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INTRAVENOUS IRON FOR IRON DEFICIENCY ANEMIA (IDA)

HEALTH TECHNOLOGY ASSESSMENT SECTION (MaHTAS)
MEDICAL DEVELOPMENT DIVISION
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DISCLAIMER

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DISCLOSURE

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EXECUTIVE SUMMARY

Background

Iron deficiency anaemia (IDA) has been recognised as one of the important public health concerns which affects not only growing children, premenopausal, and pregnant women, but also being increasingly considered as a clinical condition that can affect patients presenting to various medical and surgical specialities, especially those with chronic conditions and the elderly.[1] The Global Burden of Disease project estimated around 1.24 billion people (a sixth of worldwide population) are suffering from IDA. In fact, it is one of the five leading causes of years lived with disability in humans and affected women mostly.[2] Aetiologies of IDA may vary widely or tend to coexist in different patient populations, especially those with severe and/or recurring IDA, geographies (developing and developed countries) and specific clinical conditions, which may be categorised into three major groups: 1) imbalance between iron intake and iron needs, 2) blood losses (either occult or overt), and 3) malabsorption.[1,3]

The mainstay treatment of IDA treatment remains to investigate and manage the underlying cause of IDA. Patients age and sex, the underlying condition and cause of IDA, the severity of anaemia or ID and their symptoms, and the time frame available or acceptable for correction are among factors that should be taken into consideration during decision making. Though there is no clear benefit on treating ID without anaemia, patients presenting with IDA should be treated with iron supplementation that can be administered either orally or parenterally. Unless contraindicated, oral iron therapy is the first line of treatment of IDA. Intravenous iron (IVI) can be considered in cases of intolerance or when signs of non-response are noted despite efforts to improve tolerance, adherence, or absorption of oral iron. intravenous iron can be considered with appropriate dosing. Haemoglobin (Hb) and iron indices should be monitored continuously every 1-3 months until normalisation of laboratory values.[1] With regards to IVI use, a recent systematic review discovered that many of the existing national and international clinical guidelines are lacking updated and clarified information on IDA management modalities across different therapeutic areas.[4]

In the Ministry of Health healthcare facilities, IVI is mostly prescribed in selected cases, such as in Obstetrics & Gynaecology (O&G) and Chronic Kidney Disease (CKD) patients, and some may even require a prescription from haematologists. It is thought that there is scepticism around the use of IVI for other IDA-related indication due to its limited access in the pragmatic setting. Furthermore, IVI may provide a safer alternative to blood transfusion in treating anaemia. Hence, this technology review was conducted following a request by a transfusion medicine specialist from National Blood Centre, Ministry of Health Malaysia to ascertain the benefit of using intravenous iron for the treatment of patients with IDA, particularly its impact on Hb concentration, blood transfusion requirement and their safety profile.

Objective/aim

To compare the effectiveness, safety, cost-effectiveness, and organizational issues of IVI preparations that are available in the Malaysian market with oral iron or other alternatives in the treatment of adult patients with iron deficiency anaemia (IDA).

Results & Conclusion

A total of 3,901 records were screened, and 3,738 studies that did not meet the inclusion criteria were excluded. One hundred and sixty-three of potentially relevant abstracts were retrieved in full text and assessed for eligibility. Out of these, 22 studies comprising of six systematic reviews of randomised controlled trials (RCTs), nine RCTs, four prospective cohort studies, two cost-effectiveness analyses and one cost-minimization analysis were finally selected for this review.

The studies were conducted mainly in the United Kingdom, the United States of America, India, Spain, Korea, China, Hong Kong, Australia, Singapore, France, Thailand, Turkey, Norway, Romania, Egypt, Greece, Spain, Denmark, and Pakistan. The study populations included were among oncologic, cardiac, obstetric and gynaecologic patients undergoing surgery, traumatic patients with a critical illness as well as non-dialysis chronic kidney disease patients.

Efficacy and Effectiveness

Based on the review, the evidence showed that preoperative IVI did significantly increase Hb concentration in surgical patients when compared to oral iron. However, in trials that compared IVI to no iron therapy, there was no strong evidence to support that preoperative IVI has led to significant improvement in Hb concentration. Only one study included in this review investigated the postoperative effect of IVI and found that it has shown favourable results on day 14 of operation compared to no iron therapy. In all studies with positive results for perioperative IVI over the control group, IVI was administered at least 14 days prior to surgery, or improvement in Hb level measured 14 days after the first dose of IVI administration.

Significant improvement in Hb concentration with IVI was also observed in pregnant and postpartum women when compared to oral iron. This effect, however, was not seen in other populations included in the review, as IVI did not demonstrate any apparent benefit over the control group.

There is also a lack of head-head trial comparing different types of IVI formulations. In one study, both intravenous ferric carboxymaltose (IV FCM) and intravenous iron sucrose (IV IS) markedly improved preoperative haemoglobin concentration, with IV FCM achieving Hb correction about three days earlier than IV IS. However, no significant difference was observed between these two formulations.

Moreover, while IVI was reported to lessen the risk for blood transfusion among anaemic pregnant and postpartum women to a certain degree when compared to

oral iron, the reduction in blood transfusion requirement was uncertain for all populations included in this review.

Almost all studies that reported on serum ferritin level showed that IVI did significantly increase the mean ferritin level compared to the control group with oral iron or no iron therapy.

There were mixed results for mean transferrin saturation level as some studies reported significant increased compared to control, while a few reported comparable effects were observed between groups.

Safety

In comparison to the control group, the mortality rates (treatment-related/ infection/ all causes) within the follow-up period were comparable to patients treated with IVI. A trial involving non-dialysis CKD patients treated with IVI documented a higher incidence of hospitalised heart failure and significant lung and skin infection rates compared to the oral iron group. Nevertheless, the risk of experiencing serious adverse events and infection rate in other populations was comparable between IVI and control groups.

IVI was also associated with decreased risk for gastrointestinal adverse events, particularly with IV IS, intravenous iron dextran (IV ID) and IV FCM, and when compared to oral iron or no iron therapy. On the other hand, the risk for neurologic and muscle and skeletal adverse events increased with IVI, particularly with IV IS and IV FCM, respectively.

While there was no significant difference in risk for hypersensitivity reaction between IV FCM and IV IS, the odds of experiencing severe hypersensitivity reaction with intravenous iron derisomaltose (IV IIM) was 59% lower than that of IV FCM, and 49% lower than that of IV IS. The risk for cardiovascular adverse event was reported to comparable between IV FCM and IV IS. However, this risk was noted to be lower with IV FCM, while the use of intravenous ferric gluconate (IV FG) was associated with increased risk. There was also a risk for IVI-related infusion reaction, with increased risk for such reaction was observed for IV IS and IV FCM with more serious infusion reactions were seen with IV FG.

Additionally, hypophosphataemia was one the most common electrolytes imbalance documented with IVI therapy.

Organisational Issue

There was a limited fair to good level of retrievable evidence to suggest that treatment of IDA with IVI resulted in no significant difference in length of hospitalisation between IVI and control groups, be it in perioperative settings, critical care patients or pregnant women.

Cost

In comparison to no iron therapy, preoperative optimisation of Hb with IVI in a theoretical model simulation among patients with primary knee arthroplasty resulted in cost savings of €831 and €405 for blood transfusion avoided per patient and each RBC unit spared, respectively.

Similarly, in comparison to standard medical care, preoperative treatment with IVI among patients undergoing abdominal surgery has resulted in cost savings of €786 per case by reducing the blood transfusion rate and costs paid by hospitals for extended hospitalisation.

Furthermore, use of IV FCM was associated with more reduction in total costs for treating IDA in patients with colon cancer, with total costs per patient were €1,827, €2,312 and €2,101 for IV FCM, IV IS and oral iron, respectively. Thus, baseline data cost savings for IV FCM treatment were €485 when compared to IV IS and €274 when compared to oral iron.

From these studies, factors that highly influenced the resulting cost savings were the cost of the outpatient clinic, transfusion rate in all treatment arms, as well as the length of hospitalisation.

Methods

Electronic databases searched through the Ovid interface: MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to May 19, 2020; EBM Reviews - Cochrane Database of Systematic Reviews 2005 to May 14, 2020; EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2016; EBM Reviews - Cochrane Central Register of Controlled Trials April 2020; EBM Reviews - Health Technology Assessment 4th Quarter 2016; EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016. Searches were also run on PubMed, the United States Food and Drug Administration (US FDA) and INAHTA databases.

No limits were applied. Additional articles were identified from reviewing the references of retrieved articles. The search strategy was updated until 20th May 2020. In addition, Google was used to search for additional web-based materials and information.

INTRAVENOUS IRON

1.0 BACKGROUND

Iron deficiency anaemia (IDA) has been recognised as one of the important public health concerns which affects not only growing children, premenopausal, and pregnant women, but also being increasingly considered as a clinical condition that can affect patients presenting to various medical and surgical specialities, especially those with chronic conditions and the elderly.[1] The Global Burden of Disease project estimated around 1.24 billion people (a sixth of worldwide population) are suffering from IDA. In fact, it is one of the five leading causes of years lived with disability in humans and affected women mostly.[2] Aetiologies of IDA may vary widely or tend to coexist in different patient populations, especially those with severe and/or recurring IDA, geographies (developing and developed countries) and specific clinical conditions, which may be categorised into three major groups: 1) imbalance between iron intake and iron needs, 2) blood losses (either occult or overt), and 3) malabsorption.[1,3]

The development of IDA usually occurs slowly over time with three main stages involved. In the beginning, levels of circulating iron are normal due to mobilisation of iron from the stores, initially from ferritin, which is easily available, and then from hemosiderin. Over time, as iron stores are kept on mobilised to compensate for iron deficiency (ID), it will result in the total depletion of iron stores. At this moment, the serum iron is low, but erythropoiesis is not yet disturbed. Eventually, without proper treatment of underlying causes of ID, the quantity of iron delivered to the erythroblasts would be inadequate, leading to a decline in the synthesis of haemoglobin (Hb), and hypochromia occurs. Thus, hypochromic microcytic anaemia will occur in the final stage.[4]

Measurement of Hb concentration and iron status biomarkers are paramount in diagnosing and confirming IDA. Table 1 summarises the laboratory tests that have been used in evaluating iron status in adults. Serum ferritin level is the most sensitive and specific test used for the identification of ID (indicated by a level of <30 ng/ml). Patient with IDA have a low level of serum ferritin, and along with transferrin saturation level of less than 16%, it indicates that an iron supply is insufficient to support normal erythropoiesis. In the presence of inflammations such as in chronic diseases or malignancy, the diagnosis of iron deficiency anaemia can be more complicated and requires evaluation of two or more of iron indices. Hence, significantly higher cut-off levels for ferritin are used to define IDA accompanied by inflammation with the best predictor being a ferritin level of less than 100 ng/ml. Higher cut-off levels for ferritin are used in the diagnosis of iron deficiency in other conditions (e.g., < 300 ng/ml for heart failure and for chronic kidney disease in the presence of a transferrin

saturation level of less than 30%). The assessment of iron stores through iron staining of bone marrow specimens obtained by means of biopsy is an option that is not used frequently. Currently, reliable test for hepcidin levels is lacking.[5]

The mainstay of IDA management remains to investigate and manage the underlying cause of IDA. Patients age and sex, the underlying condition and cause of IDA, the severity of anaemia or ID and their symptoms, and the time frame available or acceptable for correction are among factors that should be taken into consideration during decision making. Though there is no clear benefit on treating ID without anaemia, patients presenting with IDA should be treated with iron supplementation that can be administered either orally or parenterally. Unless contraindicated, oral iron therapy is the first line of treatment of IDA. Intravenous iron (IVI) can be considered in cases of intolerance or when signs of non-response are noted despite efforts to improve tolerance, adherence, or absorption of oral iron. intravenous iron can be considered with appropriate dosing. Haemoglobin and iron indices should be monitored continuously every 1-3 months until normalisation of laboratory values.[1] Figure 1 briefly explains the difference in pharmacokinetic between oral iron and IVI. With regards to IVI use, a recent systematic review of 35 clinical guidelines available worldwide for the diagnosis and management of IDA across all indications, discovered that many of the existing national and international clinical guidelines are lacking updated and clarified information on IDA management modalities across different therapeutic areas.[6]

In the Ministry of Health healthcare facilities, IVI are mostly prescribed in selected cases, such as in Obstetrics & Gynaecology (O&G) and Chronic Kidney Disease (CKD) patients, and some may even require a prescription from haematologists. It is thought that there is scepticism around the use of IVI for other IDA-related indication due to its limited access in pragmatic setting. Furthermore, IVI may provide a safer alternative to blood transfusion in the treating anaemia. Hence, this technology review was conducted following a request by a transfusion medicine specialist from National Blood Centre, Ministry of Health Malaysia to ascertain the benefit of using intravenous iron for the treatment of patients with IDA, particularly its impact on Hb concentration, blood transfusion requirement and their safety profile.

Table 1: Laboratory test for measurement of iron status in adults[5]

Test	Iron Deficiency	Functional Iron Deficiency	Iron-Deficiency Anemia	IRIDA	Anemia of Chronic Diseases	Iron-Deficiency Anemia and Anemia of Chronic Diseases	Normal Value
Current							
Iron — μmol/liter	Low	Low–normal	Low	Low	Low	Low	10–30
Transferrin saturation — %	≥16	Low– normal	<16*	<10	Low–normal	Low–normal	>16 to <45
Ferritin — μg/liter	<30†	Normal	<10	Variable	>100‡	<100‡	
Men							40–300
Women							20–200
Hemoglobin — g/dl	Normal	Normal	Low	Low	Low	Low	
Men							>13
Women							>12
Mean corpuscular volume — fl	Normal	Normal	<80	Very low	Low–normal	Low	80–95
Mean corpuscular hemoglobin — pg	Normal	Normal	<27	Very low	Low–normal	Low	27–34
Proposed							
sTFR — mg/liter§	High	High	High	High	Low–normal	Variable	Varies¶
sTFR/log ferritin index‖	NA	NA	>2	NA	<1	>2	Varies¶
Hepcidin	Low	Low	Very low	Normal–high	High	Normal–high	Varies¶
Zinc protoporphyrin**	Normal	High	High	High	High	High	Varies¶
Reticulocyte hemoglobin content — pg††	<25	<29	Low	Low	Low	Low	31.2±1.6
Perl's staining of bone marrow for iron	Negative	Variable	Negative	Positive	Strongly positive	Positive	Positive

* The value for transferrin saturation in the diagnosis of iron-deficiency anemia is from Beutler and Waalen.[11]
† The value for ferritin in the diagnosis of iron-deficiency anemia has a sensitivity of 92% and a specificity of 83% according to Goodnough et al.[4]
‡ The value for ferritin in the anemia of chronic disease and the combined value for the anemia of chronic disease and iron deficiency are from Weiss and Goodnough.[3]
§ The value for the soluble transferrin receptor (sTFR), which is shed by the erythroblast membrane in serum, may be useful in the assessment of iron-deficiency anemia, but the methods used to measure sTFR have been not standardized.[3]
¶ Normal values vary according to the method of measurement used.
‖ The sTFR/log ferritin index has been proposed to distinguish iron-deficiency anemia in the anemia of chronic disease from the anemia of chronic disease alone.[3]
** The values for zinc protoporphyrin are used only in screening for or monitoring iron-deficiency anemia..[3]
†† Reduction of reticulocyte hemoglobin content is an early sign of functional iron deficiency.[12]

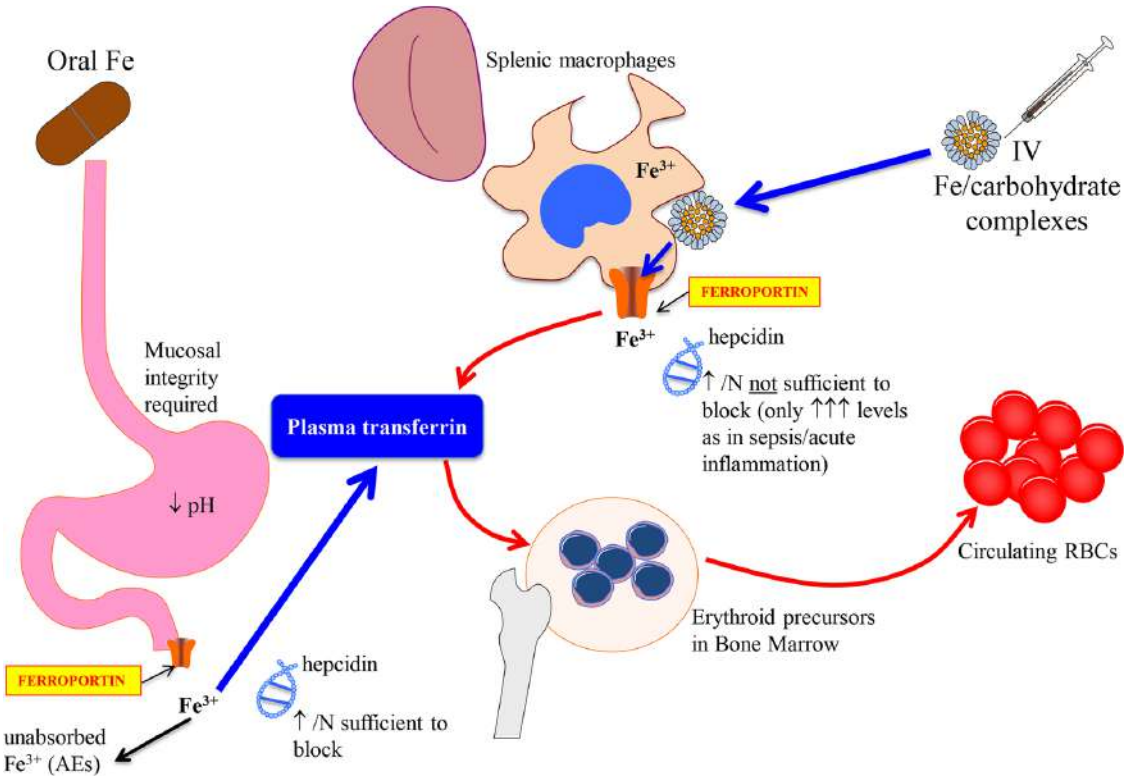


Figure 1: Different pharmacokinetic between oral and IV iron, revisited in the hepcidin era. Pharmacokinetic of oral iron requires the integrity of the mucosa of the stomach (acidity is needed to solubilize iron) and duodenum/proximal jejunum (where most of iron is absorbed). This integrity can be compromised by several conditions leading to malabsorption. The maximum absorption capacity during oral iron treatment is estimated to be near 25–30 mg/die, i.e. near ten to twenty-fold the typical daily absorption of dietary iron in steady-state condition (1–2 mg). Unabsorbed iron is mainly responsible of gastrointestinal adverse effects (AEs). IV iron has a completely different pharmacokinetic that circumvents these problems. The iron-carbohydrate complexes are rapidly taken up by macrophages, then iron atoms of the core are slowly released in the circulation through ferroportin. Both oral and IV iron requires ferroportin to be released in the plasma. Hepcidin production is typically suppressed in uncomplicated IDA, allowing maximal iron absorption. However, slightly elevated (or even inappropriately normal) hepcidin levels appear sufficient to inhibit intestinal ferroportin. This can be due to a genetic disorder (IRIDA), to concomitant low-grade inflammation (i.e. in chronic heart failure), or even to transient stimulation after a first dose of oral iron. This constitutes the basis for current recommendation of using oral iron on an alternate day schedule instead of the classical daily schedule (see the text for details). On the other hand macrophage ferroportin, whose expression is much higher than at the intestinal level, requires much more elevated hepcidin levels (i.e. like during acute inflammation) to be substantially suppressed.[3]

2.0 OBJECTIVE/ AIM

The objective of this technology review was to compare the effectiveness, safety, cost-effectiveness, and organizational issues of IVI preparations that are available in the Malaysian market with oral iron or placebo or standard care or other IVI formulations for the treatment of patients with IDA.

3.0 TECHNICAL FEATURES

IVI preparations are iron-carbohydrate complexes that have been bioengineered to deliver high doses of iron in a stable, non-toxic form. Table 2 highlights the clinical characteristics of IVIs that are available worldwide. They consist of colloidal suspensions of iron oxide nanoparticles with a polynuclear Fe (III)-oxyhydroxide/ oxide core surrounded by a carbohydrate ligand. In essence, IVI behaves as a prodrug, retaining ionic iron until the iron–carbohydrate complex is metabolised. The physicochemical differences between the IV irons (shown in Table 2) include mineral composition, crystalline structure, conformation, size and molecular weight. The carbohydrate ligand is the important property that makes each individual IVI unique and has a big influence on the complex stability, iron release and immunogenicity.[7]

Table 2: Clinical characteristics of currently available IV irons[7]

Generic name	**Ferumoxytol**	**Iron Carboxymaltose**	**Iron Derisomaltose**	**Low Molecular Weight Iron Dextran**	**Iron Sucrose**	**Iron Gluconate**
Brand name	Feraheme®	Ferinject®	Monofer®	Cosmofer®	Venofer®	Ferlixit®
Maximum single dose	510 mg	1000 mg	20 mg/kg	20 mg/kg	200 mg	125 mg
Minimum administration time (minutes)	15	15	15	60	30	30-60
Replacement dose possible in a single infusion	No	Yes	Yes	Yes	No	No

Table 3: Comparison of physicochemical characteristics and pharmacokinetics of IV irons[7]

Generic name	**Ferumoxytol**	**Iron Carboxymaltose**	**Iron Derisomaltose**	**Low Molecular Weight Iron Dextran**	**Iron Sucrose**	**Iron Gluconate**
Molecular weight (Da)	185,000	150,000	150,000	103,000	43,000	37,500
Carbohydrate ligand	Polyglucose sorbitol carboxymethylether	Carboxymaltose	Derisomaltose	Dextran polysaccharide	Sucrose	Gluconate, loosely associated sucrose

Relative stability of iron carbohydrate complex	High	High	High	High	Medium	Low
Reactivity with transferrin	Low	Low	Low	Low	Medium	High
Relative labile iron release	Low	Low	Low	Medium	High	High
Plasma half-life (hrs)	~15	7-12	20	5-20	6	~1

Currently, only intravenous iron dextran (IV ID), iron sucrose (IS) and iron derisomaltose/ isomaltoside 1000 (IIM) are available on the Malaysian market. Low molecular weight iron dextran (INFED®) and iron sucrose (VENOFER®) were approved by the U.S. Food & Drug Administration (US FDA) in 1974 and 2000, respectively, and have been in the market since. The third generation IVI, iron derisomaltose (MONOFER®) has been approved for use in other countries such as Canada and just recently obtained its approval by the US FDA in early 2020.[8]

For efficacy endpoints assessment, in line with the currently licensed indication of use for the intravenous iron (IVI),[9–11] only studies that clearly defined their population to be of iron deficient, anaemic patients will be included. Other studies without iron status clearly defined in inclusion or exclusion criteria will be considered for inclusion only if the published baseline data suggested absolute or functional IDA. In this case, anaemia will be defined as haemoglobin (Hb) concentration < 12.0 g/dL for non-pregnant women and < 13.0 g/dL for men.[12] The following cut-off values for corresponding biomarkers will be utilized as a guide in assessing the baseline ID status in the population of interest (if ID status was not explicitly stated in inclusion or exclusion criteria of included studies): serum ferritin concentration < 30 ng/ml (or < 100 ng/ml in inflammatory conditions); or serum ferritin level of 100 to 300 ng/ml with transferrin saturation below 20%.[1] The safety endpoints for IV IS, IV ID and IV IIM, on the other hand, will consider any prospective trial that used these IVIs regardless of the iron deficiency status of the population being studied.

4.0 METHODS

4.1. Searching

Electronic databases searched through the Ovid interface:

- MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to May 19, 2020
- EBM Reviews - Cochrane Database of Systematic Reviews 2005 to May 14, 2020

- EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2016
- EBM Reviews - Cochrane Central Register of Controlled Trials April 2020
- EBM Reviews - Health Technology Assessment 4th Quarter 2016
- EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016

Other databases:
- PubMed
- Other websites: US FDA, INAHTA database.

General databases such as Google and Yahoo were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles were also included. There was no language limitation in the search. **Appendix 1** showed detailed search strategies. The last search was conducted on 20th May 2020.

4.2. Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then appraised the full-text articles for final article selection. The inclusion and exclusion criteria were:

Inclusion criteria

Population	Adults patients, age ≥ 18 years old, with absolute or functional iron deficiency anaemia as defined in the studies or reported baseline iron status indices suggestive of IDA.
Interventions	Intravenous iron (IVI), namely LMW iron dextran (ID), iron sucrose (IS) and iron derisomaltose (IIM) as monotherapy; in cases where two or more IVI formulations were used in an intervention arm, only studies reporting separate results for each IVI will be included.
Comparators	Other IV iron formulations/ oral iron (including preparations which contain folic acid, vitamin C or both)/ placebo/ standard medical or usual care/ no iron therapy/ iron sucrose similar (ISS).
Outcomes	Effectiveness: i. Change in haemoglobin (Hb) concentration* ii. Requirement for allogeneic blood transfusion* iii. Number of red blood cells (RBCs) units transfused (if available) iv. Measurements of biomarkers of iron status, especially serum ferritin and/or transferrin saturation (if available)

	*only trials with both of these outcomes reported will be considered for inclusion in this review Safety: i. Mortality/ survival ii. Adverse events (AEs) - Hypersensitivity reactions (HSRs) - Serious adverse events (SAEs) - Other AEs/ Adverse drug reactions (ADRs) - Infusion-related AEs iii. Infection rate iv. Other complications Organizational: i. Length of hospital stay Economic evaluation: i. Cost-effectiveness/ cost-utility/ cost-analysis/ budget impact model
Study design	Health Technology Assessment (HTA) reports, systematic reviews (SRs), randomised controlled trials (RCTs) including cross-over RCTs, non-randomised controlled trials (non-RCTs), prospective observational studies with a comparator group.
Other	English full-text articles

Exclusion criteria

Population	Paediatrics patients; patients with cancer-related or chemotherapy-induced anaemia (unless baseline data on relevant biomarkers for iron status, e.g. serum ferritin or transferrin saturation were reported and suggestive of IDA; non-anaemic iron deficiency; anaemia not caused by iron deficiency.
Intervention	IVI was a co-intervention combined with another alternative agent in a single arm of the study (e.g. IVI plus ESA versus IVI alone, IVI plus ESA versus placebo); use of IVI to augment autologous blood donation.
Comparator	Different doses, the period of infusion and timing of the same IV formulation/ erythropoiesis-stimulating agents (ESA)/ blood transfusion.
Study design	Retrospective observational studies, case reports, surveys, anecdotal, review articles, letters to the editor, commentaries, conference abstracts, laboratory or animal studies, and other non-relevant studies.
Other	Non-English full-text articles.

Relevant articles were critically appraised using the Critical Appraisal Skills Programme (CASP) checklist and graded according to US/Canadian Preventive Services Task Force (**Appendix 2**). Data were extracted and summarised in the evidence table, as in **Appendix 3**.

