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