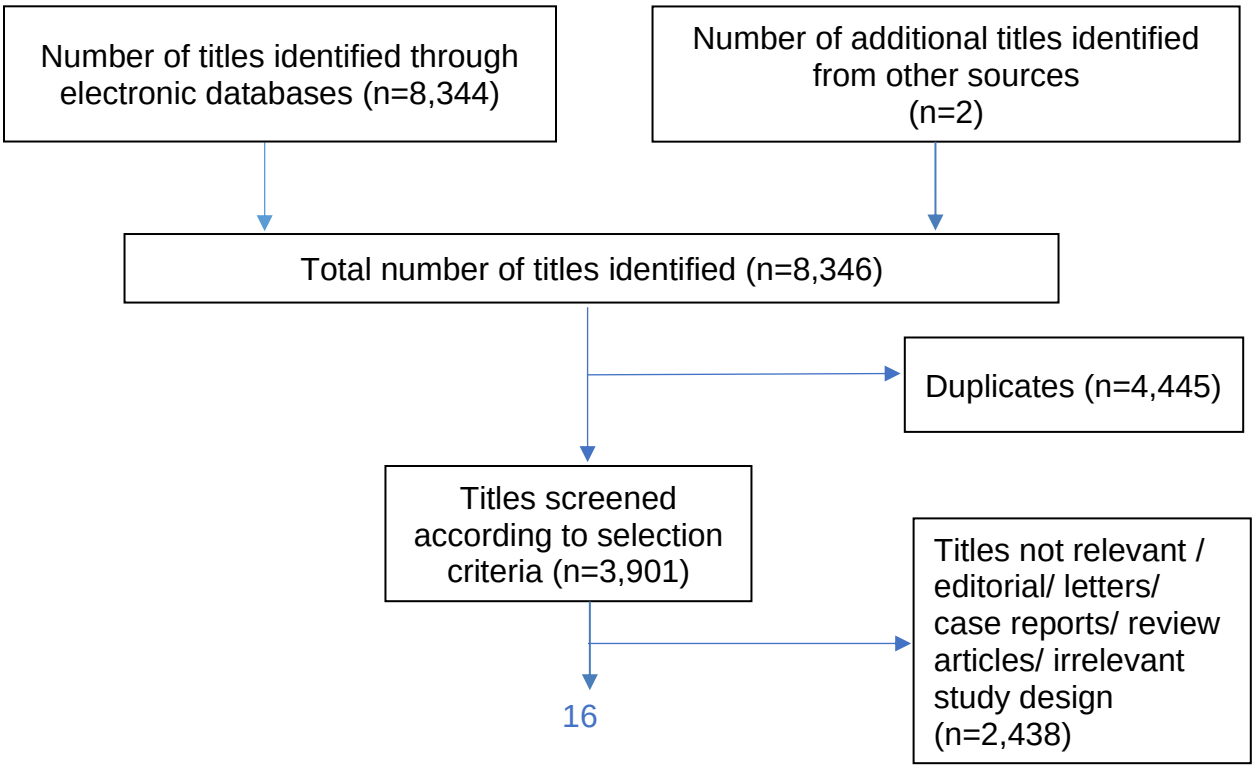
5.0 RESULTS AND DISCUSSION

Up to 20th May 2020, a total of **8,346** records were identified through the Ovid interface and PubMed. After removal of **4,445** duplicates, **3,901** records were screened, and **2,438** were excluded. Of **1,463** titles, **163** relevant abstracts were retrieved in full text. After reading, appraising, and applying the inclusion and exclusion criteria to the **163** full-text articles, **22** articles were included while **141** were excluded. The articles were excluded due to the study was already included in a systematic review (n=15), studies not addressing pre-specified population, intervention, and comparison characteristics (n=116), no full text retrieved (n=7), and non-English language (n=3). The **22** full-text articles finally selected for this review are:

- Systematic review (n=6)
- Randomised controlled trial (n=9)
- Prospective cohort (n=4)
- Cost-effectiveness analysis (n=2)
- Cost-minimization analysis (n=1)

The studies were conducted mainly in the United Kingdom, the United States of America, India, Spain, Korea, China, Hong Kong, Australia, Singapore, France, Thailand, Turkey, Norway, Romania, Egypt, Greece, Spain, Denmark, and Pakistan.

The study populations included were oncologic, cardiac, and gynaecologic patients undergoing surgery, obstetric patients, traumatic patients with critical illness as well as non-dialysis chronic kidney disease patients.



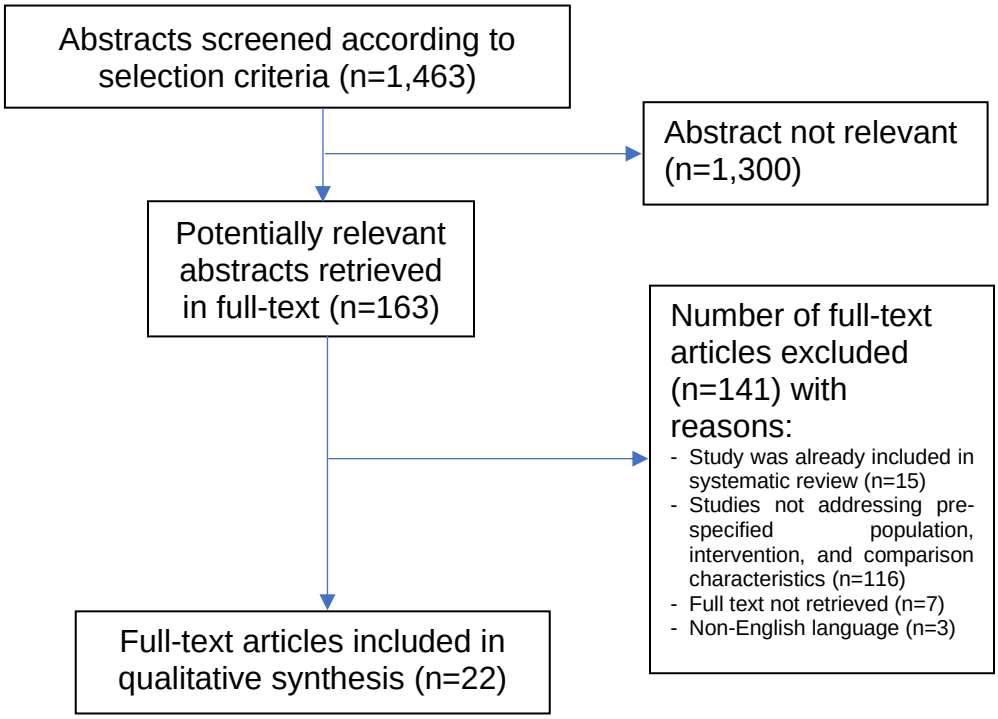


Figure 2: Flow chart of study selection

Critical Appraisal and Risk of Bias

One of the tools that are being used by MaHTAS for quality assessment of the included studies is the CASP checklist which consists of eight critical appraisal tools designed for SR, RCT, cohort studies, case-control studies, economic evaluations, diagnostic accuracy studies, qualitative studies and clinical prediction rule. This is achieved by answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias or study quality as either:

+	Indicates YES
?	indicates UNCLEAR
-	Indicates NO

Overall, the risk of bias was low to moderate for RCTs. In almost all RCTs patients and investigators were not blinded for obvious reasons (mostly due to the nature of the interventions – the colour of IVI and difficulty to find placebo with similar colour, or the onerous work required to cover infusion bottles and tubing). As for cohort studies, most have reported sufficient information pertaining to their study design; however, the adequacy of the duration of follow-up for most participants was not made clear. The results of the risk of bias and critical appraisal of included studies are summarised in **Figure 5.1 to 5.5**.

Criteria assessed	Authors look for the right type of papers?	Selection of studies (all relevant studies included?)	Assessment of quality of included studies?	If the results of the review have been combined, is it reasonable to do so (heterogeneity)?
Qassim A et al.[13]	+	+	+	+
Sultan P et al.[14]	+	+	+	?
Pollock RF et al.[15]	+	+	-	?
Salim SA et al.[16]	+	+	+	+
Shin HW et al.[17]	+	+	+	+
Avni T et al.[18]	+	+	+	+

Figure 5.1: Critical appraisal of systematic review (CASP)

Criteria assessed	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data addressed	Free of selective reporting	Free of other bias
Lee S et al.[19]	+	?	-	?	+	?
Edwards TJ et al.[20]	+	+	+	+	+	?
Xu H et al.[21]	+	+	-	+	+	+
Pieracci FM et al.[22]	?	-	-	-	?	?
Ng O et al.[23]	?	+	-	+	+	+
Noronha V et al.[24]	+	-	-	+	+	+
Agarwal R et al.[25]	+	+	-	+	+	+
Neogi SB et al.[26]	+	+	-	+	+	+
Auerbach M et al.[27]	+	?	-	+	+	+

Figure 5.2: Assessment of risk of bias of RCT (Cochrane)

Criteria assessed	Selection of cohort	Exposure accurately measured	Outcome accurately measured	Confounding factors	Follow-up of subjects
Kam PMH et al.[28]	+	+	+	+	?
Klein AA et al.[29]	+	+	+	-	+
Alexander RJ et al.[30]	+	?	-	?	?
Diez-Lobo A et al.[31]	+	+	+	+	?

Figure 5.4: Critical appraisal of cohort studies (CASP)

Criteria assessed	Basora M et al.[32]	Froessler B et al.[33]	Calvet X et al.[34]
A well-defined question posed?	+	+	+
Comprehensive description of competing alternative given?	+	+	+
Effectiveness established?	+	+	+
Effects of intervention identified, measured and valued appropriately?	+	+	+
All important and relevant resources required and health outcome costs for each alternative identified, measured in appropriate units and valued credibly?	+	+	+
Costs and consequences adjusted for different times at which they occurred (discounting)?	-	-	-
Results of the evaluation?	+	+	+
Incremental analysis of the consequences and costs of alternatives performed?	-	-	-
Sensitivity analysis performed?	+	+	+

Figure 5.5: Critical appraisal of economic evaluation studies (CASP)

5.1 Effectiveness

5.1.1 Haemoglobin (Hb) Concentration

5.1.1.1 Surgery

A) Preoperative Setting:

Comparison with no iron therapy

Kam PMH et al. (2020) have investigated the effect of IVI in a cohort of anaemic colorectal cancer patients planned for surgery and found that there was a significant difference (*P* < 0.001) between IVI group (patients received either IS or IIM; n=38) and no iron therapy group (n=62) for preoperative Hb level on admission, measured at least two weeks after administration of intravenous iron (10.63 g/dL; 95% confidence interval [CI]: 10.2, 11.1 and 9.46 g/dL; 95% CI: 9.05, 9.8, respectively). Significant rise in median Hb from baseline to admission was also observed in IVI group (1.9 g/dL versus 0.6 g/dL in no iron therapy; *P* < 0.001). A subgroup analysis in patients who had not been on preoperative oral iron supplement prior to administration of IVI (12 in IVI and 18 in no iron group) showed a similar increase in mean Hb on admission (10.54 g/dL in IVI and 9.17 g/dL in no iron group; *P* < 0.001) and higher median Hb rise after intravenous iron (2.05 in IVI and 0.2 in no iron group; *P* < 0.001).[28, level II-2]

However, a previous RCT that analysed a subgroup of colorectal cancer patients undergoing surgery whose baseline serum iron markers were suggestive of iron deficiency anaemia has shown no significant difference between IV IS group (n=9) and placebo (n=9) in mean Hb before surgery, POD 1 and at discharge. Median Hb before surgery for IV IS and placebo were 11.2 (interquartile range [IQR] 3.0) g/dL and 12.5 (4.0) g/dL, respectively (*P* = 0.427). The mean change in Hb from recruitment to preoperative value in IV IS group also did not differ significantly from that of placebo (*P* = 0.223).[20, level I]

On the other hand, the UK CAVIAR study found that IVI (either IIM or FCM) was efficacious in improving Hb concentration, and the average Hb prior to cardiac surgery in IDA patients treated with IVI (n=64) has increased significantly compared with those without treatment (n=72); the mean (95% CI) change in Hb in patients treated with IVI was +8.4 (5.0-11.8) g/L between treatment and surgery (P < 0.001). However, the mean (standard deviation, SD) Hb after surgery for both anaemic treated and not treated with IVI groups were similar (9.3 [1.1] and 9.4 [1.2], respectively).[29, level II-2]

Comparison with oral iron therapy

Alexander RJ et al. (2010) evaluated the effect of IV IS (n=11) and IV ID (n=19) against oral iron (n=23) in improving preoperative Hb level of patients undergoing colorectal cancer surgery. Each IVI group has recorded significantly higher total Hb increment over the course of treatment than that

of oral iron (*P* = 0.048 [IV IS]; *P* = 0.034 [IV ID]). Similar pattern was observed for Hb rise per day for each IV group versus oral iron (*P* = 0.002 [IV IS]; *P* = 0.001 [IV ID]). There was no significant difference between both IVI formulations on the Hb rise per day (*P* = 0.16).[30, level II-2]

Another cohort study involving women undergoing abdominal hysterectomy observed that the magnitude of increase in Hb was inversely correlated with the baseline Hb levels (*P* < 0.0001), i.e. the lower the Hb level at baseline, the greater improvement would be seen with IVI treatment. The Hb level on preoperative day as well as postoperative day (POD) 1 and 21 in IV IS group (n=31) were significantly higher than that of oral iron (n=44); mean difference (95% CI): 0.74 (0.31, 1.17); *P* < 0.05. The proportion of patients with Hb ≥ 12 g/dL was also higher in the IV IS group than in the control group (77% versus 32%, respectively; *P* < 0.01). Anaemic women at POD 21 (with the exclusion of women who received blood transfusion) was noted to have lower Hb at POD 1 than in those who were not (*P* < 0.01).[31, level II-2]

Comparison with other IVIs therapy

Lee S et al. (2019) in an RCT that investigated the effect of IV FCM (n=52) and IV IS (n=49) on preoperative anaemia in patients with menorrhagia found no significant difference in the proportion of patients achieving Hb level ≥ 10g/dL between both IVI groups (*P* = 0.452). The mean Hb levels were noted to be higher in patients treated with IV FCM than in those treated with IV IS, but this difference was not statistically significant (*P* = 0.079). In terms of Hb correction time, IV FCM was observed to achieve Hb level ≥ 10 g/dL in significantly lesser time (7.7 days) than IV IS (10.5 days; *P* = 0.013).[19, level I]

B) Postoperative Setting:

Comparison with no iron therapy

Xu H et al. (2019) in an RCT evaluating the effectiveness of postoperative IVI in patients undergoing cardiac valvular surgery found that those treated with IV IS (n=75) has significantly higher Hb concentration at POD 14 than those in the placebo group (n=73; *P* = 0.023). However, no significant differences were observed between the two groups at POD 7 (*P* = 0.833). The similar trend was seen in the proportion of patients achieving Hb increments of > 2g/dL at POD 14 in IV IS and placebo groups (45.5% and 19.2%, respectively; *P* = 0.001). Again, no significant differences were observed at POD 7 (17.3% versus 15.1%, respectively; *P* = 0.709). Overall, the proportion of patients with anaemia corrected in the IVI group rose more than twice that of the placebo group (24% versus 11%, respectively; *P* = 0.037). Similar results were observed despite the exclusion of patients who received a blood transfusion.[21, level I]

5.1.1.2 Critical Care

Comparison with no iron therapy

One multicentre RCT reported the finding of the effect of IV IS supplementation in anaemic ICU patients with a primary diagnosis of trauma. Results were reported only for 57 out of 150 patients (38%) who had completed the scheduled six total doses (27 in IVI group; 30 in the placebo group). Even though the baseline Hb was higher in the placebo group (9.9 g/dL vs 8.8 g/dL, respectively, *P* = 0.03), there was no significant difference in haemoglobin concentration observed between the groups at any time point over the subsequent 14 days. A subgroup analysis of patients with an ICU length of stay more than or equal to 14 days also did not show any apparent benefit of iron supplementation.[22, level I]

5.1.1.3 Cancer

Comparison with oral iron therapy

The effect of IV IS on the haematopoietic response in iron-deficient patients with malignancy requiring chemotherapy was studied by Noronha V et al. (2018). A total of 192 patients (95% patients had solid tumours, most commonly gynaecologic, lung, head and neck and breast cancer) were randomised to IV IS or oral ferrous sulphate, with 77% completed the entire planned therapy. No statistically significant difference in the mean absolute increase in Hb at six weeks was observed between the groups (0.11 g/dL (standard deviation [SD]: 1.48) in the IVI and −0.16 g/dL (SD: 1.36) in the oral iron group, *P* = 0.23). Similarly, no significant differences were noted for increment in Hb of ≥ 1 g/dL and 1.5 g/dL at three weeks (*P* = 1.0 and *P* = 1.0, respectively) and six weeks (*P* = 0.45 and *P* = 0.27, respectively). Moreover, neither three weeks nor six weeks assessment recorded significant differences between the two groups in the proportion of patients having Hb concentration increment of ≥ 1 g/dL and ≥ 1.5 g/dL.[24, level I]

Comparison with no iron therapy

Ng O et al. (2018) evaluated the impact of IVI in a small number of patients (n=27) receiving palliative chemotherapy for their esophagogastric adenocarcinoma. A single dose of IV IIM was administered to the IVI group followed up with three visits performed at the start of each three-week cycle of chemotherapy, in which 62.9% managed to complete the full three cycles. No statistically significant decrease in the mean Hb was noted over the three cycles of chemotherapy in the standard care group (*P* = 0.336), while there was an increment in haemoglobin in the intravenous iron group, resulting in a difference between groups in mean Hb change of 1.1 g/dl (*P* = 0.903). There was no statistically significant difference in Hb concentration observed between the two groups after completion of each cycle (*P* = 0.101, *P* = 0.935 and *P* = 0.885), despite IVI group having much lower Hb level at recruitment (*P* = 0.044). Similarly, a subgroup analysis of 17 patients who had not received blood transfusion revealed no difference in mean Hb between the two groups after cycle two (10.9 g/dl in standard care group

versus 10.8 g/dl in IVI group; *P* = 0.737) in spite of the significant difference in mean Hb at recruitment (12.1 g/dl and 10.4 g/dl, respectively; *P* = 0.021).[23, level I]

Non-dialysis CKD:

Comparison with oral iron

REVOKE study which investigated the impact of IVI on renal function among patients with moderate to advanced CKD and IDA, observed improvement in Hb level over time in both IV IS and oral iron groups of patients (n=136) with iron deficiency anaemia and moderate to severe chronic kidney disease (CKD) not on dialysis. However, the mean differences between groups at baseline to three, six, 12 and 24 months were not statistically significant (*P* = 0.72, *P* = 0.3, *P* = 0.85 and *P* = 0.56, respectively). With regards to the use of ESA, the average dose and length of use over the course of two years were similar in both groups. At baseline, 8.1% of the study participants were on ESA, which has increased to 27.9% at the end of the two-year follow-up visit.[25, level I]

5.1.1.5 Pregnancy

Comparison with oral iron

A systematic review of 15 RCTs that included pregnant women with either Hb level < 11 g/dL or serum ferritin level < 30 ng/ml, with mean gestational age at enrolment ranged from 22 to 33.3 weeks, found that IVI resulted in higher maternal Hb at delivery with a mean difference (MD) of 0.7 g/dL (95% CI: 3.9, 11 g/dL; *P* < 0.0001; I^2 = 91%; results from nine RCTs with 506 in IVI group and 503 in the oral iron group). Twelve out of 15 included RCTs had IV IS administered in the intervention arm, with the dosing varied according to the baseline Hb and patients' weight, except for two studies that administered fixed dose of IV IS of 400 or 500 mg.[13, level I]

In another recent multicentre clinical trial, 2018 pregnant women with mean gestational age at the time of recruitment was 27.6 weeks (SD 3.7) were recruited and randomised to either IV IS (n=999) and oral iron group (n=1019). Both groups showed an increment in Hb from baseline; however, the increase was significantly higher in the IV IS group than in the oral iron group with the mean difference in Hb increment varied from 0.45 g/dL to 0.95 g/dL at three different time points. The highest mean difference (0.95 g/dL, 95% CI: 0.80, 1.10) was observed at six weeks post-randomisation, which translated into an effect size of 0.56, exceeding 0.5 SD set by the researchers as the minimum criterion for the difference to be of clinically significant.[26, level I]

5.1.1.6 Postpartum

Comparison with oral iron

A meta-analysis of four studies (n=385) out of 15 RCTs included in a systematixc review by Sultan P et al. (2019) has shown statistically significant higher Hb concentration at week 6 among women with postpartum anaemia treated with IVI (n=251) than that of those in the oral iron group (MD 0.9 g/dL; 95% CI: 0.4, 1.3; *P* = 0.0003). In all four studies, the mean rise in haemoglobin was higher in the IVI groups than the oral iron groups (4.2 vs 3.7 g/dL, 3.2 vs 2.2 g/dL, 3.0 vs 1.6 g/dL, and 3.4 vs 2.1 g/dL). Similar trends were noted for Hb concentration at postpartum weeks 1, 2 and 3, while week 4 shown no significant increase with no reported Hb concentration at week 5. Sensitivity analysis was not performed due to insufficient data.[14, level I]

5.1.2 Allogeneic Red Blood Cell (RBC) Transfusion Requirement

5.1.2.1 Surgery

A) Preoperative Setting:

Comparison with no iron therapy

Kam PMH et al. (2020) reported that colorectal cancer patients treated with IV IS or IV IIM significantly required less transfusion (8 in IVI versus 30 patients in no iron, *P* = 0.006). Subgroup analysis based on the timing of transfusion showed that significantly fewer patients in the treatment group required transfusions in preoperative period (1 in IVI group, 20 in no iron, *P* < 0.001). Those required this preoperative transfusion had mean Hb less than 8 (7.6 in the only patient in IVI, mean Hb 7.9 g/dL in no iron with range 7.0–9.0). The difference in the mean number of packs of RBCs transfused between both groups, however, was not significant (0.55 in IVI and 1.42 in no iron group; *P* = 0.076). There was no difference between IV IS and IV IIM in median time from the first dose of intravenous iron to operation (22 days and 21 days, respectively; *P* = 1.0). The authors also highlighted that their introduction of IVI at their tertiary centre coincided with a shortage of blood products in blood banks which may in some way led to the difference in the transfusion rate between the two groups.[28, level II-2]

The transfusion requirement among the anaemic group of colorectal cancer patients during the whole study period (before surgery, at POD 1 and at discharge) was noted by Edwards TJ et al. (2009) to be slightly higher in the placebo group (five of nine patients). Meanwhile, there were two out of nine patients in the IV IS group who required blood transfusion. This difference though were not statistically significant (*P* = 0.335). The median number of units transfused was 0 (interquartile range [IQR] 1) for IVI group versus 2 [IQR 3] units for placebo.[20, level I]

On the contrary, Klein AA et al. (2020) reported no difference between those treated with IV IIM or IV FCM and untreated anaemic, iron-deficient group in transfusion rate (56% versus 42%, respectively; *P* = 0.127; adjusted odd ratio [OR] [95% CI]: 1.33 [0.52, 3.40]), quantity of blood transfused (median [interquartile range, IQR], 0 [0-2] versus 1 [0-2], respectively; *P* = 0.082). Twenty-five out of 31 patients (39.1%) in the IVI group transfused with an average of one to two units of RBCs, while the rest required on average three to four units of RBCs for Hb correction. A similar pattern was noted in the untreated group with 18 out 28 (25.4%) required an average of one to two RBCs units, and the rest being transfused with an average of three to four units of RBCs. Fourteen patients (nine in IVI group; five in the untreated group) were excluded from the analysis as they required more than four units of transfused RBCs. It should be highlighted that this UK CAVIAR study was designed to detect an increase in Hb concentration, thus underpowered to detect other outcome changes.[29, level II-2]

Comparison with oral iron therapy

The RBC transfusion requirement among colorectal cancer patients (n=53) treated with IV IS (9%), and IV ID (11%) were reported by Alexander RJ et al. (2010) to be significantly lesser (*P* = 0.04 and *P* = 0.01, respectively) than that of the oral iron group (44%). The total number of blood units transfused was 25, three and four in oral iron, iron sucrose and iron dextran, respectively.[30, level II-2]

Similar results were reported by Diez-Lobo AI et al. (2007) among women undergoing abdominal hysterectomy. The RBC transfusion rate was significantly reduced in the IV IS group than the oral iron group (0% and 32%, respectively; *P* < 0.001). Overall, 14 women in the control group received 29 packed RBC units (one unit, six women; two units, five women; ≥ three units, three women). All transfusions were given on the day of surgery. None in the IV IS group required RBCs transfusion.[31, level II-2]

Comparison with other IVIs therapy

Lee S et al. (2019) that examined the effect of IV IS and IV FCM in treating preoperative IDA in women with menorrhagia reported no RBC transfusion in either IVI group.[19, level I]

B) Postoperative Setting:

Comparison with no iron therapy

Among patients undergoing cardiac valvular surgery (n=150), Xu H et al. (2019) observed a higher proportion of patients in the placebo group requiring RBC transfusion than that of the IV IS group ((21.3% versus 13.3%, respectively), though, the difference was not significant (*P* = 0.196).[21, level I]

5.1.2.2 Critical Care

Comparison with no iron therapy

Pieracci FM et al. (2014) reported 55 subjects in the IVI group (73.3%) and 47 subjects in the placebo group (62.7%) received at least one packed RBC transfusion (*P* = 0.16). There was no difference in the proportion of subjects transfused during the study period between the iron and placebo groups (65.6% vs 52.3%, respectively, *P* = 0.27). Even after controlling for baseline estimated blood loss (EBL), there remained no difference in risk of transfusion between groups (*P* = 0.04; OR: 1.56, 95% CI: 0.77, 3.17, *P* = 0.21). Additionally, the IVI group had a significantly lower percentage of transfusion-free days per subject than the placebo group, (84.0% versus 90.5%, respectively, *P* = 0.02). It was noted that a significant difference in the percentage of patients transfused between the IVI and placebo group was only observed on study day 1 (29.3% vs 13.3%, respectively, *P* = 0.02). This could be explained by larger EBL in the IVI group than the placebo group prior to study entry (196 mL vs 57 mL, respectively, *P* = 0.02) and on study day 1 (87 mL vs 24 mL, respectively, *P* = 0.04). A subgroup analysis of 70 subjects who had not received a blood transfusion prior to study entry showed no difference in the baseline EBL between the iron and placebo groups (62 mL vs 41 mL, respectively, *P* = 0.36).[22, level I]

5.1.2.3 Cancer

Comparison with oral iron therapy

No significant difference in RBC transfusion requirement was observed between patients with malignancy treated with IV IS and oral iron (*P* = 1.0). Thirteen out of 94 patients in IV IS group (13.8%) required transfusion compared to 14 out of 98 patients in the oral iron group (14.3%).[24, level I]

Comparison with no iron therapy

After a single dose of IV IIM, RBC transfusion was required by three patients in the IVI group (27%) versus one in the standard care group (7.7%) after cycle one of chemotherapy. After cycle two, RBC was transfused in three further patients and one previous patient in the standard care group, while none required transfusion in the IVI group. No patients in either group required a transfusion after cycle three of chemotherapy. The mean number of RBC units transfused after cycle one of chemotherapy in the IVI group and standard care group was 5.3 (n=3) vs 3 (n=1), respectively (*P* = 0.594). After cycle 2, four patients in the standard care group received an average of one unit of blood. There was no significant difference in the total number of transfused patients between both groups (*P* = 0.851).[23, level I]

5.1.2.4 Chronic Kidney Disease (CKD)

A) Non-dialysis CKD:

Comparison with oral iron therapy

Twelve study participants in each group (17.9% in IV IS group and 17.4% in the oral iron group) received RBC transfusions. Of those who needed transfusions, the mean number of units needed over two years was reported at 5.3 (range two to 20 units) in the oral group, and 3.5 (range one to seven) in the IV IS group (P = 0.3).[25, level I]

5.1.2.5 Pregnancy

Comparison with oral iron therapy

A meta-analysis of nine RCTs (n=555 intervention versus 535 control) found that compared to oral iron, there was a lesser risk for RBC transfusion in women treated with IVI (Peto OR: 0.19; 95% CI: 0.05, 0.78). This translated to the prevention of one blood transfusion for every 95 women treated with IVI (95% CI: 81, 348 women). Further, the sensitivity analysis using a range of different meta-analytic techniques revealed a fairly consistent pooled estimate for postpartum blood transfusion rate.[13, level I]

In contrast, Neogi SB et al. (2019) found no significant difference in the requirement of RBC transfusion among pregnant women during pregnancy, delivery or postpartum (OR: 0.74; 95% CI: 0.45, 1.21). A posthoc subgroup analysis, however, revealed that transfusion requirement was significantly reduced in women with severe anaemia treated with IVI than those who have been taking oral iron (OR: 0.31; 95% CI: 0.17, 0.92). During delivery or postpartum period, 22/955 (2%) women in the IV IS group was reported to require transfusion compared to 25/975 (3%) women in the oral iron group (adjusted OR: 0.90; 95% CI: 0.50, 1.60).[26, level I]

5.1.2.6 Postpartum

Comparison with oral iron therapy

Only two studies in the systematic review by Sultan P et al. 2019 have reported outcomes on RBC transfusion among women with IDA. Therefore, no meta-analysis was conducted due to insufficient information and results from each study was presented qualitatively. Both studies reported the transfusion rates to be higher in the oral iron group compared to the IVI group, with one of the included RCT noted a more sizable difference in rates between both groups (22.9% vs 8.9%, respectively).[14, level I]

5.1.3 Biomarkers of Iron Status

5.1.3.1 Surgery

A) Preoperative Setting:

Comparison with oral iron therapy

Alexander RJ et al. (2010) found that the total rise in the mean corpuscular volume (MCV) in the group of colorectal cancer patients treated with IVI did not differ significantly than that of those in the oral iron group. However, MCV rise per day was seen improving significantly with IV ID when compared to oral iron and was significantly more than IV IS as well (*P* = 0.04).[30, level II-2]

On the other hand, ferritin and iron levels were observed to increase significantly from baseline to POD 21 in both groups of women undergoing elective abdominal hysterectomy (*P* < 0.05). Whilst no significant differences were observed between IV IS and oral iron for other laboratory iron parameters at POD 21, there was a significant difference seen in the mean (SD) ferritin level (53.1 (14.7) and 34.3 (14.8) ng/ml, respectively; *P* = 0.001). Furthermore, the prevalence of ID was noted to be lower in the IVI group than in the oral iron group (42% versus 68%, respectively; *P* < 0.05).[31, level II-2]

Comparison with no iron therapy

In another earlier study, Edwards TJ et al. (2009) reported no significant difference at any time point for haematocrit, mean corpuscular haemoglobin (MCH), ferritin, serum iron or transferrin saturation between the IV IS and placebo groups. Both groups showed an increment in ferritin concentration, and transferrin saturation, with the greatest mean change per individual between recruitment and at the preoperative value was observed in the IVI group (109.3 versus 85.3 ng/ml and 4.9 versus 3.2 per cent, respectively).[20, level I]

B) Postoperative Setting:

Comparison with no iron therapy

In patients undergoing cardiac valvular surgery, Xu H et al. (2019) observed a statistically significant difference at POD 14 for haematocrit (HCT) value and RBC count at between the IV IS and placebo groups (*P* = 0.034 and *P* = 0.04, respectively), although no statistical difference was reported at POD 7 (*P* = 0.948 and *P* = 0.984, respectively). Postoperative iron resulted in significantly higher serum ferritin at POD 7 and POD 14 (*P* < 0.001 for both periods). On the other hand, whilst significant difference was noted between both groups at POD 7 for transferrin saturation (*P* = 0.025), the difference was not statistically significant at POD 14 (*P* = 0.104).[21, level I]

5.1.3.2 Critical Care

Comparison with no iron therapy

In critically ill trauma patients that received all planned six doses of IV IS (n=57), Pieracci FM et al. (2014) reported no significant difference in serum iron concentration and erythrocyte zinc protoporphyrin (eZPP) concentration between the iron and placebo groups at any time point. Serum ferritin was significantly higher in the IVI group as compared with placebo group on both day 7 (808.0 ng/mL vs 457.0 ng/mL, respectively, $P < 0.01$) and 14 (1,046.0 ng/mL vs 551.5 ng/mL, respectively, $P < 0.01$). Comparably, a significant increase in transferrin saturation was noted on day 7 (15% in the IVI group versus 11% in the placebo group; $P = 0.02$), despite the difference was not clinically meaningful. However, there was no difference in transferrin saturation between IVI and placebo groups on day 14 (16% vs 13%, respectively, $P = 0.23$).[22, level I]

5.1.3.3 Cancer

Comparison with no iron therapy

Ferritin concentration in patients receiving palliative chemotherapy treated with IV IIM showed a significant increase after chemotherapy cycle one from 105 ng/ml to 1015 ng/ml ($P < 0.05$) and then began to decline with the mean ferritin 558 ng/ml after cycle three ($P = 0.366$). No statistical differences between groups were seen beyond cycle one of chemotherapy. Similarly, transferrin saturations increased above 20% in the IV IIM rising from 11.1% to 26.1% after cycle 1, while transferrin saturations never exceeded 20% in the standard care group but did rise from 11.9 to 19% after cycle three of chemotherapy. No statistical differences between groups were seen after each chemotherapy cycle.[23, level I]

5.1.3.4 Chronic Kidney Disease (CKD)

A) Non-dialysis CKD:

Comparison with oral iron therapy

Agarwal R et al. (2015) found no statistically significant in the mean difference for the transferrin saturation between the IVI and oral iron groups from baseline to three, six, 12 and 24 months ($P = 0.10$, $P = 0.08$, $P = 0.85$ and $P = 0.14$, respectively). Similar trends were observed in the mean difference for serum ferritin concentration at the same time points, except at six months where it was significantly higher in the IVI group compared to the oral iron group (MD, 0.63; 95% CI: 0.41, 0.85; $P < 0.001$).[25, level I]

5.1.3.5 Pregnancy

Comparison with oral iron therapy

Maternal ferritin level at delivery was reported by only three studies included in the systematic review by Qassim A et al. (2019). The meta-analysis

showed favourable results towards IVI with a MD of 21.24 ng/ml (95% CI: 6.54, 35.95; *P* = 0.005; I^2 = 96%).[13, level I]

Neogi SB et al. (2019) also reported higher serum ferritin concentration at six weeks postpartum in women who were treated with IV IS (n=72) during their pregnancy compared to the oral iron group (n=58). They recorded a median rise of 20.6 ng/mL (IQR 7.4 to 29.5) and 1.6 ng/mL (IQR –7.8 to 14), respectively.[26, level I]

5.1.3.6 Postpartum

Comparison with oral iron therapy

Overall, the IVI group was reported to have statistically significantly higher ferritin concentrations than the oral iron group for postpartum week 1 (n=8 studies), week 2 (n=7 studies), week 4 (n=5 studies) and week 6 (n=4 studies). None of the included RCTs in this systematic review by Sultan P et al. (2019) reported ferritin concentrations at week 3 and 5.[14, level I]

5.2 Safety

5.2.1 Mortality/ survival

Salim SA et al. (2019) investigated infectious complications and mortality associated with the use of IVI therapy in haemodialysis patients. Twenty-four studies comprise seven RCTs (n=2,796) and 16 observational studies (n=395, 817) were included in this systematic review. The IVIs in the intervention arms include IV ID, IV IS, IV ferric gluconate (FG), IV ferumoxytol, IV polymaltose and IV ferric chloride hexahydrate with combination with ESA, were used in some populations. Overall, most studies compared the use of high-dose against low-dose of the same IVI formulations, with three RCTs compared IVI to no iron therapy, two RCTs employed oral iron as the control group, and the other two RCTs examined the effect of a high and low dose of IVIs. Data on all-cause mortality obtained from six RCTs revealed that high-dose IV iron conferred 17% less all-cause mortality compared to controls; however, this outcome was not statistically significant (OR = 0.83; 95% CI: 0.7, 1.01; *P* = 0.07). The pooled data from observational studies showed opposite results – the hazard ratio (HR) was higher in the high-dose group, but this was not statistically significant (HR = 1.1; 95% CI: 1, 1.22; *P* = 0.06).[16, level I]

Previously, Avni T et al. (2015) have conducted one of, if not the largest study on the safety of IVI by far, which encompassed 103 RCTs that have been published over a span of 48 years. A total of 10,390 patients treated with IVI were compared with 4,044 patients treated with oral iron, 1,329 treated with no iron, 3,335 treated with placebo, and 155 treated with intramuscular iron. In this systematic review, IV IS was used on 57 trials, followed by IV FCM in 15, IV ID in 14, IV FG in seven, IV ferumoxytol in four, IV iron polymaltose in three and IV IIM in two. As for comparators, there

were 56 trials of oral iron, 20 trials of placebo, 14 trials of no iron, eight trials of oral iron and placebo or no iron, four trials of IM iron, and one trial of IM iron and no iron. All-cause mortality was reported in 57 trials, and of these trials, no deaths occurred during the follow-up period in 29 trials. Overall, there was no increased risk of mortality with IVI therapy (Risk ratio [RR]: 1.06; 95% CI: 0.81,1.39; I^2=0%).[18, level I]

There was no statistically significant change in mortality rate with perioperative use of IVI in orthopaedic surgery, as reported by Shin HW et al. (2019). This systematic review of 12 clinical studies comprised four RCTs (n=616) and eight case-controlled studies (CCSs; n=1,253). Pooled analysis across either six trials (two RCTs and four CCSs) or the RCTs alone failed to show any significant change in mortality rate (RR: 0.56; 95% CI: 0.17, 1.79; I^2 = 74%; P = 0.33 and RR: 0.34; 95% CI: 0.03, 3.81; I^2 = 91%; P = 0.39, respectively).[17, level I] Xu H et al. 2019 also reported non-significant difference in the death rate among cardiac surgical patients who were treated with postoperative IV IS or placebo infusion (zero versus two death, respectively; P = 0.210).[21, level I]

Pieracci FM et al. (2014) reported a trend toward increased mortality among critically ill trauma patients in the IVI group as compared with the placebo group (9.3% versus 2.7%, P = 0.09). This trend persisted in a subgroup analysis of subjects who received six doses of study drug (11.1% vs 3.3%, P = 0.25). However, after controlling for gender, baseline APACHE II score, and baseline EBL, there was no independent association between the study group and mortality (OR for iron supplementation: 1.12; 95% CI: 0.92, 1.33, P = 0.67), suggesting that baseline differences between groups confounded this relationship.[22, level I]

A nonsignificant difference in all-cause mortality between IV IIM and standard care group were observed among esophagogastric adenocarcinoma patients who were on palliative chemotherapy. A total of seven death reported during the study period, with two patients in the standard care group and five patients in the IVI group (P = 0.182). All deaths related to progression or complications from their esophagogastric malignancy.[23, level I] Noronha V et al. (2018) also shared their findings on the mortality and survival rate among patients with cancer-related IDA. At a median estimated follow-up of 24 months (95% CI: 19.5, 28.5), 78 patients (40.6%) have died, 37 in the IV iron arm and 41 in the oral iron arm. Estimated median overall survival (OS) for patients on IV iron was 16 months (95% CI: 7.3, 24.7) and that of patients on oral iron was 20 months (95% CI: 11.7, 28.4 months; standard error [SE]: 4.3 months; P = 0.73 by log-rank test).[24, level I]

Agarwal R et al. (2015) reported six death in the IVI group and four in the oral iron group of their non-dialysis CKD study population (P > 0.2). A total

of 104.5 patient-years (PY) of follow-up was recorded in the oral iron treatment group and 101 PY of follow up in the intravenous iron treatment group.[25, level I]

One of the trials included in the systematic review of IVI therapy for postpartum anaemia by Sultan P et al. (2019) reported one death due to peripartum cardiomyopathy that occurred 13 days after vaginal delivery and seven days after exposure to IV FCM. This death then was not directly attributable to IVI therapy.[14, level I]

5.2.2 Adverse events (AEs)

5.2.2.1 Hypersensitivity reaction (HSR)

Pollock RF and Biggar P (2020) conducted an indirect treatment comparison study about the safety of IV IIM, IV IS and IV FCM by using reported data on serious or severe hypersensitivity reaction (HSRs) from 21 published prospective trials with over 8,000 patients. These HSRs are classified in accordance with the standardized Medical Dictionary for Regulatory Activities queries (SMQs) namely, narrow hypersensitivity terms (A), and broad terms pertaining to potential respiratory HSRs (B), skin HSRs (C), and cardiovascular HSRs (D). Bayesian inference, naïve pooling, and adjusted indirect approaches were employed to compare the rate of HSR incidence. For all SMQ groups (A + B + C + D), the odds of experiencing any serious or severe HSR were 59%, 61% and 55% lower with IV IIM relative to IV FCM according to the Bayesian, naïve pooling and adjusted approaches, respectively. Similarly, results from Bayesian, naïve and random effects meta-analysis have shown lower odds of developing HSRs across all SMQ groups with IV IIM (49%, 51% and 44%, respectively) relative to IV IS. Comparison between IV FCM and IV IS using Bayesian technique resulted in mean OR of 1.30 (95% highest posterior density interval [HDI]: 0.70, 1.98), while naïve pooling yielded an OR of 1.25 (95% CI: 0.75, 2.08). Hence, the authors concluded that the risk of serious or severe HSRs was lower with IV IIM relative to IV FCM and IV IS.[15, level I]

With regards to safety comparison between IV IIM and IV IS, Auerbach M et al. (2019) conducted an RCT in which 50% and 26% of its population comprised gynaecology and gastroenterology patients, respectively. A total of three serious or severe HSRs were reported in 3/989 (0.3%; 95% CI: 0.06,0.88) patients in the IV IIM group, and two serious or severe HSRs were reported in 2/494 (0.4%; 95% CI: 0.05, 1.45) in the IS group. The risk difference between both IVI formulations was estimated to −0.10% (95% CI: −0.9, 0.71), but it was not statistically significant.[27, level I]

In a population of cancer patients with IDA, five patients in the IVI group and none in oral iron group experienced HSRs of any grade (*P* = 0.059). Three

of the non-fatal hypersensitivity reactions (3%) were of ≥ grade 3, with one case fell into grade 4 category.[24, level I]

Sultan P et al. (2019) reported rare occurrences of features of HSRs, namely urticaria (0.6%) and rash (4.6%) following IVI exposure. Nonetheless, there were no significant differences between oral and IVI groups observed for the two reactions (OR for urticaria: 4.23; 95% CI: 0.47, 38.33; P = 0.20 and OR for rash: 2.37; 95% CI: 0.72, 7.85; P = 0.16).[14, level I]

5.2.2.2 Serious adverse events (SAEs)

In a previously published systematic review, 97 trials (95%) reported serious AEs. Overall, there was no increase in the risk of serious AEs with IVI compared with control (RR: 1.04; 95% CI: 0.93, 1.17, I^2=9%). In comparison to placebo in double-blind trials, IVI resulted in a nonsignificantly lower risk of SAEs (RR: 0.83; 95% CI: 0.64, 1.03; I^2=41%). It was noted that the use of IVI in patients with chronic heart failure was associated with a decreased rate of AEs compared with controls (RR: 0.45; 95% CI: 0.29, 0.70; I^2=0%; number needed to predict [NNP]: 10; 95% CI: 6, 25). Meanwhile, trials in gynaecology and obstetrics revealed an increased rate of SAEs with the use of IV iron (RR: 2.00; 95% CI: 1.15, 3.62; I^2=0%; number needed to harm [NNH]: 119; 95% CI: 61,1725). Subdividing the trials by indication for therapy (pregnancy, peripartum, and other) or compound revealed a trend toward an increased rate of SAEs with IVI that was statistically nonsignificant in all subgroups. In trials of chronic kidney disease, inflammatory bowel disease, and cancer-induced anaemia, perioperative trials, and other trials of mixed causes, there was no increased risk of SAEs with IVI therapy. No deaths related to SAEs were also reported.[18, level I]

In REVOKE study, the IVI group reported more serious adverse events, a total of 201 events in 37 patients (199/100 PY) than those in the oral iron group, 176 events in 40 patients (168.4/100 PY). Unadjusted incidence rate ratio (IRR) 1.18 (95% CI: 0.97, 1.45; P = 0.106), while adjusted IRR was 1.60 (1.28, 2.00; P < 0.0001).[25, level I]

A trial that investigated the effect of IV IS against oral iron in pregnant women reported a total of 28 non-fatal serious adverse events; 16 of 958 (2%) patients treated with IV IS and 13 of 976 (1%) patients treated with oral iron. Additionally, there was one death due to an accident unrelated to the trial in the IVI group. The incidence of postpartum haemorrhage between both groups did not differ significantly (adjusted OR: 1.01; 95% CI: 0.25, 4.05).[26, level I]

5.2.2.3 Other AEs/ Adverse drug reactions (ADRs)

The rate of cardiovascular AEs was reported in only one RCTs which found no significant differences between high-dose and low-dose iron groups

(22.3% versus 25.6%; *P* = 0.12). Similar results were seen with pooled data from six observational studies (HR = 1.18; 95% CI: 0.89, 1.57; *P* = 0.24).[16, level I]

Likewise, the difference in the incidence of composite cardiovascular AEs between IV IIM and IV IS was reported to be nonsignificant by Auerbach M et al. (2019). In the trial, eight composite cardiovascular AEs were reported in eight (0.8%) patients in the IV IIM group, while seven were reported in six patients (1.2%) in the IV IS group.[27, level I]

Previously, Avni T et al. (2015) presented similar results pertaining to the risk of cardiovascular AEs related to the overall use of IVI. Looking at individual IVI formulation, however, they noted decreased risk of cardiovascular AEs with IV FCM (RR: 0.57; 95% CI: 0.42, 0.79; I^2=0%; NNP: 28; 95% CI: 17, 71). In contrast, an opposite effect was observed with IV FG (RR: 1.33; 95% CI: 1.05, 1.69; I^2=0%; NNH: 39; 95% CI: 21, 235). The use of IVI was associated with a decreased risk of gastrointestinal AEs (RR: 0.55; 95% CI: 0.51, 0.61; I^2=84%; NNP: 10; 95% CI: 8, 14), particularly with IV IS, IV ID, and IV FCM, and when the comparator was oral iron or no iron. There was an increase in neurologic AEs (RR: 1.35; 95% CI: 1.13, 1.61; I^2=35%; NNH: 78; 95% CI: 44, 336), which was more pronounced when IV IS was used (RR: 1.63; 95% CI: 1.10, 2.42; I^2=0%; NNH: 71; 95% CI: 30, 237). Hypotension was also reported to increase with IVI (RR: 1.39; 95% CI: 1.09,1.77; I^2=39%; NNH: 97; 95% CI: 58,305). This effect was more pronounced when IV IS was used (RR: 3.01; 95% CI: 1.12, 8.11; I^2=0%; NNH: 68; 95% CI: 37, 364) and when compared with no iron (RR: 3.83; 95% CI: 1.33, 11.02; I^2=38%; NNH: 50; 95% CI: 25, 100). There was, however, a trend toward hypertension responses with IV iron (RR: 2.25; 95% CI: 1.00,5 .08; I^2=0%). Adverse events related to skin (excluding urticaria) were also reported to be higher in the IVI group (RR: 1.60; 95% CI: 1.05, 2.45; I^2=35%; NNH: 99; 95% CI: 59, 304). Comparably, IVI use was associated with increased risk for muscle and skeletal AEs, particularly with IV FCM (RR: 3.42; 95% CI: 2.02, 5.79; I^2=40%; NNH: 32; 95% CI: 23, 49). Besides, the use of IVI was associated with an increased risk of electrolyte disorder (most trials reported on the occurrence of hypophosphataemia) (RR: 2.45; 95% CI: 1.84, 3.26; I^2=49%; NNH: 19; 95% CI: 11, 67).[18, level I]

A recent trial reported a total of 230 ADRs in 124 patients (12.5%) in the IV IIM group, and 138 ADRs in 63 patients (12.8%) in the IV IS group (*P* > 0.05). The most common ADR reported in the IV IIM and IV IS groups was nausea (20 events in 20 patients [2.0%] and 10 events in eight patients [1.6%], respectively). In the IV IIM group, rash (17 ADRs in 15 patients [1.5%]) and chest discomfort (11 ADRs in 11 patients [1.1%]) were more frequently reported while none in the IV IS group reported experiencing such symptoms. Instead, dysgeusia and overdose were more commonly reported in the IV IS group (20 ADRs; n=9; 1.8% and 10 ADRs; n=8; 1.6%),

respectively, compared with one and zero, respectively, reported in the IV IIM group. Moreover, the incidence of hypophosphataemia (s-phosphate < 2.0 mg/dL) was low and similar in the two groups (3.9% in the IV IIM and 2.3% in the IV IS group). These events, however, were transient, and in most cases normalized at the end of the trial. For the majority, the lowest s-phosphate values were reached at week one or two.[27, level I]

In addition, Noronha V et al. (2018) reported that toxicity to iron supplementation was minimal among patients with cancer-related IDA and easily manageable. Three per cent of patients on IVI and 7% of patients on oral iron suffered from Grade 3 diarrhoea. Two per cent of patients on oral iron experienced grade 3 vomiting. Overall, gastrointestinal toxicity (any grade) were experienced by 41% of patients on IVI and 44% of patients on oral iron (P = 1.0).[24, level I]

In another trial that investigated the effect of IVI on kidney function, Agarwal R et al. (2015) found little nonsignificant difference in the measured glomerular filtration rate (mGFR) between the IVI and oral iron groups (−0.35 mL/min/1.73m^2 per year; 95% CI: −2.9, 2.3; P = 0.79), even after additional adjustment for demographics data, medication use and cardiovascular disease (P = 0.94). There was no significant difference between groups in proteinuria, although it was observed to increase significantly over time in both treatment groups (P = 0.04). The cardiovascular events were significantly higher in the IVI group than the oral iron group (adjusted IRR: 2.51; 95% CI: 1.56, 4.04); P < 0.001). The incidence of hospitalized heart failure was also documented to increase about 2-fold in the IVI group. Moreover, patients in the oral iron group reported more frequently of gastrointestinal AEs, particularly diarrhoea, while gout was more commonly reported by patients treated with IVI.[25, level I]

In a population of pregnant women treated with over the course of 4,651 IVI infusion, only one woman required discontinuation of IVI treatment. In another case, 13% of them reported immediate, and 24% reported late self-limiting minor adverse effects. The risk of having any minor adverse effects was noted to lower by 22% in the IV IS group than in the oral iron group.[26, level I]

Pooled analysis of trials evaluating the safety profile of IVI on postpartum anaemia has shown increased skin flushing (OR: 6.95; 95% CI: 1.56, 31.03) and decreased gastrointestinal related side effects, particularly constipation (OR: 0.08; 95% CI: 0.03, 0.21), and dyspepsia (OR: 0.07; 95% CI: 0.01, 0.42) among women treated with IVI than those treated with oral iron.[14, level I]

5.2.2.4 Infusion related AEs

Increased risk of serious infusion reactions were seen with IVI (RR: 2.47; 95% CI: 1.43,4.28; I^2=0%; NNH: 292; 95% CI: 164, 1316) and particularly with IV FG (RR: 5.32; 95% CI: 1.49, 18.99; I^2=0%; NNH: 118; 95% CI: 68, 423), as reported in the findings by Avni T et al. (2015). The other iron preparations were not associated with a statistically significant increased risk of severe infusion reactions (IV IS - RR: 1.75; 95% CI: 0.69, 4.43; IV FCM – RR: 1.47; 95% CI: 0.40, 5.39; IV ferumoxytol – RR: 2.26; 95% CI: 0.19, 26.22; IV ID - RR: 3.1; 95% CI: 0.86, 11.22). Infusion reactions were noted to be higher with IVI (RR: 2.74; 95% CI: 2.13, 3.53; I^2=26%; NNH: 64; 95% CI: 44, 115) and further increased when compared with oral iron (RR: 3.49; 95% CI: 2.22, 5.49; I^2=0%; NNH: 50; 95% CI: 32, 113), placebo (RR: 2.42; 95% CI: 1.50, 3.91; I^2=0%; NNH: 92; 95% CI: 52, 422), and no iron (RR: 2.19; 95% CI: 1.05, 4.56; I^2=0%, NNH: 86; 95% CI: 41, 133). Infusion reactions were further increased when IV IS, IV FG, and IV FCM were used. A subgroup analysis restricted to trials that used placebo as the comparator revealed an increased risk of a severe infusion reaction (RR: 2.96; 95% CI: 1.16, 7.51; I^2=0%; NNH: 255; 95% CI: 136,1910).[18, level I]

5.2.3 Infection Rate

Meta-analysis using fixed effect model of four RCTs included in the systematic review by Salim SA et al. (2019) revealed that there was no difference in the infection rate between high-dose iron and control group (OR = 0.97; 95% CI: 0.82, 1.16; *P* = 0.77). Pooled data from eight observational studies reported increased yet insignificant risk of infection in the high-dose group (HR = 1.13; 95% CI: 0.99, 1.28; *P* = 0.07).[16, level I]

Avni T et al. (2015) found no significant increased risk of serious infections with IVI (RR: 0.96; 95% CI: 0.63,1.46; I^2=8.2%). The occurrence of any infections was not increased with IVI regardless of formulation, comparator, and indication (RR: 1.17; 95% CI: 0.83,1.65; I^2=0%).[18, level I]

Furthermore, results from two RCTs that reported postoperative infection rate among patients undergoing orthopaedic surgery, failed to show any significant reduction with the use of perioperative IVI (RR: 0.34; 95% CI: 0.03, 3.81; I^2 = 91%; *P* = 0.39). The combined results from three RCTs and seven CCSs however, revealed significant reduction in postoperative infection rate with IVI (RR, 0.67; 95% CI: 0.49, 0.91; I^2 = 15%; *P* = 0.01).[17, level I]

No significant results were seen with IVI supplementation in patients with anaemia of traumatic critical illness. At least one infection occurred in 44 subjects in the IVI group (58.7%) and 52 subjects in the placebo group (69.3%, *P* = 0.17). The median number of infections per subject was two for both groups (*P* = 0.18). Specifically, there was no difference in the risk of pneumonia (*P* = 0.55), bacteraemia (*P* = 0.95), urinary tract infection (*P* =

0.66), or infections from other sources (*P* = 0.83). Both the antibiotic days (*P* = 0.64) and antibiotic days per study day (*P* = 0.55) were equivalent between groups. Finally, there remained no association between the study group and infection risk in a subgroup analysis of subjects who received all six doses of study drug (92.6% for the iron group and 90.0% for the placebo group, *P* = 0.73).[22, level I]

In a trial that assessed IVI impact on kidney function, the occurrence of infection was documented 37 times in 19 subjects (36.6/100 PY) of the IVI group, compared with 27 times in 11 patients in the oral iron group (25.8/100 PY). The difference in the infection rate between both groups was presented as an adjusted IRR of 2.12 (95% CI: 1.24, 3.64; *P* < 0.006). Furthermore, the incidence of lung and skin infections were observed to increase between 3 to 4 folds in the intravenous iron group than compared with the oral iron group. These findings have led the Data and Safety Monitoring Board (DSMB) to unanimously recommended early stopping of the trial.[25, level I]

There was no difference in puerperal sepsis reported between women treated with IV IS and those treated with oral iron (adjusted OR: 1·01; 95% CI: 0·46, 2·22).[26, level I]

5.2.4 Other complication

Salim SA et al. (2019) reported on all-cause hospitalisation between high-dose vs control groups. Data from one RCT showed no difference between both groups in the rate of hospitalisation (OR = 1.03; 95% CI: 0.87, 1.23; *P* = 0.71), whereas there was increased yet insignificant rate of hospitalisation in the high-dose group from observational studies (HR = 1.11; 95% CI: 0.99, 1.24; *P* = 0.07).[16, level I]

The complications related to the use of preoperative IVI in colorectal cancer surgical patients were found not to differ significantly with those without IVI treatment (15.8% and 19.4% respectively; *P* = 0.599) or reoperation rate (2.2% in both, *P* = 1.0).[28, level II-2] Similar results were seen with postoperative IVI in cardiac valvular surgical patients, where there was no difference in rates of poor wound healing (*P* = 1.0) and perivalvular leakage (*P* = 1.0) between IVI and placebo groups were recorded. None of these events occurred in the IVI group.[21, level I]

Ng O et al. (2018) reported no significant difference in unplanned hospitalisation between the two groups of patients with IDA undergoing palliative chemotherapy (*P* = 0.675).[23, level I]

5.3 Organizational Issue

5.3.1 Length of stay (LOS)

5.3.1.1 Surgery

A) Preoperative Setting:

The median LOS between colorectal cancer patients that have been treated with or without IVI showed no significant difference (8.5 days versus nine days; *P* = 0.685).[28, level II-2] Preoperative IVI among cardiac surgical patients also did not significantly reduce neither days spent in intensive treatment unit (median days: three in IVI versus two in no iron group; *P* = 0.158) nor hospitalisation duration (median days: 10.5 in IVI versus nine in no iron group; *P* = 0.492).[29, level II-2] Similar results were seen with women who have undergone hysterectomy where there was no statistically significant difference in length of hospital stay recorded between those treated with preoperative IV IS and oral iron (*P* = 0.083). Further analysis revealed that women receiving blood transfusion (n=14) have significantly longer LOS than those without transfusion (n=61); mean (SD), 6.9 (2.3) and 5.8 (1.0) days, respectively; *P* < 0.01).[31, level II-2]

B) Postoperative Setting:

Xu H et al. (2019) also reported no significant differences in the proportion of patients who have undergone cardiac valvular surgery that required ventilator time more than 24 hours (13 [17.3%] in the IVI group versus 14 [18.7%] in the placebo group; *P* = 0.832) as well as longer than 10 days postoperative hospital stay (13 [17.3%] in the IVI group versus 10 [13.3%] in the placebo group; *P* = 0.497).[21, level I]

C) Perioperative Setting:

Pooled data from the RCTs and CCSs included in the systematic review by Shin HW et al. (2019) showed that perioperative IVI use in orthopaedic surgical patients has led to significantly shorter length of hospital stay (MD: −1.60; 95% CI: −2.52, −0.68; I^2 = 66%; *P* = 0.0006). However, pooled results from the four RCTs alone did not show any significant difference between IVI and control groups (MD: −0.98; I^2 = 38%; *P* = 0.21/ RR: 0.61, I^2 = 71%; *P* = 0.31).[17, level I]

5.3.1.2 Critical Care

Pieracci FM et al. (2014) observed no significant difference in the mean [range] days spent in an intensive care unit (ICU) between the IVI group and the placebo group (10 [2 – 4] and 11 [2 – 37], respectively; *P* = 0.53). There was no significant difference reported between both groups for the length of hospitalisation as well (14 [2–62] days in IVI versus 16 [2–65] days in placebo; *P* = 0.50).[22, level I]

5.3.1.5 Pregnancy

Only a small number of patients in the IVI and oral iron groups (59/885 [7%] and 68/879 [8%], respectively) have prolonged hospitalisation due to maternal causes which were defined as more than three days for normal delivery and seven days for lower segment Caesarean section (LSCS). The odds of this prolonged hospitalisation, however, did not differ significantly between both groups (adjusted OR:0.85; 95% CI: 0.59, 1.22). Admission to ICU or referral to higher centres were reported to be very low, with less than 1% in each group (2/895 in the IVI group and 1/889 in the oral iron group).[13, level I]

5.4 Economic Evaluation

Basora M et al. (2018) conducted a cost-effectiveness analysis of a preoperative Hb optimisation with IV FCM to reduce RBC transfusion in patients undergoing primary knee arthroplasty. The analysis was performed from the hospital perspective and a temporal horizon limited to the duration of hospitalisation. The main outcomes evaluated were the cost per unit of RBC spared and patient transfusion avoided in the optimisation arm as compared with the control arm. Data on the effectiveness of the optimisation was obtained from a recent cohort of 52 patients who underwent Hb optimisation with IV FCM prior to knee arthroplasty. A total of 20,000 patients were randomly assigned in a strict 1:1 ratio to either Hb optimisation arm or the non-optimisation, control arm using a computer simulation model built on Excel spreadsheets. The probabilities of transfusion and the number of RBC units transfused were derived from previous studies. Costs were derived from the clinical accounting and pharmacy records of the hospital and included only direct costs attributable to the Hb optimisation. The simulated preoperative optimisation protocol resulted in fewer patients being exposed to allogeneic RBC transfusion (2,212 vs 6,595 out of 10,000 patients) and a relevant decrease in the number of transfused RBC units (4,342 vs 13,336). In the reference case scenario, the cost of one patient avoiding transfusion and one RBC unit being spared were €831 and €405, respectively. These cost savings were found to be very sensitive to the cost of the outpatient clinic, which contributed the largest (54%) to the increased cost in the optimisation arm, and to the transfusion rate in both optimisation and control arms. With either 50% reduction or increment in the cost of the outpatient clinic, the average cost per patient not transfused were €606 and €1,055, respectively, and the cost per RBC unit spared ranged from €296 and €514. On the other hand, both costs were noted to increase exponentially as the probability of transfusion decreased and fell to zero when the transfusion rate decreased to about 18%. Hence, it was suggested that this Hb optimisation using IV FCM would be cost-effective in patients with IDA undergoing primary knee arthroplasty.[32]

Another cost-effectiveness analysis carried out by Froessler B et al. (2018) concurred with the above findings. In this study, an Excel-based model was

developed to investigate estimates the average cost per case treated preoperatively with IV FCM compared with usual care (all anaemia treatment modalities as per primary care physician or surgical team) until the point of discharge. The model considered only the immediate outcomes and associated costs from the German hospital perspective. Data input for transfusion rate (12.5% in patients receiving FCM compared with 31.5% of patients receiving standard of care) and change in Hb concentration were obtained from a previously published study which included 72 patients with IDA prior to abdominal surgery. In the IV FCM group, RBC transfusion was administered on average 1.6 units (versus 3.2 units in the standard care group), and their hospital length of stay was shorter (six versus nine days). Costs and outcomes were accounted at different stages as patients transitioned through the model according to the treatment allocated. Excluding surgical expenses, the average cost per case treated with IV FCM and usual care were estimated to be at €2,461 and €3,246, respectively. Treatment with IV FCM in IDA resulted in cost savings of €786 per case in Germany based on reductions in transfusion and costs paid by hospitals for extended hospitalization. The individual costs per case were most sensitive to changes in the number of patients transfused, the number of units transfused and cost of RBC. Length of hospitalisation and hospital cost per day, preoperative dosing and postoperative dosing had a limited impact on the incremental results.[33]

Calvet X et al. (2016) investigated cost implications of three strategies, namely, preoperative IV FCM, IV IS or oral iron for the treatment IDA in patients with colon cancer. The total cost of IVI infusion (including costs of the drug and direct and indirect costs of outpatient infusion in a day-care unit) in the IV FCM and IV IS groups, the costs of the transfusions needed and hospitalization costs, made up the three major components of the cost being compared and analysed. This cost-minimization analysis was conducted from a third-payer perspective utilizing individual data from a previously published study consisted of a cohort of patients with colon cancer and preoperative IDA treated with IV FCM, while data for patients receiving IV IS and oral iron were collected retrospectively. The analysis showed that, under baseline costs and assumptions, IV FCM was less costly than IV IS or oral iron. Total costs per patient were €1,827, €2,312 and €2,101 for IV FCM, IV IS and oral iron, respectively. Therefore, baseline data cost savings for IV FCM treatment were €485 when compared to IV IS and €274 when compared to oral iron. In the two-way sensitivity analysis, the cost savings were very sensitive to the length of hospitalisation. Baseline hospitalization reductions with IV FCM treatment were 2.3 days when compared to IV IS and 2.6 days when compared to oral iron, resulting in respective cost savings of €485 and €274, respectively. IV IS would need to save 0.2 days or more when compared to IV FCM to achieve a cost-saving. Whereas IV FCM treatment may result in cost savings if hospitalisation days saved are 1.2 or more days when compared to oral

iron. Probabilistic sensitivity analysis performed using Monte Carlo simulations also favoured the use of IV FCM over IV IS (84.7% of 10,000 iterations) with a mean incremental cost of €578 per patient. It was noted that a smaller number of infusions required to administer larger doses of iron would lead to lesser costs incurred. The cost for IV IS was higher due to the cost of repeated infusions despite lower total iron dose being infused which did not visibly reduce the transfusion rate and length of hospitalisation.[34]

5.5 Limitation

Some limitations of this review deserve to be mentioned and these should be considered when interpreting the results. The selection of the studies and appraisal was made by one reviewer. Although there was no restriction in the language during the search, only full-text articles in English published in peer-reviewed journals were included in the report, which may have excluded some relevant articles and further limited our study numbers. The most important limitation was the inclusion of RCTs and prospective cohort study that were of low methodological quality. The small sample size in most of the included studies may contribute to the insignificant or mixed outcome as they were not powered enough to detect any clinically meaningful changes in Hb concentration as well as allogeneic blood transfusion requirement. Most of the RCTs also lacked blinding, which may, in some way, introduced performance and ascertainment bias. However, it may not directly affect the measurement of objective outcomes, such as changes in laboratory biomarkers. Besides, this is not a comprehensive review of all IVIs available worldwide as the focus is only on IVI preparations that are marketed in Malaysia. Hence, the results presented in this review should be interpreted cautiously. Some of the included studies also did not state pre-defined blood transfusion trigger, which may affect the transfusion rate observed between intervention and control groups. With regards to the economic analyses in this review, the two cost-effectiveness studies used IV FCM that was administered as a single dose, thus require less visit to the hospital which may not be applicable to other IVIs that necessitate several visits to complete the total dose. Finally, none included an incremental cost-effectiveness ratio (ICER) in their reports.

6.0 CONCLUSION

6.1 Effectiveness

There was a limited fair to good level of retrievable evidence to suggest that:

i. In comparison to oral iron, preoperative administration of IVI did significantly increase Hb concentration in surgical patients prior to their procedures.

ii. In comparison to no iron therapy, no strong evidence to support that preoperative IVI has led to significant improvement in Hb concentration. One study that examined the effect of postoperative IVI has shown favourable results on day 14 of operation after administration of IVI, but not earlier.

iii. Head-head trials comparing different types of IVI formulations are lacking. In one study, IV FCM and IV IS markedly improved preoperative Hb concentration, with IV FCM achieving Hb correction about three days earlier than IV IS. No significant difference was observed between the two formulations.

iv. In all studies with positive results over the control group, IVI was administered at least 14 days prior to surgery, or improvement in Hb level measured at least 14 days after the first dose of IVI administration.

v. In population other than pregnant or postpartum women, IVI did not show any apparent benefit over the control group. In the latter two populations, Hb concentration has improved significantly with IVI than that achieved by oral iron.

vi. The impact of IVI on blood transfusion requirement among surgical patients cannot be established due to mixed results obtained from the included studies.

vii. Even though IVI had to a certain extent lessened the risk for blood transfusion in women with postpartum anaemia, as well as pregnant women, especially those with severe anaemia, the evidence on the impact of IVI in reducing blood transfusion requirement was inconclusive. Similarly, no significant differences in blood transfusion avoidance between IVI and control groups reported in other population.

viii. Almost all studies that reported on serum ferritin level showed that IVI did significantly increase the mean ferritin level compared to the control group with oral iron or no iron therapy.

ix. There were mixed results for mean transferrin saturation level as some studies reported a significant increase compared to control, while a few reported comparable effects between groups.

6.2 Safety

There was a substantial good level of retrievable evidence to suggest that:

i. No significant differences in mortality (treatment-related/ infection/ all causes) within the follow-up period between patients treated with IVI and control.

ii. The odds of experiencing severe hypersensitivity reaction with IV IIM was 59% lower than that of IV FCM, and 49% lower than that of IV IS. No significant difference in risk for hypersensitivity reaction between IV FCM and IV IS.

iii. No increase in the risk of experiencing serious adverse events with IVI compared with control, except for non-dialysis CKD patients treated with IVI reported a higher incidence of hospitalised heart failure compared to the oral iron group.

iv. No difference between IV FCM and IV IS in the risk of developing cardiovascular adverse event. However, the risk was noted to be lower with IV FCM, while the use of IV FG was associated with an increased risk.

v. IVI was associated with decreased risk for gastrointestinal adverse events, particularly with IV IS, IV ID and IV FCM, and when compared to oral iron or no iron therapy. On the other hand, the risk for neurologic and muscle and skeletal adverse events increased with IVI, particularly with IV IS and IV FCM, respectively.

vi. IV IS and IV FCM were associated with increased risk of infusion reaction, while serious infusion reactions were seen with IV FG.

vii. Significant lung and skin infection rates were documented in non-dialysis CKD patients receiving IVI when compared with oral iron. However, no significant difference in infection rate between IVI and control was reported in other population.

viii. One of the most common electrolyte disturbances reported for IVI was hypophosphataemia.

6.3 Organisational Issue

There was limited fair to good level of retrievable evidence to suggest that treatment of IDA with IVI resulted in no significant difference in length of

hospitalisation between IVI and control groups, be it in perioperative settings, critical care patients or pregnant women.

6.4 Economic evaluation

i. There was evidence to suggest that preoperative optimisation of Hb with IVI was cost-effective when compared with no iron therapy in patients with primary knee arthroplasty. Preoperative IVI in the theoretical model simulation managed to avert more patients from requiring blood transfusion and reduced number of transfused RBC units, with resulting cost savings of €831 and €405 for blood transfusion avoided per patient and each RBC unit spared, respectively. These cost savings were sensitive to the cost of the outpatient clinic and to the transfusion rate in both optimisation and control arms.

ii. There was evidence demonstrating the effectiveness of preoperative treatment with IVI in reducing the blood transfusion rate and costs paid by hospitals for extended hospitalisation among patient undergoing abdominal surgery when compared to standard medical therapy, with cost savings of €786 per case. The individual costs per case were most sensitive to changes in the number of patients transfused, the number of units transfused and cost of RBC.

iii. When comparing two different IVI formulations with oral iron therapy, preoperative IV IS, or oral iron was more expensive than IV FCM. Thus, use of IV FCM was associated with reduced total costs in patients with iron deficiency anaemia and colon cancer, with total costs per patient were €1,827, €2,312, and €2,101 for IV FCM, IV IS and oral iron, respectively. Therefore, baseline data cost savings for IV FCM treatment were €485 when compared to IV IS and €274 when compared to oral iron. In the two-way sensitivity analysis, the cost savings were sensitive to the length of hospitalisation.

Overall, a limited number of evidences has shown significant improvement in Hb concentration with IVI compared to control groups in pregnant and postpartum women, as well as adult patients undergoing surgery presenting with IDA. Nevertheless, there is a lack of strong evidence to show the use of IVI will result in reduced allogeneic blood transfusion requirement. Generally, IVI therapy is safe and the potential cost-savings with IVI may been seen in cases where treatment with IVI would lead to a significant reduction in blood transfusion requirement and length of hospitalisation.

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8.0 APPENDIX

8.1 Appendix 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-Process & Other Non-indexed Citations and Ovid MEDLINE® 1946 to present	
1.	(iron adj1 compound*).tw.
2.	(ferric adj1 compound*).tw.
3.	iron compounds/
4.	Ferric compounds/
5.	Iron-dextran complex/
6.	(((dextran adj1 iron) or dextran-iron or iron-dextran) adj1 complex).tw.
7.	(iron adj1 dextran).tw.
8.	Ferric oxide, saccharated/
9.	((ferri* adj1 saccharate) or ferri*-saccharate).tw.
10.	(ferric adj2 oxide saccharate*).tw.
11.	(iron oxide or (iron adj2 oxide saccharate*)).tw.
12.	((iron adj1 saccharate) or iron-saccharate).tw.
13	(iron adj1 sucrose).tw.
14.	((iron and hydroxide) adj2 sucrose complex).tw.
15.	(sucroferric adj oxyhydroxide).tw.
16.	(iron adj1 derisomaltose).tw.
17.	(ferric adj derisomaltose).tw.
18.	(iron adj2 sucrose similar*).tw.
19.	(intravenous adj1 iron).tw.
20.	(parenteral adj1 iron).tw.
21.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22.	anemia/
23.	an*mia.tw.
24.	Anemia, iron-deficiency/
25.	(an*mia adj2 iron deficiency).tw.
26.	22 or 23 or 24 or 25
27.	21 and 26

OTHER DATABASES	
EBM Reviews – Cochrane Central Registered of Controlled Trials	Same MeSH, keywords, limits used as per MEDLINE search
EBM Reviews – Database of Abstracts of Review of Effects	
EBM Reviews – Cochrane database of systematic reviews	
EBM Reviews – Health Technology Assessment	
NHS economic evaluation database	
PubMed	Same MeSH and keywords as per MEDLINE search
INAHTA	
US FDA	

8.2 Appendix 2

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

8.3 Appendix 3(a): Summary of results for included studies on intravenous iron in patients undergoing surgery

No.	Author, Year/ Study Design/ Country	Population/ IDA confirmed?	Sample size/ Treatment regime		Time of IVI administration	ITT/ Sample size (n/N)	Baseline haemoglobin prior to IVI (g/dL)		Haemoglobin concentration after intervention (g/dL)		Mean difference (95% CI) of hemoglobin concentration (g/dL)	*P* < 0.05	Number of patients transfused		*P* < 0.05	Transfusion trigger (g/dL)	Number of pRBCs transfused		*P* < 0.05
			Intervention	Control			Intervention	Control	Intervention	Control			Intervention	Control			Intervention	Control	
1	Kam, 2020 *Prospective cohort / Hong Kong*	Oncologic surgery/ Yes	38 500 mg IV IS with a total of two doses set at 1 week apart; OR, 1000 mg IV IIM (or 20 mg/kg if bodyweight is less than 50 kg) as a single dose	62 No iron (propensity score matching, 2:1 ratio)	Preoperative: At least 14 days prior to elective operation date.	100/100	Mean (95% CI): 8.43 (8.05, 8.81)	8.79 (8.52, 9.06)	Mean (SD; 95% CI) on admission: 10.63 (1.35; 10.2, 11.1)	9.46 (1.45; 9.05, 9.8)	-	Yes	8 Pre-op: 1	30 20	Yes Yes	< 8	Mean (SD): 0.55 (1.59)	1.42 (2.71)	No
2	Klein, 2020 *Prospective cohort / UK*	Cardiac surgery/ Yes	64 IV IIM total dose calculated at 20mg/kg (mean dose of 1314 [303] mg).	72 No iron	Preoperative: At a median (IQR [range]) of 33 (15-53 [4-303]) days before surgery.	136	Mean (SD): 11.4 (0.9)	11.7 (1.0)	Mean (SD): Preoperative: 12.3 (1.3) Postoperative: 9.4 (1.2)	11.7 (1.0) 9.3 (1.1)	-	Yes NR	31	28	No	NR	Median (IQR): 0 (0-2)	1 (0-2)	No
3	Lee, 2019 *RCT / Korea*	Gynaecologic surgery/ Yes	49 200 mg (maximum 600mg/week) IV IS. Total dose calculated using Ganzoni equation. Mean total dose: 939.6 ± 352.3 mg	52 A single dose of 1000 mg IV FCM (body weight ≥ 50 kg); < 50 kg, 500 mg IV FCM) administered Mean total dose: 923.1 ± 207.3 mg	Preoperattive: At least 14 days prior to surgery.	99/101	Mean (SD): 8.4 (1.4)	8.4 (1.1)	Mean (SD) at 2 weeks: 10.3 (0.9)	10.6 (1.1)	-	No	0	0	-	NR	NR	NR	-

4	Alexander, 2010 *Prospective cohort*	Oncologic surgery/ Yes	30 (11 IV IS; 19 IV ID) 100 mg IV IS three times	23 200 mg oral	Preoperative: Mean: 27 days	53/53	NR	NR	Mean haemoglobin rise/ day: IV IS: 0.08 IV ID:0.13	0.02	-	Yes Yes	3 (1 in IV IS; 2 in IV ID)	10	Yes	NR	Total units: 7	25	NR
5	Edwards, 2009 *RCT/ UK*	Oncologic surgery/ Not mentioned explicitly in inclusion/ exclusion criteria; baseline iron markers suggested functional IDA	9 Two infusions of 300 mg iron sucrose administered 24 hours apart.	9 Two infusions of 250 ml IV placebo (0·9 per cent saline)	Preoperative: Completed within a minimum of 14 days before surgery. Median of 17 (range 11 - 32) days	18/18	Median (IQR): 11.8 (2.0) Mean (95% CI): 11.7 (10.6, 12.7)	12.4 (2.0) 11.8 (10.2, 13.5)	Median (IQR): 11.2 (3.0) Mean (95% CI) before surgery: 11.2 (9.7, 12.6) Mean at POD 1: 9.6 (8.9, 10.4) Mean at discharge: 10.2 (8.4, 12.1)	12.5 (4.0) 11.9 (9.9, 14) 10.7 (9.8, 11.6) 11.3 (10.4, 12.2)	-	No NR NR	2	5	No	< 8	Median (IQR): 0 (1)	2 (3)	NR
6	Diez-Lobo, 2007 *Prospective cohort/ Spain*	Gynaecologic surgery/ Yes	31 200 mg IV IS Every 48-72 hours until completion of total dose (maximum 600 mg/week); Mean (SD): 760 ± 290 mg; range: 300 – 1400 mg)	44 Oral iron (not specified)	Preoperative: 28 to 14 days before surgery	75/75	Mean (SD): 11.1 (1.9)	11.7 (1.8)	Mean (SD) POD 21: 12.4 (0.8)	11.7 (1.0)	Mean difference (95% CI): 0.74 (0.31, 1.17)	Yes	0	14	Yes	< 8	Mean (SD): 0	0.66 (1.26)	NR
7	Xu, 2019 *RCT / China*	Cardiac surgery/ Yes	75 200 mg IV IS each dose until total dose completed (according to calculated iron deficit).	75 Saline solution	Postoperative: POD 1 and every other day	148/150 150/150	Mean (SD): 10.8 (1.3)	10.6 (1.4)	Mean (SD): POD 7: 10.7 (1.5) POD 14: 11.4 (1.5)	10.6 (1.5) 10.8 (1.5)	0.1	No Yes	10	16	No	< 7	NR	NR	-

RCT: randomised controlled trial; IDA: iron deficiency anaemia; IVI: intravenous iron; ITT: intention-to-treat; CI: confidence interval; SD: standard deviation; IQR: interquartile range; P: significance level; POD: postoperative day; IS: iron sucrose; ID: iron dextran; FCM: ferric carboxymaltose; IIM: isomaltoside; NR: not reported

8.3 Appendix 3(b): Summary of results for included studies on intravenous iron in other populations

No.	Author, Year/ Study Design/ Country	Population/ IDA confirmed?	Sample size		Treatment regime		ITT/ Sample size (n/N)	Baseline haemoglobin prior to IVI (g/dL)		Haemoglobin concentration (g/dL)		Mean difference (95% CI) of hemoglobin concentration (g/dL)	*P* < 0.05	Number of patients transfused		*P* < 0.05	Transfusion trigger (g/dL)
			Intervention	Control	Intervention	Control		Intervention	Control	Intervention	Control			Intervention	Control		
1	Pieracci, 2014 *RCT/ USA*	Traumatic critical illness/ Yes	75	75	100 mg IV IS thrice weekly for up to six doses or until ICU discharge, whichever occurred first.	IV placebo thrice weekly for up to six doses or until ICU discharge, whichever occurred first.	Haemoglobin level: 57/150 Transfusion requirement: 150/150	*8.8	*9.9	Day 7: ~ 8.0 Day 14: ~ 8.3	~ 8.4 ~ 8.5		No	47	55	No	< 7
2	Ng, 2018 *RCT/ UK*	Cancer/ Not mentioned explicitly in inclusion/ exclusion criteria; Baseline iron markers suggested functional IDA	14	13	A single dose of IV IIM, calculated according to Ganzoni equation.	Standard medical care	Haemoglobin level: After cycle 1: 23/27 After cycle 2: 18/27 After cycle 3: 17/27 Transfusion requirement: 27/27	*Mean (SD): 9.96 (1.60)	*11.45 (1.79)	Mean (SD): 10.15 (1.49) 10.79 (0.99) 10.60 (1.19)	*0.044 11.08 (1.10) 10.83 (1.15) 10.70 (1.49)		No No No	3	4	No	< 8
3	Noronha, 2018 *RCT/ India*	Cancer/ Yes	94	98	IV IS in two divided doses (calculated according to Ganzoni equation) administered with cycle 1 and cycle 2 of chemotherapy (three weeks apart).	100 mg oral ferrous sulfate three times daily, started with cycle one of chemotherapy and continued until the end of cycle 2 (i.e. for 42 days).	192/192	Mean (range): 10.2 (7.2-11.9)	10.1 (7.2-12.5)	Mean (range): At 3 weeks: 10.3 (7.4 - 13.7) At 6 weeks: 10.0 (6.3 = 15.2) Mean absolute increase At 3 weeks: 0.01 (1.08) At 6 weeks: 0.11 (1.48)	 10.2 (7.1 - 13.2) 9.7 (6.0 - 12.8) - 0.11 (1.15) - 0.16 (1.36)		 No No No No	13	14	No	NR

4	Agarwal, 2015 *RCT/ USA*	Non-dialysis CKD/ Yes	67	69	200 mg IV IS administered at weeks 0, 2, 4, 6, and 8	325 mg oral ferrous sulfate three times daily for 8 weeks	99/136	10.7	10.5			Mean difference (95%CI): From baseline to 3 months: 0.08 (-0.34 to 0.51) From baseline to 6 months: 0.22 From baseline to 12 months: -0.04 From baseline to 24 months: 0.15	No No No No				NR
							136/136							12	12	No	
5	Qassim, 2019 *SR of 15 RCTs/ India, Australia, Singapore, France, Thailand, Turkey and multiple countries*	Pregnant women/ Yes	Maternal haemoglobin at delivery (9 RCTs): Maternal blood transfusion requirement (9 RCTs): 555	503 535	IV IS: 12 RCTs IV PM: 2 RCTs IV FCM: 1 RCT Variable IV iron dosing according to the baseline haemoglobin and weight (target haemoglobin levels ranging from 11 to 15 g/dL), or fixed IV iron doses (400 or 500 mg iron sucrose)	Oral iron						Mean difference (95% CI) at delivery: 0.74 (0.39, 1.09)	Yes	1	7	Yes	Not pre-defined in any of the included studies
6	Neogi, 2019 *RCT/ India*	Postpartum women/ included only patients with MCV: RBC ratio more than 14 (IDA is more likely)	983	1,016	200 mg IV IS administered 48 hours apart until completion of total dose (200–1600 mg, calculated based on weight) and 5 mg of folic acid daily	100 mg elemental iron and 0.5 mg of folic acid per tablet, taken twice daily until 6 weeks postpartum, and 5 mg of folic acid daily	Haemoglobin level from the baseline: At 6 weeks post randomization: 1,295/1,999 At delivery: 475/1,999	Mean (SD): 7.7 (0.9)	7.7 (1.0)	Mean (SD): 2.8 (1.3) 2.8 (1.4)	1.9 (1.7) 2.4 (1.9)	Mean difference (95% CI), adjusted for baseline haemoglobin and gestational week: 0·95 (0·80, 1·10) 0·45 (0·18, 0·73)	 Yes NR				< 5

						At 6 weeks postpartum: 1,323/1,999	3.7 (1.4)	3.0 (1.7)	0·63 (0·48, 0·78)	NR				
						Transfusion requirement: 1,930/1,999					22	25	No	
7	Sultan, 2019 *SR of 15 RCT/ UK, USA, Norway, India, Romania, Egypt, Greece, Spain, Denmark and Pakistan*	Postpartum/ Yes	Haemoglobin level at:		IV IS: 9 RCTs	Oral iron			Mean difference (95% CI):					NR
			1 week postpartum (11 RCTs): 724	512	IV FCM: 4 IV ID: 1				1.0 (0.5, 1.5)	Yes				
			6 weeks postpartum (4 RCTs): 251	134	IV IIM: 1				0.9 (0.4, 1.3)	Yes				
			Blood transfusion requirement: results from 2 RCTs reported qualitatively								1) 1% (1/97) vs 2% (2/99);		NR	
											2) 6.9% vs 14.3%;		No	

RCT: randomised controlled trial; SR: systematic review; IDA: iron deficiency anaemia; IVI: intravenous iron; ITT: intention-to-treat; CI: confidence interval; SD: standard deviation; IQR: interquartile range; P: significance level; POD: postoperative day; IS: iron sucrose; ID: iron dextran; FCM: ferric carboxymaltose; IIM: isomaltoside; NR: not reported

8.4 Appendix 4: Evidence Table

Evidence Table : Effectiveness
Question : Is preoperative intravenous iron more effective than no iron therapy in treating iron-deficiency anaemia and reducing blood transfusion requirement among colorectal cancer patients undergoing surgery?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
1. Kam PMH, Chu CWH, Chan EMY, et al. Use of intravenous iron therapy in colorectal cancer patient with iron deficiency anemia: a propensity-score matched study. Int J Colorectal Dis. 2020;35(3):521–7.	**PROSPECTIVE COHORT** **Objective:** To investigate the effect of intravenous iron therapy on haemoglobin (Hb) level change and transfusion requirements among anaemic colorectal cancer patient in a tertiary hospital in Hong Kong. **Methods:** This single centre study was carried out in a tertiary centre with more than 200 elective colorectal cancer operations per year. Patients diagnosed with colorectal adenocarcinoma and found to have iron deficiency anaemia (confirmed based on blood test) preoperatively were recruited from August 2017 to March 2019. All patients were arranged to undergo intravenous iron infusion in day admission setting at least 2 weeks prior to their elective operation date. Their haemoglobin level and iron profile were recorded again during their admission for elective surgery, which was 1 day prior to the operation. The operations were performed by specialist surgeons in	**II-2**	A total of 100 patients included in the study. Anaemic patients without iron deficiency excluded from study. There were no statistical differences between median age (70 in IVI vs. 69 in non-IVI, *P* = 0.46) and male to female ratio (50% male in both groups, *P* = 1.0). There were no statistical differences in premorbid status, medical comorbidities, or use of antiplatelet or anticoagulant. There was no difference in number of patients with red cell transfusion prior to intravenous iron (42.1% in IVI vs. 41.9% in non-IVI, *P* = 0.987). Both groups had similar proportions of patient taking oral iron supplement prior to surgery (31.6% in IVI vs. 29% in non-IVI, *P* = 0.787). Majority of patients had cancers in cecum,	Iron sucrose (IS) or iron isomaltoside (IIM): n=38 IS: 500 mg in 250 ml normal saline over 210 min intravenously, with a total of two doses set at 1 week apart IIM: 1000 mg (or 20 mg/kg if bodyweight is less than 50 kg) in 100 ml normal saline over 15 min as a single dose.	No iron therapy: n=62 (after propensity score matching in a 2:1 ratio)	Not reported	<u>Haemoglobin (Hb) concentration:</u> Most patients in both groups had operation done in laparoscopic manner (69.6% in IVI, 67.4% in no iron; *P* = 0.27), with no statistical difference in median intraoperative blood loss observed (100 ml in IVI, 150 ml in no iron; *P* = 0.848). There was no statistical difference for baseline haemoglobin level before IVI (8.43 g/dL in IVI, 8.79 g/dL in no iron; *P* = 0.117). Upon admission, which is at least 2 weeks after intravenous iron, mean haemoglobin in IVI group was significantly higher (10.63 g/dL; 95% confidence interval [CI]: 10.2, 11.1) than in no iron therapy group (9.46 g/dL; 95% CI: 9.05, 9.8; *P* < 0.001), with significantly higher median haemoglobin rise observed (i.e., haemoglobin level upon admission minus first haemoglobin level; 1.9 g/dL in IVI, 0.6 g/dL in no iron; *P* < 0.001). In subgroup analysis after excluding patients with preoperative oral iron supplement (i.e., analysis on 26 in IVI and 44 patients in non-IVI), there was the same trend of higher mean haemoglobin on admission (10.54 g/dL in IVI, 9.17 g/dL in non-IVI; *P* < 0.001) and higher median haemoglobin rise after intravenous iron (2.05 in IVI, 0.2 in non-IVI; *P* < 0.001). <u>Blood transfusion requirement:</u> There were significantly less patients that required transfusion in treatment group (8 in IVI, 30 patients in no iron; *P* = 0.006). Subgroup analysis based on timing of	Hb set for inclusion: < 10 g/dL if no previous transfusion; < 12 g/dL if previous transfusion within past 6 months Transfusion trigger: 8 g/dL Shortage of blood products in blood banks of Hong Kong coincided with introduction of IVI, and this may have caused the difference in transfusions of red cell between these groups

	laparoscopic, open, or robotic method (in selected cases of rectal cancer) under general anaesthesia. Patients were excluded if (1) histology of tumour was not adenocarcinoma; (2) anaemia was not due to iron deficiency; (3) no elective operation was performed (either because patient refused or was deemed unfit for surgery); and (4) only one dose of IS was given (due to incomplete IVI dosage use). The data of the historic cohort as control for matching was collected retrospectively from CDARS (Clinical Data Analysis and Reporting System). These were anaemic patients who underwent colorectal cancer surgery during the period of October 2014 to September 2017.		ascending colon, or hepatic flexure for both groups, followed by sigmoid and rectal cancers. Most patients' final pathology were stage III disease (47.4% in IVI and 48.5% in non-IVI) and stage II disease (36.8% IVI and 30.6% non-IVI). There was no difference in median waiting time from diagnosis to operation between two groups (34.5 days in IVI and 43.5 days in non-IVI, *P* = 0.952). Propensity score matching and statistical analysis were performed on SPSS version 23 with R-extension 3.1.0 and PSMatching, using caliper 0.5. The matching criteria included first haemoglobin level, age, sex, transfusion of red cell prior to intravenous iron, use of oral iron supplement, and tumour location.				transfusion showed that significantly less patients in treatment group required transfusions in preoperative period (1 in IVI group, 20 in no iron; *P* < 0.001). Those required this preoperative transfusion had mean Hb less than 8 (7.6 in the only patient in IVI, mean Hb 7.9 g/dL in no iron with range 7.0–9.0). No significant difference in mean number of packs RBC seen between both groups (0.55 in IVI and 1.42 in no iron; *P* = 0.076). When comparing the use of IV IS with IV IIM, the median time from first dose of intravenous iron to operation was not significantly different (22 days in IV IS vs. 21 days in IV IIM; *P* = 1.0).	

Evidence Table : Effectiveness
Question : Is preoperative intravenous iron more effective than no iron therapy in treating iron-deficiency anaemia and reducing blood transfusion requirement among patients undergoing cardiac surgery?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
2. Klein AA, Chau M, Yeates JA, et al. Preoperative intravenous iron before cardiac surgery: a prospective multicentre feasibility study. Br J Anaesth. 2020;124(3):243–50.	**PROSPECTIVE COHORT** **Objective:** To assess the introduction and efficacy of a preoperative IV iron pathway to treat anaemia in patients before cardiac surgery. **Methods:** The UK CAVIAR study was a multicentre, stepped, observational pilot and feasibility study comprising three groups of patients awaiting cardiac surgery. Patients were consecutively recruited between April 2016 until March 2018, but over different periods depending on the centre's progress in setting up preoperative anaemia services and availability of study teams. Sample size was calculated based on change in Hb from baseline to pre-surgery in patients who received IV iron. Assuming the SD for Hb would be 12 g/L based on national audit data, 72 patients would provide 90% power at a 5% significance level and 62 would provide 80% power (allowing for up to 10% loss to follow-up) to demonstrate a difference in the change from baseline in Hb of 10 g/L.	**II-2**	A total of 228 patients were recruited over 2 years in 11 UK cardiac centres. The baseline characteristics of the study groups varied significantly. In this study population, anaemic patients who received IV iron had a significantly higher rate of pre-existing renal impairment. There were higher rates of previously diagnosed anaemia (55% vs 30%), previous iron deficiency (39% vs 13%), and symptomatic angina (63% vs 39%) in the IV compared with the non-treated anaemic patients.	Anaemic with iron deficiency (n=64) treated with: 1. IIM (n=60): total dose calculated at 20mg/kg (mean dose of 1314 [303] mg) or, 2. Ferric carboxymaltose (FCM) [n=4]: up to a maximum of 1000mg IV iron was administered at a median (IQR [range]) of 33 (15-53 [4-303]) days before surgery. The mean (SD) dose of IV iron was 1293 (303) mg.	1. Non-anaemic: n=92 2. Anaemic with iron deficiency, but not treated: n=72	30 days	<u>Haemoglobin (Hb) concentration:</u> Intravenous iron was efficacious and increased the average Hb in anaemic patients before surgery compared with those without treatment; the mean (95% CI) change in Hb in patients treated with IV iron was +0.8 (0.5-1.2) g/dL between treatment and surgery (P < 0.001). After surgery, Hb was similar in all three groups. The largest drop in Hb was in the non-anaemic group (4.3 [-4.6 to -4.0] g/dL, P < 0.001), followed by anaemic treated (-2.9 [-3.2 to -2.6] g/dL) and anaemic not treated (-2.3 [-2.7 to 2.0] g/dL). <u>Blood transfusion requirement:</u> Overall, transfusion rates varied from 30% to 65% across the study centres. Twenty-three (10%) patients received a large blood transfusion with more than four units of red cells and were excluded (nine from the non-anaemic group, five from the non-treated anaemic group, and nine from the treated anaemic group). Non-anaemic patients were less likely o be transfused than anaemic patients, 22/92 (27%) vs 59/136 (42%), adjusted odds ratio (OR)=2.53 (1.38-4.63, P = 0.003). Non-anaemic patients were also transfused fewer units of red cells and had a shorter stay in hospital, and days alive at home (DAH) was higher. There was no difference in transfusion rate, quantity of blood transfused, or other outcomes between untreated anaemic patients and anaemic patients treated with IV iron.	Individual TSAT/ferritin results for all participants have not been included as the data were not complete at the time of analysis. Excluded patients who received a large transfusion defined as four or more units of red cells). Study was designed to detect increase in Hb concentration and not powered to demonstrate difference on transfusion rate or other patient outcomes. No mention on transfusion trigger.

Evidence Table : Efficacy
Question : Is preoperative intravenous iron sucrose more effective than other intravenous iron preparation in treating iron deficiency anaemia and reducing blood transfusion requirement among women with menorrhagia?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
3. Lee S, Ryu KJ, Lee ES, et al. Comparative efficacy and safety of intravenous ferric carboxymaltose and iron sucrose for the treatment of preoperative anemia in patients with menorrhagia: An open-label, multicenter, randomized study. J Obstet Gynaecol Res. 2019;45(4):858–64.	**RANDOMIZED CONTROLLED TRIAL** **Objective:** To compare intravenous ferric carboxymaltose (FCM) with iron sucrose (IS) for the effective and timely treatment of preoperative IDA in women with menorrhagia. **Methods:** This open-label, randomized, two-arm study was conducted at three centres in South Korea between February 2013 and March 2016. Women with menorrhagia and IDA (Hb level <10 g/dL and serum ferritin level <30 ng/mL) at the time of preoperative laboratory workup were eligible for the study. The indication of surgery included the benign uterine diseases, assumed to cause menorrhagia, such as uterine fibroids, adenomyosis, endometrial polyps and endometrial hyperplasia. Patients were randomized 1:1 by a computer randomization system to either preparation of IV iron.	**I**	In total, 101 women were enrolled in this study. There were no statistically significant differences in baseline characteristics (age, body weight, serum ferritin and transferrin saturation level) between the two study groups.	FCM: n=52 Mean total dose: 923.1 ± 207.3 mg The maximum weekly dose of FCM per patient did not exceed 1000 mg, and the amount of iron administered was determined based on the patient's body weight (<50 kg, 500 mg iron; ≥50 kg, 1000 mg iron). Patients in the FCM group received the maximum weekly treatment as a single dose, which was administered intravenously over a period of 15 min.	IS: 49 Mean total dose: 939.6 ± 352.3 mg Dosage period of IS was based on the calculated iron deficit using the Ganzoni formula. Patients randomized to receive IS required up to three dosing visits per week, and they received a maximum of 600 mg iron per week in 200 mg iron single administration sessions (over three to eight visits required to complete total dose)	14 days after the first IVI administration.	<u>Haemoglobin (Hb) concentration:</u> The proportion of patients achieving Hb levels ≥10 g/dL (surgery eligibility criterion) within 2 weeks after the first administration was similar in both the FCM group (78.8%) and the IS group (72.3%; *P* = 0.452). However, FCM corrected Hb levels significantly faster than IS (time to achieve Hb levels ≥10 g/dL: 7.7 days with FCM; 10.5 days with IS; *P* = 0.013), and the mean Hb levels were higher in patients treated with FCM than in those treated with IS; however, this difference was not statistically significant (*P* = 0.079). <u>Blood transfusion requirement:</u> No transfusion requirements were reported in either group. .	The mean total dose ultimately administered was similar in both the FCM group and the IS group (P=0.774). Day zero counted from first administration of both IVI – FCM given as single total dose versus IS multiple dosing, where some patient might have completed the total dose during the second week (could be less than 5 days prior to primary endpoints assessment), which may not reflect the full effect of IS cumulative doses No mention on transfusion trigger.

Evidence Table : Efficacy
Question : Is preoperative intravenous iron sucrose or iron dextan more effective than oral iron in treating iron deficiency anaemia and reducing blood transfusion requirement among women with menorrhagia?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
4. Alexander RJ. Optimal Iron Replacement for Colorectal Cancer-Induced Anaemia. Open Color Cancer J. 2010;3(1):27–31.	**PROSPECTIVE COHORT** **Objective:** To compare the effect of oral iron and two forms of parenteral iron in raising the Hb and MCV of consecutive colorectal cancer patients with iron-deficiency anaemia, and their respective effect on blood trans-fusion requirement. **Methods:** Colorectal cancer patients with IDA were initially treated preoperatively with either IV iron or oral iron. They were not randomised into treatment groups in this study and were given the iron supplement available, depending on their diagnosis date and also pharmacy supply. The requirement for preoperative transfusion was also noted and the overall cost (including blood transfusions) in each of the iron supplement groups, calculated.	**II-2**	A total of 53 were consecutively recruited into the study. Each group has comparable demographics with respect to mean age, sex distribution, cancer stage and site. The majority of patients in this study had advanced cancers: 96% of all patients had T3/T4 lesions, with 59% having nodal disease and 19% having metastases. 74% of patients in this study had a right-sided colonic cancer.	Iron sucrose (IS): n=11 - 100mg 3 times per week for a maximum of 12 cycles Iron dextran (ID): n=19 - once-only dose averaging 1100mg with a maximum of 20mg/kg.	Oral ferrous sulphate: n=23 - 200mg twice daily	Not reported	<u>Haemoglobin (Hb) concentration:</u> The total Hb rise over the course of treatment was significantly more with IS and ID, compared with oral iron (*P* = 0.048, *P* = 0.034). There was no significant difference in total Hb rise between IS and ID (*P* = 0.82). The Hb rise per day (taking in account treatment course length) was significantly more with IS and ID, compared with oral iron (*P* = 0.002, *P* = 0.001). There was no difference in the Hb rise per day between IS and ID (*P* = 0.16). <u>Blood transfusion requirement:</u> The oral iron group required significantly more blood (44%) than the IS (9%; *P* = 0.04) or ID groups (11%; *P* = 0.01). The total number of blood units transfused was 25, 3 and 4 in oral iron, iron sucrose and iron dextran, respectively. <u>Iron status biomarkers:</u> There were no significant differences between the iron supplements with regard total MCV rise. Only ID gave a significantly improved MCV rise/day over oral iron, and was significantly more than IS (*P* = 0.04).	No mention on transfusion trigger.

Evidence Table : Efficacy
Question : Is preoperative intravenous iron more effective than placebo in treating iron deficiency anaemia and reducing blood transfusion requirement among patients undergoing elective surgery for suspected colorectal cancer?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
5. Edwards TJ, Noble EJ, Durran A, et al. Randomized clinical trial of preoperative intravenous iron sucrose to reduce blood transfusion in anaemic patients after colorectal cancer surgery. Br J Surg. 2009;96(10):1122–8.	**RANDOMIZED CONTROLLED TRIAL** **Objective:** To determine whether iron sucrose reduces the likelihood of postoperative blood transfusion in patients undergoing elective colorectal cancer resection. **Methods:** A prospective randomized blinded placebo-controlled trial was undertaken at a single centre in the UK. Volunteers were recruited from all patients scheduled to undergo bowel resection for suspected colorectal cancer at the centre between May 2006 and August 2008. The study was powered at 80 per cent to detect a difference in the mean change in serum Hb concentration between recruitment and treatment of 0·5 g/dl in anaemic patients. With the prevalence of anaemia within this patient group having previously been identified as 38 per cent, to ensure that at least 20 anaemic patients were recruited, the sample size was set at 60 (n = 30 in each group). Participants were allocated to either group using a computer-generated randomization sequence provided by the	**I**	62 participants were recruited, of whom 11 were known to be anaemic at recruitment, 22 to have a normal Hb level and 29 to have no recent record of anaemia status. At baseline there was good balance between the confounding variables in the two groups. There were 18 anaemic patients in total, nine in each group.	Iron sucrose (IS): n=35 Dose: Two infusions of 300 mg iron sucrose made up to 250 ml with 0·9 per cent saline. (total dose of 600 mg iron sucrose). The minimum time between each infusion was 24 h and all infusions were completed within a minimum of 14 days before undergoing elective surgery.	Placebo: n=27 Two infusions of 250 ml intravenous placebo (0·9 per cent saline)	Minimum 14 days prior surgery until discharge or day 7 of surgery (whichever was earlier)	<u>Haemoglobin (Hb) concentration:</u> There was no significant difference between the groups in mean Hb before surgery, postoperative day (POD) 1 and at discharge. <u>Blood transfusion requirement:</u> Five patients receiving placebo required transfusion, compared with two receiving iron (P = 0·335, Fisher's exact test). The median number of units transfused was 0 (interquartile range [IQR] 1) for iron versus 2 [IQR 3] units for placebo. <u>Iron status biomarkers:</u> Haematocrit, MCH, ferritin, serum iron or transferrin saturation between the groups were not significantly difference at any time point. In both groups there was an increase in ferritin concentration and transferrin saturation between recruitment and the preoperative value, which was greatest in the iron group: 109.3 versus 85.3 ng/ml and 4.9 versus 3.2 per cent for the mean change per individual in ferritin and transferrin respectively.	Serum iron marker suggestive of FID anaemia Very small sample size for anaemic patients. Transfusion trigger followed local transfusion protocol: Haemoglobin level - 1. > 10 g/dl: No transfusion 2. 8–10 g/dl: Transfuse if: Abnormal ECG; Ischaemic heart disease; Obstructive lung disease; Consultant's discretion; Unable to absorb oral iron 3. < 8 g/dl: Transfuse to target 10 g/dl. The trial was not sufficiently powered to detect reduction in blood transfusion.

	Research and Development Support Unit. To ensure equal numbers of anaemic patients in each treatment group, randomization was stratified according to prerecruitment Hb status: normal (Hb level at least 13·5 g/dl in males and 12·5 g/dl in females), anaemic, or unknown (no test within 2 months of recruitment). Block randomization was used to ensure similar numbers in each group for each subset. Allocation codes were sealed in sequentially numbered opaque envelopes which were secured within a locked storeroom in a dedicated research unit (this was remote from the clinical areas of the hospital where participants were to undergo outpatient, ward and operative treatment). Only after recruitment was an envelope opened by the investigator administering the infusion, following the inscribed strict numerical order and for the relevant subset appropriate to the Hb status of the participant. The investigator administering the infusion was not blinded to the treatment group, but this was concealed from the patient by using an opaque sheath to cover the drug-giving set. The chief investigator and clinicians involved in perioperative care also remained blinded to the treatment group for the duration of the trial.							

Evidence Table : Efficacy
Question : Is preoperative intravenous iron more effective than oral iron in treating iron deficiency anaemia and reducing blood transfusion requirement among women undergoing abdominal hysterectomy?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
6. Diez-Lobo AI, Fisac-Martín MP, Bermejo-Aycar I, et al. Preoperative intravenous iron administration corrects anemia and reduces transfusion requirement in women undergoing abdominal hysterectomy. Transfus Altern Transfus Med. 2007;9(2):114–9.	**PROSPECTIVE COHORT** **Objective:** To investigate the utility of preoperative IV iron treatment to increase Hb levels and reduce the need for allogeneic blood transfusion (ABT) in women undergoing elective abdominal hysterectomy. **Methods:** All women with ID or IDA who scheduled for elective abdominal hysterectomy from January 2004 to June 2006 were enrolled. The presence of ID was defined by two of the following conditions: serum ferritin < 30 ng/mL, serum iron < 50 µg/dL or transferrin saturation index < 20%.9 The presence of preoperative or postoperative anaemia was defined according to World Health Organization criteria as Hb < 12 g/dL. They were assigned by the anaesthesiologist to one of the two groups depending on the time between preoperative assessment and surgery. The transfusion trigger was set at Hb < 8 g/dL. For the control group, preoperative values were	**II-2**	A total of 75 women were included in the study. Most women (63/75, 84%) were already on oral iron, as prescribed by their gynaecologist or family doctor. There were no statistically significant differences between the two groups in terms of weight or age, type of procedure, prevalence of anaemia, estimated blood loss, length of hospital stay, Hb levels or iron laboratory parameters at baseline.	Iron sucrose (IS): n=31 Administered for 2–4 preoperative weeks, at doses of 200 mg in 200 mL saline every 48–72 hours, with a maximum of 600 mg/week, according to total iron deficit calculation (760 ± 290 mg; range: 300–1400 mg) Assigned to - women having their surgical procedure at least 1 month after preoperative assessment	Oral iron: n=44 (Assigned to women having their surgical procedure within a few days after preoperative assessment	Postoperative day 21	<u>Haemoglobin (Hb) concentration:</u> Preoperative administration of IV iron sucrose induced a significant increase in preoperative Hb (11.1 ± 1.9 g/dL vs. 13.3 ± 0.9 g/dL, for baseline and preoperative, respectively; ΔHb: 2.2 ± 1.2 g/dL; *P* < 0.001). The magnitude of increase in Hb was inversely correlated with baseline Hb levels. On postoperative day 21, there were statistically significant differences in Hb levels between the groups (difference = 0.74 g/dL; 95% CI 0.31, 1.17; *P* = 0.001), and the prevalence of anaemia (Hb < 12 g/dL) was lower in the IV iron group than in the control group (23% vs. 68%, respectively; *P* < 0.01). Excluding transfused women, Hb on postoperative day 1 was lower in women who were anaemic on postoperative day 21 than in those who were not (9.3 ± 1.1 g/dL vs. 10.4 ± 1.4 g/dL, respectively; *P* < 0.01). <u>Blood transfusion requirement:</u> Preoperative and postoperative day 1 Hb levels in the IV iron group were higher than those in the control group, resulting in a significant reduction of the ABT rate (32% vs. 0%, for control and IV iron groups, respectively; *P* < 0.001. Overall, 14 women in the control group received 29 packed RBC units (1 unit, 6 women; 2 units, 5 women; ≥ 3 units, 3 women). All transfusions were given on	Transfusion trigger: Hb < 8 g/dL

	assumed to be equal to baseline values.						the day of surgery. None in the IVI group required blood transfusion. <u>Iron status biomarkers:</u> Significant improvement in ferritin and transferrin saturation were seen in both groups ($P < 0.05$). Significant difference between both groups at POD 21 were observed for ferritin level ($P = 0.001$). Furthermore, the prevalence of ID was lower in the IV group than in the control group (42% vs. 68%, respectively; $P < 0.05$).	

Evidence Table : Effectiveness
Question : Is postoperative intravenous iron more effective than placebo in treating iron-deficiency anaemia and reducing blood transfusion requirement among patients undergoing cardiac surgery?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
7. Xu H, Duan Y, Yuan X et al. Intravenous iron versus placebo in the management of postoperative functional iron deficiency anaemia in patients undergoing cardiac valvular surgery: a prospective, single-blinded, randomised controlled trial, J Cardiothorac Vasc Anesth. 2019;	**RANDOMIZED CONTROLLED TRIAL** **Objective:** to compare the safety and efficacy of intravenous iron versus placebo to correct postoperative anaemia in patients undergoing cardiac valvular surgery. **Methods:** A prospective, single-blind, randomised controlled trial at a hospital in China from March 2018 to October 2018. Eligible patients aged 20-70 years who agreed to participate were randomly assigned (1:1) to either the treatment (intravenous iron) group or the control (placebo) group using Excel 2010 (Microsoft, Redmond, WA, USA) To ensure allocation concealment, treatment codes were located in a central site, the pharmacy department. This department was not involved in any collection of trial data, follow-up, or patient activity to avoid possible bias. Randomisation allocation was delivered by pharmacy in sealed numbered opaque envelopes that were opened consecutively after informed consent was obtained. All intravenous solutions were presented in disguised form by the pharmacy department and assigned to patients according to the random numbers list.	**I**	A total of 150 patients were recruited: 75 were randomized to intravenous iron group and 75 were randomized to placebo group. There were no differences in demographic variables, preoperative Hb levels and postoperative parameters.	Iron sucrose (IS): n=75 weight-based calculated dose of iron sucrose administered with the dose of 200mg over 30 min on the day after surgery and maintained this dose every other day until the total iron deficiency was achieved. (794.8 ± 173.7mg)	Saline solution: n=75	0,4, 14 days after surgery	<u>Haemoglobin (Hb) concentration:</u> In the full analysis set (FAS) [n=148], the Hb concentration was significantly higher in the intravenous iron group at POD 14 than that in the placebo group (*P* = 0.023), but no significant between-group differences were noted at POD 7 (*P*=0.833). There were significant differences in the proportion of patients who had the anaemia corrected (IV iron, 24%; Placebo, 11%; *P* = 0.037) or in the proportion of patients who achieved Hb increments of > 2 g/dL (IV iron, 45.5%; Placebo, 19.2%; *P* = 0.001) at POD 14, but no statistical difference at POD 7). The similar results were observed in the per protocol (PP) [n=122] analysis sets. Exclusion of patients who received blood transfusion also showed similar results (*P* = 0.709). <u>Blood transfusion requirement:</u> The proportion of blood transfusion in the placebo group was higher than that in the intravenous iron group (21.3% VS 13.3%), there was no statistically significant difference between the two groups (*P* = 0.196). This significant difference in blood transfusion might require a larger trial to be powered. <u>Iron status biomarkers:</u> In the FAS, there was significant statistical difference in HCT and RBC count between the two groups at POD 14 (P = 0.034; *P* = 0.04), but no statistical difference at POD 7 (*P* = 0.948; *P* = 0.984). Serum ferritin were substantially higher at POD 7 and POD 14 in the intravenous iron group compared with the placebo group (both *P* < 0.001). In the per protocol (PP) analysis sets, changes in HCT, RBC count and serum ferritin between the	Transfusion trigger: Hb < 7 g/dL, referring to the Society of Thoracic Surgeons and the Society of Cardiovascular Anaesthesiologists Blood Conservation Clinical Practice Guidelines.

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
	The trigger for blood transfusion was a haemoglobin concentration of less than 70 g/L, referring to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines. Full analysis set (FAS): The FAS consisted of all patients who were randomised into the trial and had a follow-up assessment at POD 7 and POD 14, regardless of which treatment they actually received. Per protocol (PP) analysis set: The PP analysis set consisted of all patients in the FAS who had not received blood transfusion during the trial.						two groups were similar to the results of FAS. In the FAS, there was significant difference in transferrin saturation between the two groups at POD 7 (P = 0.025), but no statistical difference at POD 14 (P = 0.104). However, in the PP analysis sets, no significant between-group difference was noted either at POD 7 or at POD 14 (P = 0.063; P = 0.054).	

Evidence Table : Efficacy
Question : Is intravenous iron (sucrose/ dextran/ isomaltoside) more effective than placebo in reducing the blood transfusion requirement among critically ill trauma patients with iron-deficiency anaemia?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
8. Pieracci FM, Stovall RT, Jaouen B, et al. A multicenter randomized clinical trial of IV iron supplementation for anemia of traumatic critical illness. Crit Care Med. 2014;42(9):2048–57.	**RANDOMIZED CONTROLLED TRIAL** **Objective:** To evaluate the efficacy of IV iron supplementation of anaemic, critically ill trauma patients. **Methods:** This was a multicentre, randomized, single-blind, placebo-controlled trial involving four state-verified, American College of Surgeons–certified, level I trauma centres in the US. Eligible patients included those admitted to the ICU with a primary diagnosis of trauma. The inclusion criteria were 1) anaemia (latest haemoglobin concentration < 12 g/dL); 2) age 18 years old or older); 3) less than or equal to 72 hours from ICU admission; and 4) expected ICU length of stay (LOS) more than or equal to 5 days. Study group assignment was unblinded to both subjects and healthcare providers who administered the study drug and blinded to the research team abstracting and analysing the data. Randomization was accomplished by the investigational pharmacy at each satellite site using a computer-generated block pattern. The	**I**	A total of 150 patients were randomised. There was no difference between groups in enrolment site (*P* = 0.63), age (*P* = 0.71), mechanism of injury (*P* = 0.73), comorbidity score (*P*= 0.15), Injury Severity Score (ISS) (*P* = 0.28), time from ICU admission to study enrolment (*P* = 0.12). In the iron group as compared with the placebo group, there was a significantly increased proportion of male patients (77.3% vs 61.3%, *P* = 0.03), a significantly greater baseline estimated blood loss (EBL) (196 mL vs 57 mL, respectively, *P* = 0.02), and a significantly greater EBL/study day (75.9 mL vs 53.6 mL, respectively, *P* = 0.04). Both iron and hematologic markers for the sample at baseline suggested functional iron	n=75 Iron sucrose (IS) 100 mg IV thrice weekly for up to six doses or until ICU discharge, whichever occurred first.	n=75 IV placebo thrice weekly for up to six doses or until ICU discharge, whichever occurred first.	Subjects were followed for 42 days or until hospital discharge, whichever occurred first.	<u>Haemoglobin (Hb) concentration:</u> Only 57 (38.0%) received all six possible consecutive doses and thus constituted the a priori subgroup. Study drug was withheld in three subjects (3%) during the study because of a serum ferritin concentration more than 1,000 ug/dL on study day 7, two (2.7%) in the iron group, and one (1.3%) in the placebo group. At baseline, it was significantly higher for the placebo group as compared with the iron group (9.9 g/dL vs 8.8 g/dL, respectively, *P* = 0.03). No significant difference in haemoglobin concentration was observed between groups at any time point over the subsequent 14 days. <u>Blood transfusion requirement:</u> Iron supplementation did not decrease the transfusion requirement. During the study period, 55 subjects in the iron group (73.3%) and 47 subjects in the placebo group (62.7%) received at least one packed RBCs transfusion (*P* = 0.16). After controlling for baseline EBL, there remained no difference in risk of transfusion between groups (*df* = 2, model chi-square = 6.2, *P* = 0.04, OR for iron supplementation = 1.56, 95% CI, 0.77, 3.17, *P* = 0.21). As compared with the placebo group, the iron group had a significantly lower percentage of transfusion-free days per subject (84.0% vs 90.5%, respectively, *P* = 0.02). The only study day for which there was	Hb and iron markers only reported for those completed all six doses (38%). Subgroup analysis of the 70 subjects who had not received a packed RBCs transfusion prior to study entry: No difference in baseline EBL between the iron and placebo groups (62 mL vs 41 mL, respectively, *P* = 0.36). Furthermore, there was no difference in the proportion of subjects transfused during the study period between the iron and placebo groups (65.6% vs 52.3%, respectively, *P* = 0.27). Most subjects in this study were

	randomization was unblinded to the investigators only after completion of data accrual. Sample size calculation was performed based on increase in the transferrin saturation to 20%, 10% reduction in the risk of transfusion from 70% (*p*1) to 60% (*p*2) and 10% increase in the risk of infection from 50% (*p*1) to 60% (*p*2) among the iron group.		deficiency. The median baseline serum iron concentration was 18 ug/dL (range, 5–137), and 134 subjects (89.3%) were hypoferremic. The median baseline ferritin concentration was 247.0 (range, 18.0–967.0), and 51 subjects (34.0%) were hyperferritinemic. Only two subjects (1.3%) were hypoferritinemic at baseline (serum ferritin concentration, < 28 ug/mL) The median baseline transferrin saturation was 8% (range, 2–58%), and 133 subjects (88.7%) had a low transferrin saturation. Approximately one half of subjects had received at least one packed RBCs transfusion prior to study entry (*n* = 43 [57.3%] iron vs 37 [49.3%] placebo, *P* = 0.34).				a significant difference in percentage of patients transfused between the iron and placebo group was study day 1 (29.3% vs 13.3%, respectively, *P* =0.02). The only significant differences in EBL between the iron and placebo groups were prior to study entry (196 mL vs 57 mL, respectively, *P* = 0.02) and on study day 1 (87 mL vs 24 mL, respectively, *P* = 0.04). In order to address the possibility of confounding by baseline transfusion, a subgroup of the 70 subjects who had not received blood transfusion prior to study entry was analysed. There was no difference in baseline EBL between the iron and placebo groups (62 mL vs 41 mL, respectively, *P* = 0.36). Furthermore, there was no difference in the proportion of subjects transfused during the study period between the iron and placebo groups (65.6% vs 52.3%, respectively, *P* = 0.27). <u>Iron status biomarkers:</u> Iron markers at baseline, study day 7, and study day 14 among the subgroup of subjects who received all six doses of study drug (*n* = 57) showed that: 1) Serum iron: both groups remained hypoferremic at all time points, and there was no significant difference in serum iron concentration between the iron and placebo groups at any time point. 2) Serum ferritin concentration: the serum ferritin concentration was significantly higher for the iron group as compared with placebo group on both days 7 (808.0 ng/mL vs 457.0 ng/mL, respectively, *P* < 0.01) and 14 (1,046.0 ng/mL vs 551.5 ng/mL, respectively, *P* < 0.01). 3) Serum transferrin saturation: although the transferrin saturation had increased significantly for the iron group as compared with the placebo group at day 7 (15% vs 11%, respectively, *P* = 0.02),	discharged from the ICU prior to receiving the full 2-week treatment course, suggesting that most patients will not remain critically ill long enough to reap any potential benefits of iron supplementation . Even in the subgroup of patients with an ICU length of stay more than or equal to 14 days, no discernible benefit of iron supplementation was observed. Transfusion trigger: Hb < 7.0 g/dL in absence of shock or acute coronary syndrome **Some results described not consistent with figures/ tables provided -> results taken from description included in this review

							The difference was not clinically meaningful. Furthermore, there was no difference in transferrin saturation between groups at day 14 (16% vs 13%, respectively, *P* = 0.23). 4) The erythrocyte zinc protoporphyrin (eZPP) concentration began at the high end of normal range for both the iron and placebo groups (*P* = 0.73), then continued to rise at both day 7 and day 14. At no time point was a significant difference observed in eZPP concentration for the iron group as compared with the placebo group.	

Evidence Table : Efficacy
Question : Is intravenous iron (sucrose/ dextran/ isomaltoside) more effective than usual care in reducing blood transfusion requirement among patients with iron deficiency anaemia and receiving chemotherapy for their malignancies?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
9. Ng O, Keeler B, Simpson JA, et al. Feasibility of Intravenous Iron Isomaltoside to Improve Anemia and Quality of Life During Palliative Chemotherapy for Esophagogastric Adenocarcinoma. Nutr Cancer. 2018;70(7):1106–17.	**RANDOMIZED CONTROL TRIAL** **Objective:** To assess the feasibility of a single-dose intravenous iron therapy to improve anaemia, quality of life, and prevent blood transfusions in patients diagnosed with esophagogastric adenocarcinoma receiving palliative chemotherapy. **Methods:** Conducted at two recruiting sites in the UK. Adult patients with a proven histological diagnosis of Esophagogastric adenocarcinoma, anaemia (<12 g/dl in women and <13 g/dl in men) and a treatment decision for palliative chemotherapy were included. Patients were randomized 1:1 to each group using random allocations concealed in opaque envelopes. Clinical outcomes included haemoglobin, ferritin, TSAT, blood transfusion rate, number of units transfused, mortality, FACT-An, and EQ-5D quality of life scores. The indication for transfusions were severe anaemia (haemoglobin <8 g/dl) in six patients (one patient from intravenous iron group) and acute upper gastrointestinal	**I**	A total of 27 patients. No statistically significant differences in age, sex, body mass index, Charlson score, or staging between standard care and intravenous iron groups at recruitment. Hb at recruitment in the IVI group was significantly lower: mean Hb 9.96 g/dL (SD=1.60, n=11) than those receiving standard care 11.45 g/dL (SD=1.79, n=13), P=0.044. No statistically significant differences in serum ferritin mean (P=0.282)) and transferrin saturations mean (P=0.811) at recruitment between both groups.	n = 14 A single dose of intravenous iron isomaltoside 1000 (IIM). Dose were calculated using the Ganzoni equation of cumulative iron deficit. Iron isomaltoside was diluted in 250 ml 0.9% sodium chloride and infused over a period of 60 min. All subsequent treatment of anaemia was at the discretion of the clinical oncology team. No patients in either group received any oral iron therapy during the trial.	n = 13 Traditional regimens as decided by the clinical oncology team. All subsequent treatment of anaemia was at the discretion of the clinical oncology team.	Three follow-up visits were performed at the start of each three-week cycle of chemotherapy.	<u>Haemoglobin (Hb) concentration:</u> Seventeen patients completed the full three cycles of chemotherapy (62.9%), two patients had chemotherapy stopped after two cycles (7.4%), and five patients received only one cycle of chemotherapy (18.5%). No statistically significant differences were seen between groups and number of chemotherapy cycles completed. Data were analysed for 24 patients (IVI=11; standard care=13). Mean haemoglobin decreased by 0.6 g/dl over three cycles of chemotherapy in the standard care group to 10.8 g/dl (*P* = 0.336). In comparison, the haemoglobin in the intravenous iron group increased by 0.5 g/dl during the three cycles of chemotherapy to 10.5 g/dl, resulting in a difference between groups in mean haemoglobin change of 1.1 g/dl (*P* = 0.903). This change in haemoglobin was not significant (P=0.885) and no statistical difference between haemoglobins was seen after recruitment. Haemoglobin in subgroup analysis of patients not transfused during the trial again showed a significant difference at recruitment (mean haemoglobin 12.1 g/dl standard care group vs. 10.4 g/dl intravenous iron group *P* = 0.021). No difference was seen after cycle two (mean haemoglobin 10.9 g/dl standard care group vs. 10.8 g/dl intravenous iron group *P* = 0.737). Haemoglobin dropped with each cycle of chemotherapy in the standard care group from 12.1 g/dl at recruitment to	Small sample size and no power calculation. The trial was terminated early due to poor recruitment. 3 patients from the IVI group excluded from data analysis: - 1 died before given iron - 1 received multiple blood transfusions prior to IVI therapy due to massive upper GI haemorrhage. Study retention was 88.9% The indication for transfusions were severe anaemia (haemoglobin <8 g/dl) in six patients (one patient from intravenous iron group) and acute upper gastrointestinal haemorrhage

	haemorrhage in two patients (both in the intravenous iron group).						10.9 g/dl after cycle three, mean difference –1.2 g/dl. No drop in haemoglobin was seen in the intravenous iron group from a recruitment haemoglobin of 10.4 g/dl to a haemoglobin after cycle three of 10.6 g/dl, mean difference 0.2 g/dl. <u>Blood transfusion requirement:</u> After cycle one of chemotherapy; IVI vs standard care, 3 (27%) vs 4 (31%), *P* = 0.851, respectively. After cycle 2: IVI vs standard care, 0 vs 4, respectively. No patients in either group required a transfusion after cycle three of chemotherapy. Mean no. RBC units transfused: After cycle one of chemotherapy: IVI vs standard care, 5.3 (3.2) (n=3) vs 3 (n=1), *P* = 0.594, respectively. After cycle 2: none in IVI group while three further patients and one previous patient received an average of one unit of blood in the standard care group. <u>Iron status biomarkers:</u> Ferritin increased in the standard care group occurred in patients who received blood transfusions (mean increase 512 ng/ml transfused vs. 41 ng/ml non-transfused). In the intravenous iron group, all patients saw a rise in ferritin (mean 913 ng/ml transfused vs. 1,026 ng/ml). Ferritin showed a significant increase after chemotherapy cycle one in the group treated with intravenous iron 105 ng/ml to 1015 ng/ml (*P* < 0.05) and then began to decline with the mean ferritin 558 ng/ml after cycle three (*P* = 0.366). No statistical differences between groups were seen beyond cycle one of chemotherapy. Transferrin saturations increased above 20% in the intravenous iron group rising from 11.1% to 26.1% after cycle 1, while	in two patients (both in the intravenous iron group) For iron biomarkers, CRP did not correlate with the rise in ferritin in both groups. lower starting haemoglobin may improve the effectiveness of any intravenous iron administered, with quicker and larger increases in haemoglobin demonstrated the more anaemic patients.

							transferrin saturations never exceeded 20% in the standard care group but did rise from 11.9 to 19% after cycle three of chemotherapy. No statistical differences between groups were seen after each chemotherapy cycle.	

Evidence Table : Efficacy
Question : Is intravenous iron (sucrose/ dextran/ isomaltoside) more effective than oral iron in reducing blood transfusion requirement among patients with iron deficiency anaemia and receiving chemotherapy for their malignancies?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
10. Noronha V, Joshi A, Patil VM, et al. Phase III randomized trial comparing intravenous to oral iron in patients with cancer-related iron deficiency anaemia not on erythropoiesis stimulating agents. Asia Pac J Clin Oncol. 2018;14(2):e129–37.	**RANDOMIZED CONTROL TRIAL** **Objective:** To find out whether there is any difference in hematopoietic response in patients treated with oral versus IV iron. **Methods:** A prospective single-centre open label randomized controlled phase III trial in which patients over 18 years old with malignancy requiring chemotherapy, who had haemoglobin (Hb) level <12 g/dL with at least one feature indicating iron deficiency: serum ferritin <100 mcg/mL, transferrin saturation <20% or hypochromic red blood cells >10% were recruited from the outpatient medical oncology department at Tata Memorial Hospital (TMH), India. Patients were stratified according to the type of malignancy (solid tumour *vs* haematolymphoid) and the level of Hb (≤10 g/dL *vs* >10 g/dL). Randomization was by a computer-generated schedule with block randomization, using a block size of 10. IV iron administered to patients with cancer-related iron-deficiency anaemia was	**I**	A total of 192 patients were enrolled between March 2010 and March 2015. Median age was 51 years; male-to-female ratio was 0.68. Over 95% patients had solid tumours, most commonly gynaecologic, lung, head and neck and breast cancer. Intent of therapy was curative in 66%. The majority of patients (82%) were treated with platinum based two-drug combination chemotherapy regimen.	94 were randomized to IV iron sucrose (IS) in two divided doses, each diluted in 250 mL of 5% dextrose administered intravenously over 120 min with cycle 1 and cycle 2 of chemotherapy (three weeks apart). The dose of iron sucrose was calculated from the formula for total iron deficit: dose of iron in mg = weight in kg × Hb deficit (13-actual Hb in g/dL) × 2.4 + 500 The mean planned dose of IV iron was 869.35 mg (standard deviation [SD]: 203.1) and the	98 to oral ferrous sulfate capsules (100 mg) three times a day, started with cycle one of chemotherapy and continued until the end of cycle 2 (i.e., for 42 days). Oral iron could be continued beyond trial completion, if desired by the patient or the treating physician.	Week 1, 3 and 6	<u>Haemoglobin (Hb) concentration:</u> A total of 71 patients on IV iron and 77 patients on oral iron completed the entire planned therapy. The mean absolute increase in Hb at 3 weeks was 0.01 g/dL (SD:1.08) in the IV arm and −0.11 g/dL (SD: 1.15) in the oral arm, *P* = 0.49. A total of 13.8% (13 out of 94) patients on IV iron and 14.3% patients (14 out of 98) on oral iron had an increase in Hb of ≥ 1g/dL, *P* = 1.0. The number of patients who had a rise in Hb of ≥ 1.5 g/dL at 3 weeks was 8.5% (8 out of 94) in the IV iron arm and 9.2% (9 out of 98) in the oral iron arm, *P* = 1.0. The mean absolute increase in Hb at 6 weeks was 0.11 g/dL (SD: 1.48) in the IV arm and −0.16 g/dL (SD: 1.36) in the oral arm, *P* = 0.23. The number of patients who had a rise in Hb of ≥1 g/dL at 6 weeks was 23% (20 out of 94) in the IV iron arm and 18% (16 out of 98) in the oral iron arm, *P* = 0.45. 19% (14 out of 74; 95% confidence interval [CI], 11.5, 29.5) of patients on IV iron and 12% (9 out of 75; 95% CI, 6.3, 21.6) of patients on oral iron had a rise in Hb of 1.5 g/dL at 6weeks, *P* = 0.27. <u>Blood transfusion requirement:</u> Prior to competing the study, 13 patients on IV iron and 14 patients on oral iron required a blood transfusion (*P* = 1.0).	Mode of administration of iron, age, gender, intent of therapy and baseline Hb did not significantly impact response to iron therapy. True iron deficiency is defined as ferritin <15–30 mcg/mL, however in the setting of chronic inflammation and in disorders like malignancy, using a ferritin cut-off of 100 mcg/mL and a transferrin saturation <20% is widely accepted. Low response to iron (18.8%), given the fact that all patients included in the trial were iron deficient, based on measurement of baseline iron levels – in patients on cytotoxic

	hypothesised to lead to a 20% difference in hematopoietic response compared to oral iron. To prove this hypothesis with a type 1 error of 5% and a power of 80%, we needed 178 patients, assuming a binomial distribution. Accounting for an 8% rate of lost-to-follow, the final sample size was 192 patients. Patients who received blood transfusion during the 6-week study period were taken off study and their subsequent Hb values were not recorded or analysed. For patients who defaulted or died prior to completing the study and for whom the 6-week Hb value was not available were excluded from the analysis of the primary endpoint. All patients were included in the toxicity analysis, except patients who defaulted and for whom no side-effect information was available. Survival was estimated by the Kaplan–Meier method and follow-up was estimated by the reverse Kaplan–Meier technique. The hypothesis was IV iron administered to patients with cancer-related iron-deficiency anaemia would lead to a 20% difference in hematopoietic response compared to oral iron. To prove this hypothesis with a type 1 error of 5% and a power of 80%, we needed 178 patients, assuming a binomial distribution. Accounting for an 8% rate of lost-to-follow, the final sample size was 192 patients.			mean dose received was 760.17 mg (SD: 241.78).				chemotherapy, this response is likely to be blunted due to the myelosuppressive effects of chemotherapy. Other possible explanations for the low observed efficacy of iron supplementation include a possibly short time to assessment of response, an inadequate dose of iron added to the myelosuppressive effects of chemotherapy and the type of malignancy. Given the lower than expected hematopoietic response to iron therapy, this trial was underpowered to assess a difference between IV iron and oral iron. No mention on transfusion trigger.

Evidence Table : Effectiveness
Question : Is intravenous iron more effective than oral iron in reducing blood transfusion requirement among non-dialysis chronic kidney disease patients with iron deficiency anaemia?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
11. Agarwal R, Kusek JW, and Pappas MK. A randomized trial of intravenous and oral iron in chronic kidney disease. Kidney Int. 2015;88(4):905–14.	**RANDOMIZED CONTROLLED TRIAL** **Objective:** To compare the effect of intravenous and oral iron on kidney function in patients with moderate to severe CKD and iron deficiency anaemia. **Methods:** The study was conducted between August 2008 and November 2014 with study participants recruited from two hospitals located in Indianapolis, IN, USA. Study participants were required to be at least 18 years of age, have an estimated glomerular filtration rate (eGFR) by the 4-component MDRD formula of >20 and ≤ 60 ml/min/1.73m^2 using IDMS-calibrated creatinine, anemia and iron deficiency. Eligible participants were randomized in a 1:1 ratio, using permuted blocks, to either oral iron or intravenous iron using concealed opaque envelopes. The randomization sequence was computer generated by a statistician.	**I**	A total of 136 subjects with iron deficiency anaemia and chronic kidney disease not on dialysis. Compared to the oral iron group, the intravenous iron group was younger (*P* = 0.02), had less baseline cardiovascular disease (*P* = 0.04), and history of hospitalization due to infection (*P* = 0.05). Overall, the mean haemoglobin concentration at baseline was 10.6 g/dL, transferrin saturation 17.3% and serum ferritin 153 ng/mL. At baseline, erythropoiesis stimulating agents (ESA) were used by only 8.1% of the participants. Mean measured glomerular filtration rate (mGFR) was 34.5 mL/min/1.73 m^2 and proteinuria had a geometric mean of 0.5 g/g creatinine.	Iron sucrose: n=67 Dose: 200 mg intravenously over 2 hours at each of these 5 visits.	Ferrous sulfate: n=69 Dose: 325 mg three times daily for 8 weeks to provide at least the minimum dose of 200 mg elemental iron per day.	Median follow up (interquartile range) of all participants was 24.0 months (11.0–24.3) and did not differ by treatment group assignment.	<u>Haemoglobin (Hb) concentration:</u> Haemoglobin levels improved over time in both groups, and no statistically significant difference between mean levels in the treatment groups was noted during follow-up. Haemoglobin change from baseline to 3 months in the oral iron group was 0.61 g/dL and in the IV iron group 0.69 g/dL (difference + 0.08 (95% CI −0.34, +0.51, *P* = 0.72). Difference at 6 months (0.22 g/dL, *P* = 0.3), 12 months (−0.04 g/dL, p=0.85) and 24 months (0.15 g/dL, *P* = 0.56) were also not statistically significant. <u>Blood transfusion requirement:</u> Twelve study participants in each group received blood transfusions. Of those who needed packed red blood cell transfusions, the mean number of units needed over 2 years was 5.3 (range 2 to 20 units) in the oral group and 3.5 (range 1 to 7) in the IV group (t = 0.99, *P* = 0.3). <u>Iron status biomarkers:</u> Transferrin saturation change from baseline to 3 months in the oral iron group was 0.03 and in the IV iron group 0.05 (difference + 0.024 (95% CI −0.004, +0.052, *P* = 0.10). Difference at 6 months (0.026, *P* = 0.08), 12 months (−0.04 g/dL, *P* = 0.85) and 24 months (−0.024 g/dL, *P* = 0.14) were also not statistically significant. Log total iron binding capacity change from baseline to 3 months in the oral iron group was −0.031 (*P* = 0.13) and in the IV iron group −0.098 (*P* < 0.001) (difference − 0.067 (95%	The trial was stopped early on the unanimous recommendation of the DSMB based on an increase in the serious adverse event rate in participants assigned to IV iron treatment compared to oral iron therapy and little difference in mGFR between treatment groups. The average ESA use over the course of two years was similar in the two groups. In the oral iron group 22 subjects required ESA for average of 61 weeks (SD 39) with a geometric mean cumulative dose of darbepoetin of

							CI −0.122, −0.012, *P* = 0.02). Differences in change from baseline at 6 months (−0.030, *P* = 0.31), 12 months (−0.075 g/dL, *P* = 0.015) and 24 months (−0.01, *P* = 0.74) were small. Serum ferritin concentration was significantly higher in the IV iron group only from baseline to 6 months. Log ferritin change from baseline to 3 months in the oral iron group was −0.20 (*P* = 0.01) and in the IV iron group 0.84 (*P* < 0.001) (difference 0.63 (95% CI 0.41, 0.85, *P* < 0.001). Differences between groups in change from baseline at 6 months (0.39, *P* = 0.001), 12 months (0.21g/dL, *P* = 0.085) and 24 months (0.04, *P* = 0.77) diminished.	483 mcg. In the IV iron group 16 subjects required ESA for average of 54 weeks (SD 41) with a geometric mean cumulative dose of darbepoetin of 614 mcg. No mention on transfusion trigger.

Evidence Table : Efficacy
Question : Is intravenous iron (sucrose/ dextran/ isomaltoside) more effective than oral iron in reducing blood transfusion requirement among pregnant women with iron deficiency anaemia?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
12. Qassim A, Grivell RM, Henry A, et al. Intravenous or oral iron for treating iron deficiency anaemia during pregnancy: systematic review and meta-analysis. Med J Aust. 2019;211(8):367–73.	**SYSTEMATIC REVIEW** **Objective:** To compare the effects on perinatal maternal and neonatal outcomes of intravenous and oral iron therapy as first-line treatment of iron deficiency anaemia (IDA) in pregnant women. **Data sources and searches:** Relevant randomised controlled trials (RCTs) MEDLINE, EMBASE, Scopus, Cochrane Register of Controlled Trials, Web of Science searched up to 20 January 2019; earlier reviews, bibliographies of published trials, and cross-references were also checked for relevant publications. **Quality assessment:** Two investigators (AQ, LG) independently evaluated the methodologic quality of included studies with the Cochrane risk of bias tool, as well as the quality of evidence of studies contributing data to each outcome according to the five GRADE categories. **Data synthesis and analysis:** Meta-analyses were performed with the Cochrane review manager. Peto odds ratios (ORs) in a fixed effects model were calculated for rare dichotomous outcomes	**I**	A total of 15 eligible RCTs (16 publications) and data for 1938 participants. The total number of women (intervention and control arms) in the included studies ranged from 50 to 252. Most studies were undertaken in India (eight); two were undertaken in Australia, and one each in Singapore, France, Thailand, Turkey, and multiple countries. Baseline mean haemoglobin levels (range, 60–109 g/L) and mean gestation at enrolment (range, 22–33.3 weeks) differed between studies.	The most frequently used intravenous iron preparation was **iron sucrose (12 studies)**; iron polymaltose was used in two and ferric carboxymaltose in one. Twelve studies employed variable doses according to baseline haemoglobin level and (in eleven studies) weight, with the target haemoglobin levels ranging from 110 to 150 g/L. Two studies used fixed intravenous iron doses (400 or 500 mg iron sucrose).	Oral iron		<u>Haemoglobin (Hb) concentration):</u> Intravenous iron therapy led to higher maternal haemoglobin at delivery [MD 0.7 g/dL; 95% CI: 0.4, 1.1 g/dL; nine RCTs (506 intervention, 503 control participants) , low quality evidence], and higher ferritin levels at delivery [MD, 21.2 ng/ml; 95% CI: 6.5, 36.0 ng/ml; three RCTs (195 intervention, 195 control participants), low quality evidence]. <u>Blood transfusion requirement:</u> Maternal blood transfusion (Nine RCTs; 555 intervention, 535 control participants): Intravenous iron therapy was associated with reduced risk of women requiring blood transfusions (Peto OR: 0.19; 95% CI: 0.05, 0.78; low quality evidence). This corresponded to a number needed to treat with intravenous iron (*vs* oral iron) of 95 women to avoid one blood transfusion (95% CI: 81, 348 women). Sensitivity analyses indicated that the pooled estimate for the primary outcome (post-partum blood transfusion) was reasonably consistent across a range of alternative meta-analytic approaches. In stratified analyses, outcomes were similarly consistent regardless of baseline haemoglobin level, gestational age at treatment, and study setting. <u>Iron status biomarkers:</u> Compared with oral iron, intravenous iron therapy led to higher maternal ferritin levels (MD 21.2 ng/ml; 95% CI, 6.5–36.0 ng/ml; three RCTs, low quality evidence)	Evidence regarding differences in the effectiveness of intravenous and oral iron for improving maternal and neonatal outcomes at delivery is at best weak. Small numbers of participants in individual studies, were underpowered for detecting clinically relevant differences in outcomes. No outcome had been assessed by at least ten eligible studies, thus no publication bias

	(frequency lower than 5% in each treatment arm); pooled relative risks (RRs) in a random effects model were calculated for frequent dichotomous outcomes, we calculated; mean differences (MDs) in a random effects model were calculated for continuous outcomes. Sensitivity analyses was carried out for primary outcome; pre-specified stratified analyses done to determine whether treatment effects differed by study setting, pre-treatment haemoglobin level, gestational age at treatment, study quality or iron formulations							assessment. Daily iron dose in the control arms of the included studies ranged from 80 to 300 mg elemental iron, and this may have affected treatment response in control participants No transfusion trigger was pre-defined in any of the included studies.

Evidence Table : Efficacy
Question : Is intravenous iron (sucrose/ dextran/ isomaltoside) more effective oral iron in reducing blood transfusion requirement among pregnant women with iron deficiency anaemia?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
13. Neogi SB, Devasenapathy N, Singh R, et al. Safety and effectiveness of intravenous iron sucrose versus standard oral iron therapy in pregnant women with moderate-to-severe anaemia in India: a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Glob Heal. 2019;7(12):e1706–1716.	**RANDOMIZED CONTROLLED TRIAL** **Objective:** To assess the safety and clinical effectiveness of intravenous iron sucrose (intervention) versus standard oral iron (control) therapy in the treatment of women with moderate-to-severe iron deficiency anaemia in pregnancy. **Methods**: Multicentre, open-label, phase 3, RCT done at four government medical college hospitals in India. Women aged 18 years and older who were between 20 and 32 weeks of gestation with MCV: RBC more than 14, randomized (1:1) to receive either intravenous iron sucrose or standard oral iron therapy using web-based random sequence generator with block sizes of six and eight, stratified by site and severity of anaemia (haemoglobin concentration ≤7 g/dL and >7 g/dL). The central randomisation procedure was implemented using an interactive voice response system managed by an independent information technology firm. All parties involved were not blinded to group assignment.	**I**	A total of 2018 pregnant women. Baseline information was available for 983 patients in the intravenous iron sucrose group and 1016 participants in the standard therapy group. Patient characteristics were similar in both groups. Mean age was 24·4 years (SD 3·6), and 695 (35%) women were primigravida. The mean gestational age at the time of recruitment was 27·6 weeks (SD 3·7). Concomitant medications as reported by the participants were similar in both groups. The baseline characteristics of women whose primary outcomes were recorded (958 [97%] in the intravenous iron sucrose group and 976 [96%] in the standard therapy group) were similar to those whose outcomes could not be	n = 999 Intravenous iron sucrose (IS) administered as 200 mg elemental iron in 100 mL 0·9% sodium chloride infusion over 30–60 min, scheduled 48 hours apart until completion of total dose; total dose was calculated based on patient's weight on first antenatal visit. No further oral iron tablets were given until 6weeks postpartum if the woman completed the required dose.	n = 1019 Oral iron tablets supplied by respective hospitals (100 mg elemental iron and 0·5 mg of folic acid per tablet), to be taken twice a day until 6 weeks postpartum. Both groups given 5 mg of folic acid daily during the trial period. When the blood picture at baseline or during follow-up was suggestive of dimorphic anaemia, vitamin B12 injections or tablets were prescribed at the discretion of the treating physician.	Up to 6 weeks post-delivery	<u>Haemoglobin (Hb) concentration:</u> This multicentre clinical trial, which was stopped because of futility, involving pregnant women with moderate-to-severe anaemia, did not demonstrate superiority of intravenous iron sucrose over standard (oral) therapy in reducing adverse maternal and foetal outcomes. Data of events during childbirth were available from 1943 mothers (961 [98%] in the intravenous iron sucrose group and 982 [97%] in the standard therapy group). 143 (7%) of these women delivered at home and among 1800 women who delivered in hospitals, 349 (19%) had caesarean section. Median duration of hospital stay for vaginal deliveries was 2 days (IQR 1–2) and 4 days (3–5) in caesarean deliveries. Mean (SD) change in haemoglobin: 1) from the baseline at 6weeks post randomization: IVI (n=666): 2·8 (1·3) vs oral iron (n=629): 1·9 (1·7); adjusted mean difference (95% CI): 0·95 (0·80, 1·10) 2) from the baseline at delivery: IVI (n=254) 2·8 (1·4) vs oral (n=221) 2·4 (1·9); adjusted mean difference (95% CI): 0·45 (0·18, 0·73) 3) from the baseline at 6wks postpartum: IVI (n=697): 3·7 (1·4) vs oral iron (n=626): 3·0 (1·7); adjusted mean difference (95% CI): 0·63 (0·48, 0·78) <u>Blood transfusion requirement:</u> Intravenous iron sucrose reduced the requirement of blood transfusion among pregnant women with severe anaemia: Need for blood transfusion during	22 (2%) patients in the intravenous iron sucrose group and 34 (3%) patients in the standard therapy group were lost to follow-up. No withdrawals or loss to follow-up resulted from adverse events. In terms of clinical significance of the magnitude of difference between the two groups, the difference ranged from 0.45 g/dL to 0.95 g/dL, which translates to an effect size of 0.56 and 0.24. Considering a minimum clinically significant difference to be at least 0.5

			obtained (25 [3%] in the intravenous iron sucrose group and 40 [4%] in the standard therapy group).				delivery or postpartum period: IVI: 22/955 (2%) vs oral iron: 25/975 (3%), adjusted odds ratio (95% CI): 0·90 (0·50,1·60). <u>Iron status biomarkers:</u> Serum ferritin concentration at 6 weeks postpartum: higher in the intravenous iron sucrose group - IVI (n=72): median rise 20·6 ng/mL (IQR 7·4 to 29·5); oral iron (n=58): median rise 1·6 ng/mL (IQR –7·8 to 14)	SD, only the 6 weeks post-randomisation comparison of haemoglobin concentration met this criterion. Not statistically powered to detect effect on blood transfusion requirement per se. No *P* value presented as the trial was stopped early. Blood transfusion is mandated in severe anaemia (haemoglobin concentration <5 g/dL any time in pregnancy and <6 g/dL if a woman presents after 36 weeks of gestation).

Evidence Table : Efficacy
Question : Is intravenous iron (sucrose/ dextran/ isomaltoside) more effective than oral iron in the reducing blood transfusion requirement among women with postpartum iron-deficiency anaemia?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
14. Sultan P, Bampoe S, Shah R, et al. Oral vs intravenous iron therapy for postpartum anemia: a systematic review and meta-analysis. Am J Obstet Gynecol. 2019;221(1):19-29.e3.	**SYSTEMATIC REVIEW** **Objective:** To determine whether oral iron or intravenous iron should be the primary treatment modality for women with postpartum iron-deficiency anaemia. **Data sources and searches:** Searches were performed on November 6, 2017, to identify randomized trials in PubMed (includes MEDLINE) (1972-2017); Cochrane Central Register of Controlled Trials, CENTRAL (1972-2017); Cumulative Index to Nursing and Allied Health Literature, CINAHL (1972-2017); Web of Science; Excerpta Medica Database, EMBASE (1972-2017); and clinicaltrials.gov for unpublished or ongoing studies. **Quality assessment:** Quality of studies was assessed using the Cochrane Collaboration tool for evaluating the risk of bias. Data extraction was independently carried out by 5 individuals. **Data synthesis and analysis:** Quantitative data were analysed using the Review Manager software. For pooled continuous data, mean differences with 95% confidence intervals (Cis) were calculated. For pooled	**I**	Fifteen randomized trials met the inclusion criteria. Study cohort comprised 2182 women, with 1001 and 1181 women receiving oral iron and IV iron therapy, respectively. Included studies used the following haemoglobin upper limit cut-off values for inclusion criteria: 8 g/dL (4 studies), 8.5 g/dL (1 study), 9 g/dL (3 studies), 10 g/dL (5 studies), and 10.5 g/dL (1 study) and one study used postpartum haemorrhage as the primary inclusion criterion. Fourteen trials consisted of 2 treatment arms (oral and IV iron). One study had 3 treatments arms; 2 arms comprised IV iron preparations (ferrous sucrose and ferrous carboxymaltose, respectively), and 1 arm comprised oral iron ascarbate. Two studies included women with other comorbid disease.	Ferric sucrose was the most common IV iron formulation (9 of 15 studies). In these studies, the total dose of ferric sucrose ranged from 300 to 600 mg. Other IV iron formulations studied were ferric carboxymaltose, iron dextran, and iron maltoside. Among the studies investigating ferric carboxymaltose, the total dose ranged from 1000 to 3000 mg. In 1 study, the total dose of iron dextran was 1000 mg. In another	Oral iron supplements studied were administered as divalent (ferrous) salts or trivalent (ferric) salts: ferrous sulphate (9 studies18,20,32-34,36,39-41), ferrous ascarbate (2 studies19,22), iron protein succinylate (2 studies35,37) and ferrous fumarate (1 study38). The oral preparation was not described in 1 study.21 Oral iron dosing regimens varied. For example, ferrous	Duration of follow-up varied from 14 days to 12 weeks, with 6 studies describing a 6-week study period.	<u>Haemoglobin (Hb) concentration:</u> Absolute haemoglobin concentrations at 6 weeks postpartum were almost 1 g/dL higher (equivalent to 1-unit red blood cell transfusion) in women receiving IV compared to oral iron. Similar between group differences in haemoglobin concentrations were observed at 1, 2, and 3 weeks postpartum. Meta-analysis of 4 studies showed that the postpartum week 6 haemoglobin concentration was higher in the IV iron group (mean difference, 0.9 g/dL; 95% CI 0.4, 1.3; *P* = 0.0003). In all 4 studies, the mean rise in haemoglobin was higher in the IV iron groups than the oral iron groups (4.2 vs 3.7 g/dL, 3.2 vs 2.2 g/dL, 3.0 vs 1.6 g/dL, and 3.4 vs 2.1 g/dL). For postpartum weeks 1, 2 and 3, haemoglobin concentrations were found to be significantly higher in women receiving IV iron. There was a nonsignificant trend toward a higher haemoglobin concentration at week 4 for women receiving IV iron. No studies reported haemoglobin concentrations at postpartum week 5. High study heterogeneity was observed for all meta-analyses of postpartum haemoglobin by week, with the I^2 statistic ranging from 75% to 98%. <u>Blood transfusion requirement:</u> Data for postpartum red blood cell transfusion were reported in only 2 studies. Because of limited data and information regarding the indications for transfusion, transfusion data were presented qualitatively. Holm et al reported that the rate of postpartum transfusion was slightly higher in the oral iron group compared to the IV iron group (2% vs 1%,	Funnel plot of included studies and the Egger test demonstrated no evidence of publication bias (*P* = 0.09) Main findings are limited by the degree of heterogeneity between trials. This heterogeneity may be due to differences in mode of delivery, iron formulations, doses, dosing frequency, duration of drug exposure, baseline haemoglobin and iron status of study patients, and other unreported differences between study groups. There were insufficient data to

	dichotomous data, odds ratios (OR) and 95% Cis were calculated. Data were analysed using the Der-Simonian random effects model.		One study excluded women with known nutritional disorders. In 11 studies, patients were recruited within 48 hours of delivery, 2 studies recruited patients up to 10 days following delivery, and 2 studies did not state the timing of recruitment. Modest differences were observed in the baseline postpartum haemoglobin concentrations across the 4 studies: 7.4 g/ dL,32 8.8 g/dL,19 8.5 g/dL,20 and 8.1 g/dL.	study, iron maltosidase was administered as a single dose of 1200 mg.	sulphate doses ranged from 200 mg to 975 mg per day with their duration of treatment ranging from 1 month to 12 weeks.		respectively). The transfusion rates reported by Westad et al were substantially higher in both groups, with a more sizeable difference in rates between groups (22.9% vs 8.9% for oral iron vs IV iron, respectively). <u>Iron status biomarkers:</u> No studies assessed ferritin concentrations at weeks 3 or 5. For all other weeks, compared to the oral iron group, the IV iron group had statistically significantly higher ferritin concentrations.	perform sensitivity analyses, because only 4 studies reported haemoglobin concentrations at week 6 postpartum. Cost or perform cost-effectiveness analysis for different iron formulations were not examined due to the extent of study heterogeneity.

Evidence Table : Safety
Question : Do all intravenous iron have comparable safety profile?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
1. Pollock RF, and Biggar P. Indirect methods of comparison of the safety of ferric derisomaltose, iron sucrose and ferric carboxymaltose in the treatment of iron deficiency anemia. Expert Rev Hematol. 2020;13(2):187–95.	**SYSTEMATIC REVIEW** **Objective:** To use standardized Medical Dictionary for Regulatory Activities queries (SMQs) to compare the safety of ferric derisomaltose/ iron isomaltoside 1000 (IIM), iron sucrose (IS), and ferric carboxymaltose (FCM) using prospective trial data. **Data sources and searches:** Published, prospective studies of IIM, FCM and IS were identified by targeted literature searches of PubMed and Google Scholar, with a view to identifying all prospective studies reporting serious or severe hypersensitivity reaction (HSRs) categorized by SMQs. Data on ferumoxytol were not included on the grounds that it does not have marketing authorization in the European Union, and that the largest ferumoxytol registration trial (comparing ferumoxytol with FCM) reported moderate-to-severe HSRs rather than serious or severe HSRs. HSR SMQs were used to classify serious or severe hypersensitivity reactions into four categories covering: anaphylactic reactions (group A), respiratory reactions potentially related to hypersensitivity (group B), skin	**I**	The literature searches identified a total of 21 prospective studies of IIM, FCM, and IS for which SMQ-coded serious or severe HSR data were available, with a total enrolment of 8,599. Of the 21 prospective studies, 19 published studies of IIM for which HSR data categorized by SMQs were available from the manufacturer and two published studies of FCM versus IS for which SMQ-categorized HSR data were available from a 2013 report from the US FDA Center for Drug Evaluation and Research (CDER). Of the 19 prospective studies of IIM identified, four were RCTs comparing FDI with IS [29,30,35,36], and two were RCTs comparing FDI with FCM. Three of the included studies were extensions to other studies identified in the review; in these instances, the HSR data were obtained	IIM	IS and FCM	-	<u>Hypersensitivity reaction:</u> The 19 studies of IIM had a total enrolment of 3,922 in the IIM arms, who experienced a total of 23 serious or severe HSRs, corresponding to 0.59% or one event per 171 treatments. REPAIR-IDA and VIT09031 included a total of 1,775 patients treated with FCM, of whom 26 experienced at least one serious or severe HSR, corresponding to 1.5% or one event per 68 patients treated. The REPAIR-IDA and VIT09031 comparator arms included 1,503 patients treated with IS, of whom 24 experienced at least one serious or severe HSR, corresponding to 1.6% or one event per 63 patients treated. The Bayesian inference approach of comparing HSR incidence showed that the mean odds of experiencing any HSR in SMQ groups A + B + C + D were 59% lower with IIM relative to FCM (odds ratio 0.41) and 49% lower with IIM relative to IS (odds ratio 0.51). The naïve pooling approach, with the addition of odds ratios derived directly from the event counts, binomial confidence intervals derived using the Clopper Pearson methodology, and p values derived using Fisher's exact test showed that the odds of experiencing any HSR in SMQ groups A + B + C + D with IIM were 61% lower than with FCM (odds ratio 0.39; 95% CI 0.23, 0.68; *P* = 0.001), and 51% lower than with IS (odds ratio 0.49; 95% confidence interval 0.29, 0.84; *P* = 0.009). The random effects meta-analysis of four RCTs of IIM versus IS reported an odds ratio of 0.56 (95% CI: 0.23, 1.37) across SMQ groups A + B + C + D. The ITC conducted by combining the results of the random effects meta-analysis of IIM versus IS with the pooled odds ratios from	The primary limitation of the analysis was the loss of randomization arising from the naïve pooling of the SMQ data reported in the CDER report. REPAIR-IDA and VIT09031 were conducted in different trial populations and the crude pooling of data from both trials in the CDER report resulted in a loss of anchoring via a matched IS population.

	reactions potentially related to hypersensitivity (group C), and cardiovascular reactions potentially related to hypersensitivity (group D). In addition to the individual groups, combinations of groups B and C; B and D; B, C and D; and A, B, C, and D were also analysed throughout. **Data synthesis and analysis:** Given that reporting of HSRs using SMQs would only be available in a subset of studies, a variety of statistical techniques were planned to compare the rates across studies and between products: 1) a Bayesian inference of proportions using an uninformative prior to capture uncertainty around the pooled treatment effect; 2) a naïve pooled analysis; and 3) an indirect treatment comparison (ITC) using the Bucher et al. approach. The Bayesian inference of proportions analysis was selected as the primary analysis based on the a priori understanding that HSR data categorized by SMQs would not be widely available and that the use of uninformative priors would factor a level of uncertainty into the analysis, informed by the challenges encountered in previous studies attempting to compare the safety of the IV iron formulations.		from the extension period only to avoid double counting. The only data source identified for which SMQ-coded HSR data were available for FCM and IS was a 2013 report from the US FDA CDER. The report included data that was pooled from two studies: REPAIR-IDA, conducted in patients with chronic renal failure, and VIT09031, a trial conducted in patients with IDA associated with a broad range of etiologies.				the naïve comparison of FCM with IS yielded an overall odds ratio of 0.45 (95% CI: 0.16, 1.25), corresponding to a 55% reduction in the odds of any HSR in SMQ groups A + B + C + D with FDI relative to FCM. A comparison of the findings of the three different approaches to comparing IIM with FCM, and IIM with IS showed a high level of agreement, particularly for the combined A + B + C + D SMQ group. The two approaches to comparing FCM with IS similarly showed a high level of agreement for the combined A + B + C + D SMQ group. The Bayesian inference of proportions approach showed that, based on 23 serious or severe HSR events occurring across a total enrolment of 3,922, and 28 serious or severe HSR events occurring in 1,892 patients treated with FCM, the mean odds ratio for HSR was 0.41 with IIM relative to FCM, with an highest posterior density interval (HDI) spanning from 0.20 to 0.64 and 0% of the posterior distribution falling above 1, reflecting an infinitesimally small probability that FCM would be associated with reduced odds of serious or severe HSRs relative to IIM. The frequentist ITC, in which the IIM versus IS comparison was driven by a random effects meta-analysis and the FCM versus IS comparison was driven by naïve pooling, yielded a similar mean estimated odds ratio of 0.45, with 95% confidence intervals spanning 0.16–1.25, which would not be considered statistically significant by a conventional $P < 0.05$ interpretation.	

Evidence Table : Safety
Question : Is intravenous iron safe?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
2. Salim SA, Cheungpasitporn W, Elmaraezy A, et al. Infectious complications and mortality associated with the use of IV iron therapy: a systematic review and meta-analysis. Int Urol Nephrol. 2019;51(10):1855–65.	**SYSTEMATIC REVIEW** **Objective:** To evaluate infectious complications and mortality with use of parenteral Iron in ESRD **Data sources and searches:** Medical electronic databases [PubMed, EMBASE, Scopus, Web of Science, and cochrane central register for controlled clinical trials (CENTRAL)] were queried for studies that investigated the association between intravenous iron administration and infection in haemodialysis patients. **Quality assessment:** Quality of the included RCTs was assessed using the Cochrane risk of bias assessment tool and for observational studies, the Newcastle–Ottawa scale was used to assess the risk of bias. **Data synthesis and analysis:** Comprehensive meta-analysis (CMA) software was used for meta-analysis. Most RCTs reported raw data for the studied outcomes, so data from RCTs were pooled as odds ratio (OR) and 95% CI. Survival data were reported in the observational studies, thus, HR and 95% CI were employed as a summary estimate for meta-analysis of the included	**I**	24 studies (7 randomized control trials (RCTs), [n = 2,796] and 16 observational studies [n = 395,817) of patients on dialysis (including haemodialysis and peritoneal dialysis) were eligible for inclusion. Most studies compared different doses of same IV formulation; relevant IVI were used with ESA	High-dose iron	low-dose iron, no iron, and oral iron	-	<u>All-cause mortality:</u> Six RCTs provided data for all-cause mortality. The fixed effect model was used due to the absence of heterogeneity among the pooled studies (I^2 = 0%; *P* = 0.73). High-dose IV iron conferred 17% less all-cause mortality compared to controls; however, this outcome was not statistically significant (OR = 0.83; 95% CI [0.7, 1.01]; *P* = 0.07). Data from 9 observational studies were pooled under the random effects model due to significant heterogeneity (I^2 = 83%; *P* < 0.001). The overall HR showed increased risk of all-cause mortality in the high-dose group but was statistically non-significant (HR = 1.1; 95% CI [1, 1.22]; *P* = 0.06). <u>Infection rate:</u> Infection rate was reported in four RCTs with no heterogeneity among their data (I^2 = 0%; *P* = 0.61). Under the fixed effect model, there was no difference in the infection rate between high-dose iron and control group (OR = 0.97; 95% CI [0.82, 1.16]; *P* = 0.77). Eight observational studies reported data for infection rate in high-dose iron and control groups. Significant heterogeneity existed among these studies (I^2 = 75%; *P* < 0.001); therefore, the random-effects model was employed. The summary HR showed increased yet insignificant risk of infection in the high-dose group (HR = 1.13; 95% CI [0.99, 1.28]; *P* = 0.07). <u>Adverse event(s):</u> Cardiovascular adverse events: One RCT compared the rate of adverse cardiovascular events between high-dose and	The included RCTs were at moderate to high risk of bias. Randomization and allocation concealment were not adequately achieved in most of the RCTs. In addition, all the studies were open label with no attempts to blind the participants and investigators. Macdougall et al. (2019) performed a blinding of outcome assessment procedure. Attrition bias was present in most of the included RCTs. According to the Newcastle–Ottawa scale, 8 of the

	observational studies. Heterogeneity among studies was measured using the Chi-square test and the I2 statistic was used to quantify its extent. Fixed effect model was used whenever there is no or minimal heterogeneity, while random effects model was employed in case of significant heterogeneity. Publication bias was investigated using funnel plot and Egger's regression test.						low-dose iron. No significant difference was observed between the two groups (22.3% vs 25.6%; *P* = 0.12). Six heterogeneous observational studies (I^2 = 65%; *P* < 0.001) reported on the rate of cardiovascular events. No significant difference was observed between high-dose iron and controls (HR = 1.18; 95% CI [0.89, 1.57]; *P* = 0.24). <u>Other complication:</u> Hospitalization: One RCT and six observational studies provided data for the rate of all-cause hospitalization between high-dose vs control groups. There was marked heterogeneity among the observational studies data (I^2 = 72%; *P* < 0.001). Data from the RCT showed no significant difference between high-dose iron and controls in the rate of hospitalization (OR = 1.03; 95% CI [0.87, 1.23]; *P* = 0.71). The summary HR for observational data showed increased rate of hospitalization in the high-dose group; however, this effect was not statistically significant (HR = 1.11; 95% CI [0.99, 1.24]; *P* = 0.07).	observational studies were at low risk of bias, 4 were at moderate risk, and 4 possessed high risk of bias due to questionable statistical methods.

Evidence Table : Safety
Question : Is intravenous iron isomaltoside safer than intravenous iron sucrose for the treatment of iron-deficiency anaemia?

Bibliographic citation	Study Type/Methods	LLE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
3. Auerbach M, Henry D, Derman RJ et al. A prospective, multicenter, randomized comparison of iron isomaltoside 1000 versus iron sucrose in patients with iron deficiency anemia; the FERWON-IDA trial. Am J Hematol. 2019; 94:1007–1014	**RANDOMISED CONTROLLED TRIAL** **Objective:** To evaluate and compare safety and efficacy of IIM to IS in patients with IDA when oral iron formulations were ineffective or could not be used, or where there was a clinical need to deliver iron rapidly. Stratified block randomization methodology was used in the trial, and randomization was a 2:1 ratio to receive IIM or IS, respectively. Randomization was stratified according to the type of underlying disease (gastroenterology, gynaecology, oncology, and "other"), and baseline cardiovascular risk (history of myocardial infarction, stroke, or congestive heart failure). The block size was six. The intention to treat (ITT) analysis set (N = 1512) included all randomized. This was used for evaluating efficacy. The safety analysis set (N = 1483) included all randomized who received at least one dose of the trial drug. This was used for evaluating safety. Time to Hb response was estimated using the Kaplan-Meier method. The hypothesis of no treatment difference was	**I**	3108 patients were screened of whom 1512 were randomized 2:1 to the IIM group (1009) or IS group (503). Of the 1512 enrolled, 1356 (90%) completed the trial. Baseline characteristics were comparable between the treatment groups. Approximately 50% were gynecology patients and 26% were gastroenterology patients. Country: USA	989 patients received IIM One infusion in the IIM group Mean dose for IIM: 975 mg (SD: 145)	494 patients received IS. one to five infusions in the IS group were administered, with the majority receiving five (80%; mean: 4.5 administrations, median: 5 administrations). Mean dose fo IS: 905 mg (SD: 217)	1-, 2-, 4- and 8-week	The **safety analyses** were conducted on the safety analysis set (N = 1483). <u>Hypersensitivity reaction:</u> A total of three serious or severe hypersensitivity reactions were reported in 3/989 (0.3%; 95% CI: 0.06;0.88) patients in the IIM group, and two serious or severe hypersensitivity reactions were reported in 2/494 (0.4%; 95% CI: 0.05;1.45) in the IS group. As the upper boundary of the 95% CI was <3%, the co-primary safety endpoint was met. The risk difference between IIM and IS, with respect to adjudicated and confirmed treatment emergent serious or severe hypersensitivity reactions was estimated to −0.10% (95% CI: −0.91.71). The difference between the two treatment groups was not statistically significant as the confidence interval included zero. <u>Adverse event (AE)/ Adverse drug reaction (ADR):</u> Eight **composite cardiovascular AEs** were reported in eight (0.8%) patients in the IIM group, and seven were reported in six (1.2%) in the IS group. The incidence of composite cardiovascular AEs was, however, not statistically significantly different between the two treatment groups (P >.05). A total of 230 **ADRs** in 124 patients (12.5%) were reported in the IIM group, and 138 ADRs in 63 patients (12.8%) were reported in the IS group (P > .05). The most common ADR was nausea (20 events in 20 patients [2.0%] in the IIM group and 10 events in 8 patients [1.6%] in the IS group). Rash (17 ADRs in 15 patients [1.5%]) and chest discomfort (11 ADRs in 11 patients [1.1%]) were reported more frequently in the IIM group than in the IS group (0 ADR and 0 ADR, respectively). Dysgeusia (20 ADRs in 9 patients [1.8%]) and	Patients and investigators were not blinded to trial medications during the trial.

	assessed by a two-sided log-rank test. The hypersensitivity reactions and cardiovascular AEs were evaluated centrally by a blinded independent adjudication committee. Also, laboratory parameters were evaluated at a central laboratory, so it was not deemed necessary to have a blinded trial design.						overdose (10 ADRs in 8 patients [1.6%]), were more common in the IS group than in the IIM group (1 and 0 ADRs, respectively). The incidence of **hypophosphatemia** (s-phosphate <2.0 mg/dL) was low and similar in the two groups (3.9% in the IIM and 2.3% in the IS group). The hypophosphatemia events were transient, and in most cases normalized at the end of the trial. For the majority, the lowest s-phosphate values were reached at week one or two.	

Evidence Table : Safety
Question : Is intravenous iron safe?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
4. Avni T, Bierber A, Grossman A, et al. The safety of intravenous iron preparations: Systematic review and meta-analysis. Mayo Clin Proc. 2015;90(1):12–23.	**SYSTEMATIC REVIEW** **Objective:** To amass all available evidence regarding the safety of intravenous (IV) iron preparations to provide a true balance of efficacy and safety **Data sources and searches:** MEDLINE (January 1, 1966, through December 31, 2013), CENTRAL (The Cochrane Library up to 2013, March, issue 3), LILACS, KOREAMED, and NLM gateway were searched from inception to December 31, 2013. The conference proceedings of the American Society of Hematology, European Haematology Association, American Society of Nephrology, European Renal Association, European Dialysis and Transplant Association, and American Heart Association from 2008 onward and the clinical trials databases for ongoing and unpublished trials were also searched online for further trials. The references of all identified studies were inspected for more trials. **Quality assessment:** Quality of the included RCTs was assessed using the criteria specified in the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0. Quality measures	**I**	A total of 103 RCTs published from January 1, 1966, through December 31, 2013, fulfilled the inclusion criteria. Pooled together, 10,390 patients treated with IV iron were compared with 4044 patients treated with oral iron, 1329 treated with no iron, 3335 treated with placebo, and 155 treated with IM iron.	Ferric carboxymaltose (FCM) was used in 15, iron sucrose (IS) in 57 trials, ferric gluconate (FG) in 7, iron dextran (ID) in 14, ferumoxytol in 4, iron polymaltose in 3, and iron isomaltoside (IIM) in 2 (1 trial used both FCM and IS). Among the trials that reported the total amount of IV iron given, the median dosage was 1400 mg (range, 70-3200 mg).	14 trials of no iron, 20 trials of placebo, 56 trials of oral iron, 4 trials of IM iron, 8 trials of oral iron and placebo or no iron, and 1 trial of IM iron and no iron.	1 to 52 weeks (median, 8 weeks); follow-up losses were reported in only a few trials.	<u>All-cause mortality:</u> All-cause mortality was reported in 57 trials, and of these trials, no deaths occurred during the follow-up period in 29 trials. Overall, there was no increased risk of mortality with IV iron (RR: 1.06; 95% CI: 0.81,1.39; I^2=0%). <u>Infection rate:</u> There was no increased risk of serious infections with IV iron (RR: 0.96; 95% CI: 0.63,1.46; I^2=8.2%). The occurrence of any infections was not increased with IV iron regardless of compound, comparator, and indication (RR: 1.17; 95% CI: 0.83,1.65; I^2=0%). <u>Serious adverse events (SAEs):</u> Serious adverse events were reported by 97 trials (95%). Overall, there was no increase in the risk of SAEs with IV iron compared with control (RR, 1.04; 95% CI: 0.93,1.17, I^2=9%). A statistically nonsignificant lower risk of SAEs was shown when IV iron was compared with placebo in double-blind trials (RR: 0.83; 95% CI: 0.64, 1.03; I^2=41%). Sensitivity analysis restricted to studies that reported SAEs with adequate allocation concealment (n=49) and studies with adequate AE definitions (n=19) did not alter the results (RR: 1.02; 95% CI: 0.93,1.18; I^2=9%; and RR: 0.94; 95% CI: 0.74,1.20; I^2=48%, respectively). The use of IV iron in patients with chronic heart failure was associated with a decreased rate of SAEs compared with controls (RR: 0.45; 95% CI: 0.29,0.70; I^2=0%; NNP: 10; 95% CI: 6,25). In trials in gynaecology and obstetrics, the use of IV iron was associated with an increased	Randomized clinical trials are not the best tools for examining the risk of rare and severe adverse events (SAEs). AEs are less dependent on the underlying disorder, which is why the authors have chosen to look at AEs of IV iron in all the trials of IV iron. The included trials were heterogeneous regarding the type of patients, different iron preparations, schedule, and total dose of IV iron administered. Although most trials

	addressed by the CONSORT guidelines for AEs were assessed and adjusted to the design of the included trials. **Data synthesis and analysis:** To include trials with no occurrence of AEs, the value 0.1 was used instead of 0 in the event counter, thus enabling trials that did not observe AEs in both study arms to be used for calculation of the relative risk (RR). Commutative risk difference (RD) (which is synonymous to absolute risk reduction) and number needed to harm (NNH) or number needed to prevent (NNP) were also calculated for all outcomes. Dichotomous data were analysed by calculating the RR for each trial, with the uncertainty in each result being expressed using 95% CIs. Heterogeneity was assessed by calculating the χ^2 and I^2 tests of heterogeneity. A fixed-effect model was used throughout the review, except in the event of significant heterogeneity among the trials (P<0.10, I^2>40%), in which we used a random-effects model (REM). Potential sources of heterogeneity were explored: type of IV iron preparation, comparator (placebo, oral, no iron, IM iron, or other), indication for iron therapy, adequacy of collecting and reporting methods of the AEs, and the adequacy of allocation generation, concealment, and masking. Review Manager, version 5.2) and Comprehensive Meta-Analysis version 2.2 (BioStat) for statistical calculations.						rate of SAEs (RR: 2.00; 95% CI: 1.15,3.62. I^2=0%; NNH: 119; 95% CI: 61,1725). Subdividing the trials by indication for therapy (pregnancy, peripartum, and other) or compound revealed a trend toward increased rate of SAEs with IV iron that was statistically nonsignificant in all subgroups. In trials of chronic kidney disease, inflammatory bowel disease, and cancer-induced anaemia, perioperative trials, and other trials of mixed causes, there was no increased risk of SAEs with IV iron therapy. The risk of cardiovascular, neurologic, thromboembolic, or gastrointestinal SAEs was not increased with IV iron. Sensitivity analysis was performed based on quality measures did not alter the reported results. Subgroup analysis was performed on the basis of indication for treatment, type of comparator, and type of IV iron formula did not alter the results. No deaths related to SAEs were reported. <u>Infusion reactions:</u> Serious infusion reactions were increased with IV iron (RR: 2.47; 95% CI: 1.43,4.28; I^2=0%; NNH: 292; 95% CI: 164-1316) and particularly with FG (RR: 5.32; 95% CI: 1.49,18.99; I^2=0%; NNH: 118; 95% CI: 68,423). The other iron preparations were not associated with a statistically significant increased risk of severe infusion reactions (IS - RR: 1.75; 95% CI: 0.69,4.43; FCM – RR: 1.47; 95% CI: 0.40,5.39; FML – RR: 2.26; 95% CI: 0.19,26.22; ID - RR: 3.1; 95% CI: 0.86,11.22). Infusion reactions were increased with IV iron (RR: 2.74; 95% CI: 2.13,3.53; I^2=26%; NNH: 64; 95% CI: 44,115) and further increased when compared with oral iron (RR: 3.49; 95% CI: 2.22,5.49; I^2=0%; NNH: 50; 95% CI: 32,113), placebo (RR: 2.42; 95% CI: 1.50,3.91; I^2=0%; NNH: 92; 95% CI: 52,422), and no iron (RR: 2.19; 95% CI: 1.05,4.56; I^2=0%, NNH: 86; 95% CI: 41,133). Infusion reactions were further increased when IS, FG, and FCM were used. A subgroup analysis restricted to trials that used placebo as the comparator revealed an	were of good methodologic design and reporting, 80% of the trials did not report quality measures addressed by the CONSORT guidelines for AEs. Another possible concern comes from including trials that were diverse in follow-up time and methods. Trials of chronic heart failure, for instance, had relatively long follow-up and concentrated on cardiovascular AEs in contrast to trials of obstetric or perioperative iron administration, which had short follow-up and concentrated on administration

							increased risk of a severe infusion reaction (RR: 2.96; 95% CI: 1.16,7.51; I^2=0%; NNH: 255; 95% CI: 136,1910). <u>Other adverse events:</u> There was no increased risk of AEs that required discontinuation of treatment with IV iron (RR: 0.92; 95% CI: 0.76,1.12; I^2=11%). There was a trend toward decreased risk of AEs requiring discontinuation with FCM (RR: 0.69; 95% CI: 0.46-1.00; I^2=8%). The occurrence of any AEs was reported by 38 trials. There was no increased risk of any AEs with IV iron (RR: 1.04; 95% CI: 0.99,1.08; I^2=74%). Among the trials that defined AEs as treatment related (n=43), there was no increased risk of treatment-related AEs (RR: 1.08; 95% CI: 0.96,1.21; I^2=78%). Subgroup analysis was performed based on indication for treatment and comparator did not change these results. There was no increased risk of cardiovascular AEs; however, FCM was associated with a decreased risk of cardiovascular AEs (RR: 0.57; 95% CI: 0.42,0.79; I^2=0%; NNP: 28; 95% CI: 17,71), and FG was associated with an increased risk of cardiovascular AEs (RR: 1.33; 95% CI: 1.05,1.69; I^2=0%; NNH: 39; 95% CI: 21-235). The use of IV iron was associated with a decreased risk of gastrointestinal AEs (RR: 0.55; 95% CI: 0.51,0.61; I^2=84%; NNP: 10; 95% CI: 8,14), particularly with IS, ID, and FCM and when the comparator was oral iron or no iron. There was an increase in neurologic AEs (RR: 1.35; 95% CI: 1.13,1.61; I^2=35%; NNH: 78; 95% CI: 44,336), which was more pronounced when IS was used (RR: 1.63; 95% CI: 1.10, 2.42; I^2=0%; NNH: 71; 95% CI: 30,237). Hypotension was increased with IV iron (RR: 1.39; 95% CI: 1.09,1.77; I^2=39%; NNH: 97; 95% CI: 58,305). This effect was more pronounced when IS was used (RR: 3.01; 95% CI: 1.12,8.11; I^2=0%; NNH: 68; 95% CI: 37,364) and when compared with no iron (RR: 3.83; 95% CI:	and general AEs.

							1.33,11.02; I^2=38%; NNH: 50; 95% CI: 25,100). There was a trend toward hypertension responses with IV iron (RR: 2.25; 95% CI: 1.00,5.08; I^2=0%). Adverse events related to skin (excluding urticaria) were increased with IV iron (RR: 1.60; 95% CI: 1.05,2.45; I^2=35%; NNH: 99; 95% CI: 59,304). Muscle and skeletal AEs were increased with IV iron and particularly FCM (RR: 3.42; 95% CI: 2.02,5.79; I^2=40%; NNH: 32; 95% CI: 23,49). The use of IV iron was associated with an increased risk of electrolyte disorder (most trials reported on the occurrence of hypophosphatemia) (RR: 2.45; 95% CI: 1.84,3.26; I^2=49%; NNH: 19; 95% CI: 11,67). No statistically significant increase in the occurrence of abnormal laboratory results, constitutional symptoms, or thromboembolic and respiratory AEs was found with any IV iron preparation, comparator, or indication of use. Sensitivity analysis restricted to studies with adequate allocation concealment and studies with adequate AEs definitions did not alter any result.	

Evidence : Safety
Question : Is preoperative intravenous iron safe in colorectal cancer patients undergoing surgery?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
5. Kam PMH, Chu CWH, Chan EMY, et al. Use of intravenous iron therapy in colorectal cancer patient with iron deficiency anemia: a propensity-score matched study. Int J Colorectal Dis. 2020;35(3):521–7.	**PROSPECTIVE COHORT** **Objective:** To investigate the effect of intravenous iron therapy on haemoglobin level change and transfusion requirements among anaemic colorectal cancer patient in a tertiary hospital in Hong Kong. **Methods:** This single centre study was carried out in a tertiary centre with more than 200 elective colorectal cancer operations per year. Patients diagnosed with colorectal adenocarcinoma and found to have iron deficiency anaemia (confirmed based on blood test) preoperatively were recruited from August 2017 to March 2019. All patients were arranged to undergo intravenous iron infusion in day admission setting at least 2 weeks prior to their elective operation date. Their haemoglobin level and iron profile were recorded again during their admission for elective surgery, which was 1 day prior to the operation. The operations were performed by specialist surgeons in laparoscopic, open, or robotic method (in selected cases of	**II-2**	A total of 100 patients included in the study. There were no statistical differences between median age (70 in IVI vs. 69 in non-IVI, *P* = 0.46) and male to female ratio (50% male in both groups, *P* = 1.0). There were no statistical differences in premorbid status, medical comorbidities, or use of antiplatelet or anticoagulant. There was no difference in number of patients with red cell transfusion prior to intravenous iron (42.1% in IVI vs. 41.9% in non-IVI, *P* = 0.987). Both groups had similar proportions of patient taking oral iron supplement prior to surgery (31.6% in IVI vs. 29% in non-IVI, *P* = 0.787). Majority of patients had cancers in cecum, ascending colon, or hepatic flexure for both groups, followed by sigmoid and rectal cancers. Most patients' final pathology were stage	Iron sucrose or iron isomaltoside : n=38 IS: 500 mg in 250 ml normal saline over 210 min intravenously, with a total of two doses set at 1 week apart IIM: 1000 mg (or 20 mg/kg if bodyweight is less than 50 kg) in 100 ml normal saline over 15 min as a single dose.	No iron therapy: n=62 (after propensity score matching in a 2:1 ratio)	Not reported	<u>Other complication:</u> There were no differences in complications (15.8% in IVI, 19.4% in non-IVI, *P* = 0.599) or reoperation rate (2.2% in both, *P* = 1.0). There was no death observed in either groups.	

	rectal cancer) under general anaesthesia. Patients were excluded if (1) histology of tumour was not adenocarcinoma; (2) anaemia was not due to iron deficiency; (3) no elective operation was performed (either because patient refused or was deemed unfit for surgery); and (4) only one dose of IS was given (due to incomplete IVI dosage use). The data of the historic cohort as control for matching was collected retrospectively from CDARS (Clinical Data Analysis and Reporting System). These were anaemic patients who underwent colorectal cancer surgery during the period of October 2014 to September 2017.		III disease (47.4% in IVI and 48.5% in non-IVI) and stage II disease (36.8% IVI and 30.6% non-IVI). There was no difference in median waiting time from diagnosis to operation between two groups (34.5 days in IVI and 43.5 days in non-IVI, *P* = 0.952). Propensity score matching and statistical analysis were performed on SPSS version 23 with R-extension 3.1.0 and PSMatching, using caliper 0.5. The matching criteria included first haemoglobin level, age, sex, transfusion of red cell prior to intravenous iron, use of oral iron supplement, and tumour location.					

Evidence Table : Safety
Question : Is postoperative intravenous iron safe in patients undergoing cardiac surgery?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
6. Xu H, Duan Y, Yuan X et al. Intravenous iron versus placebo in the management of postoperative functional iron deficiency anaemia in patients undergoing cardiac valvular surgery: a prospective, single-blinded, randomised controlled trial, J Cardiothorac Vasc Anesth. 2019;	**RANDOMIZED CONTROLLED TRIAL** **Objective:** to compare the safety and efficacy of intravenous iron versus placebo to correct postoperative anaemia in patients undergoing cardiac valvular surgery. **Methods:** A prospective, single-blind, randomised controlled trial at a hospital in China from March 2018 to October 2018. Eligible patients aged 20-70 years who agreed to participate were randomly assigned (1:1) to either the treatment (intravenous iron) group or the control (placebo) group using Excel 2010 (Microsoft, Redmond, WA, USA) To ensure allocation concealment, treatment codes were located in a central site, the pharmacy department. This department was not involved in any collection of trial data, follow-up, or patient activity to avoid possible bias. Randomisation allocation was delivered by pharmacy in sealed numbered opaque envelopes that were opened consecutively after informed consent was obtained. All intravenous solutions were presented in disguised form by the pharmacy department and assigned to patients according to the random numbers list.	**I**	A total of 150 patients were recruited: 75 were randomized to intravenous iron group and 75 were randomized to placebo group. There were no differences in demographic variables, preoperative Hb levels and postoperative parameters.	Iron sucrose (IS): n=75 weight-based calculated dose of iron sucrose administered with the dose of 200mg over 30 min on the day after surgery and maintained this dose every other day until the total iron deficiency was achieved. (794.8 ± 173.7mg)	Saline solution: n=75	0,4, 14 days after surgery	<u>Mortality:</u> Zero in IVI group versus two (2.7%) in placebo group; *P* = 0.210. <u>Other complication:</u> There were no significant differences in rates of death, poor wound healing and perivalvular leakage between the two groups. Intravenous iron sucrose was well tolerated by all patients, and no adverse events or infusion reactions were noted.	

Evidence Table : Safety
Question : Is perioperative intravenous iron safe in patients undergoing orthopaedic surgery?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
7. Shin HW, Park JJ, Kim HJ et al. Efficacy of perioperative intravenous iron therapy for transfusion in orthopedic surgery: A systematic review and meta-analysis. PLoS ONE. 2019; 14(5): e0215427.	**SYSTEMATIC REVIEW** **Objective:** To evaluate the efficacy of IVIT with respect to details of transfusion and recovery profiles, such as length of hospital stay (LOS), rate of post-operative infection, and mortality among patients undergoing orthopaedic surgery. **Data sources and searches:** PubMed, Embase, Cochrane Central, KoreaMed, and Google Scholar databases up to September 2017, with no language restrictions. **Quality assessment:** Two authors independently evaluated the quality of clinical trials using the Cochrane Risk-of-Bias tool to assess the quality of randomized controlled trials (RCTs) and the Newcastle-Ottawa scale to assess the quality of non-randomized controlled studies [case-controlled studies (CCSs)] in the meta-analysis. **Data synthesis and analysis:** Authors attempted to contact the authors of studies with insufficient or missing data. If this was impossible, they extrapolated data from the figures to obtain the target information. The values for units of RBCs transfused and LOS	**I**	A total of 12 clinical studies, comprising 4 RCTs with 616 patients and 8 CCSs with 1,253 patients. 2 RCTs (n=227) and 5 CCSs (n=947) have used iron sucrose in the studies. Countries: Australia, Republic of Korea, Spain and Canada	IV iron sucrose (IS) & IV ferric carboxymaltose (FCM)	No iron therapy		<u>Infection rate:</u> Overall, IVI reduced the rate of postoperative infection (%) (RR, 0.67; 95% CI: 0.49, 0.91; I^2 = 15%; P = 0.01), in comparison with the control group. However, IVI did not change the mortality rate (%) (RR: 0.56; 95% CI: 0.17 to 1.79; I^2 = 74%; P = 0.33) Results from RCTs alone, showed that IVI did not reduce postoperative infection rate (3 studies; RR: 0.34; 95% CI: 0.03, 3.81; I^2 = 91%; P = 0.39) nor reduced mortality rate (2 studies; RR: 0.34; 95% CI: 0.03, 3.81; I^2 = 91%; P = 0.39).	

	were converted to units per patient or days per patient, and the proportion of patients who received transfusion, the rate of postoperative infection, and the mortality were reported as the number of patients per total patients. Statistical analysis was performed using RevMan version 5.3 (Cochrane Collaboration, London,U K). The mean difference (MD) with its 95% confidence interval (CI) was calculated for continuous variables, and the relative risk (RR) with its corresponding 95% CI was obtained for dichotomous outcome data. Due to the relatively small number of clinical trials and the resulting clinical heterogeneity in the meta-analysis, the Mantel–Haenszel test or inverse-variance random-effects model was used instead of the fixed-effects model. To assess the heterogeneity of outcomes, a sensitivity analysis was performed to evaluate the influence of a single study on the overall effect estimated by excluding one study at a time.							

Evidence Table : Safety
Question : Is intravenous iron safe critically ill trauma patients?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
8. Pieracci FM, Stovall RT, Jaouen B, et al. A multicenter randomized clinical trial of IV iron supplementation for anemia of traumatic critical illness. Crit Care Med. 2014;42(9):2048–57.	**RANDOMIZED CONTROLLED TRIAL** **Objective:** To evaluate the efficacy of IV iron supplementation of anaemic, critically ill trauma patients. **Methods:** This was a multicentre, randomized, single-blind, placebo-controlled trial involving four state-verified, American College of Surgeons–certified, level I trauma centres in the US. Eligible patients included those admitted to the ICU with a primary diagnosis of trauma. The inclusion criteria were 1) anaemia (latest haemoglobin concentration < 12 g/dL); 2) age 18 years old or older); 3) less than or equal to 72 hours from ICU admission; and 4) expected ICU length of stay (LOS) more than or equal to 5 days. Study group assignment was unblinded to both subjects and healthcare providers who administered the study drug and blinded to the research team abstracting and analysing the data. Randomization was accomplished by the investigational pharmacy at each satellite site using a computer-generated block pattern. The randomization was unblinded to		A total of 150 patients were randomised. There was no difference between groups in enrolment site (*P* = 0.63), age (*P* = 0.71), mechanism of injury (*P* = 0.73), comorbidity score (*P* = 0.15), Injury Severity Score (ISS) (*P* = 0.28), time from ICU admission to study enrolment (*P* = 0.12). In the iron group as compared with the placebo group, there was a significantly increased proportion of male patients (77.3% vs 61.3%, *P* = 0.03), a significantly greater baseline estimated blood loss (EBL) (196 mL vs 57 mL, respectively, *P* = 0.02), and a significantly greater EBL/study day (75.9 mL vs 53.6 mL, respectively, *P* = 0.04). Both iron and hematologic markers for the sample at baseline suggested functional iron	n=75 Iron sucrose 100 mg IV thrice weekly for up to six doses or until ICU discharge, whichever occurred first.	n=75 IV placebo thrice weekly for up to six doses or until ICU discharge, whichever occurred first.	Subjects were followed for 42 days or until hospital discharge, whichever occurred first.	<u>All-cause mortality:</u> By univariate analysis, there was a trend toward an increased mortality in the iron group as compared with the placebo group (9.3% vs 2.7%, *P* = 0.09). This trend persisted in subgroup analysis of subjects who received six doses of study drug (11.1% vs 3.3%, *P* = 0.25). However, after controlling for gender, baseline APACHE II score, and baseline EBL, there was no independent association between study group and mortality (*df* = 4, model chi-square = 8.8, *P* = 0.04, OR for iron supplementation: 1.12, 95% CI: 0.92, 1.33, *P* = 0.67), suggesting that baseline differences between groups confounded this relationship. <u>Infection rate:</u> Iron supplementation did not increase the risk of infection. At least one infection occurred in 44 subjects in the iron group (58.7%) and 52 subjects in the placebo group (69.3%, *P* = 0.17). The median number of infections per subject was 2 for both groups (*P* = 0.18). Specifically, there was no difference in the risk of pneumonia (*P* = 0.55), bacteraemia (*P* = 0.95), UTI (*P* = 0.66), or infections from other sources (*P* = 0.83). Both the antibiotic days (*P* = 0.64) and antibiotic days per study day (*P* = 0.55) were equivalent between groups. Finally, there remained no association between study group and infection risk in subgroup analysis of subjects who received all six doses of study drug (92.6% for the iron group and 90.0% for the placebo group, *P* = 0.73).	Study limitation: 1) trial was limited by baseline differences in groups despite randomization, practice variability between centres, and generalizability outside of the critically ill trauma patient. 2) Only single blinding could be achieved reliably due to the colour of iron sucrose. 3) Hepcidin concentration was not measured due to prohibitive cost; thus, any correlation Between hepcidin concentration, degree of functional iron deficiency, and response to iron supplementation could not be addressed. 4) Enrolment was 75% of the target sample size of 200.

	the investigators only after completion of data accrual. Sample size calculation was performed based on increase in the transferrin saturation to 20%, 10% reduction in the risk of transfusion from 70% (*p*1) to 60% (*p*2) and 10% increase in the risk of infection from 50% (*p*1) to 60% (*p*2) among the iron group.		deficiency. The median baseline serum iron concentration was 18 mcgg/dL (range, 5–137), and 134 subjects (89.3%) were hypoferremic. The median baseline ferritin concentration was 247.0 (range, 18.0–967.0), and 51 subjects (34.0%) were hyperferritinemic. Only two subjects (1.3%) were hypoferritinemic at baseline (serum ferritin concentration, < 28 mcg/mL) The median baseline transferrin saturation was 8% (range, 2–58%), and 133 subjects (88.7%) had a low transferrin saturation. Approximately one half of subjects had received at least one packed RBCs transfusion prior to study entry (*n* = 43 [57.3%] iron vs 37 [49.3%] placebo, *P* = 0.34).					5) The proportion of subjects enrolled from each study centre was not equal, although the same number of subjects per group was enrolled from each centre.

Evidence Table : Safety
Question : Is intravenous iron safe in patients with malignancy receiving palliative chemortherapy?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
9. Ng O, Keeler B, Simpson JA, et al. Feasibility of Intravenous Iron Isomaltoside to Improve Anemia and Quality of Life During Palliative Chemotherapy for Esophagogastric Adenocarcinoma. Nutr Cancer. 2018;70(7):1106–17.	**RANDOMIZED CONTROL TRIAL** **Objective:** To assess the feasibility of a single-dose intravenous iron therapy to improve anaemia, quality of life, and prevent blood transfusions in patients diagnosed with esophagogastric adenocarcinoma receiving palliative chemotherapy. **Methods:** Conducted at two recruiting sites in the UK. Adult patients with a proven histological diagnosis of Esophagogastric adenocarcinoma, anaemia (<12 g/dl in women and <13 g/dl in men) and a treatment decision for palliative chemotherapy were included. Patients were randomized 1:1 to each group using random allocations concealed in opaque envelopes. Clinical outcomes included haemoglobin, ferritin, TSAT, blood transfusion rate, number of units transfused, mortality, FACT-An, and EQ-5D quality of life scores.	**I-II**	A total of 27 patients. No statistically significant differences in age, sex, body mass index, Charlson score, or staging between standard care and intravenous iron groups at recruitment. Hb at recruitment in the IVI group was significantly lower: mean Hb 9.96 g/dL (SD=1.60, n=11) than those receiving standard care 11.45 g/dL (SD=1.79, n=13), P=0.044. No statistically significant differences in serum ferritin mean (P=0.282)) and transferrin saturations mean (P=0.811) at recruitment between both groups.	n = 14 A single dose of intravenous iron isomaltoside 1000 (Monofer VR). Dose were calculated using the Ganzoni equation of cumulative iron deficit. Iron isomaltoside was diluted in 250 ml 0.9% sodium chloride and infused over a period of 60 min. All subsequent treatment of anaemia was at the discretion of the clinical oncology team.	n = 13 Traditional regimens as decided by the clinical oncology team. All subsequent treatment of anaemia was at the discretion of the clinical oncology team.	Three follow-up visits were performed at the start of each three-week cycle of chemotherapy.	Seventeen patients completed the full three cycles of chemotherapy (62.9%), two patients had chemotherapy stopped after two cycles (7.4%), and five patients received only one cycle of chemotherapy (18.5%). No statistically significant differences were seen between groups and number of chemotherapy cycles completed. Data were analysed for 24 patients (IVI=11; standard care=13). <u>All-cause mortality:</u> Seven patient deaths occurred during the study: two patients in standard care, five patients in the intravenous iron group (P = 0.182). All deaths related to progression or complications from their esophagogastric malignancy. <u>Serious adverse events (SAEs):</u> There were no serious adverse events related to intravenous iron administration. One patient reported some diarrhoea following intravenous iron administration that settled within 24 hours. <u>Other complication:</u> There were no significant differences in unplanned hospital admissions between the two groups (P = 0.675).	Small sample size and no power calculation. The trial was terminated early due to poor recruitment. 3 patients from the IVI group excluded from data analysis: - 1 died before given iron - 1 received multiple blood transfusions prior to IVI therapy due to massive upper GI haemorrhage. Study retention was 88.9%

Evidence Table : Safety
Question : Is intravenous iron (sucrose/ dextran/ isomaltoside) safe in patients with iron deficiency anaemia and receiving chemotherapy for their malignancies?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
10. Noronha V, Joshi A, Patil VM, et al. Phase III randomized trial comparing intravenous to oral iron in patients with cancer-related iron deficiency anaemia not on erythropoiesis stimulating agents. Asia Pac J Clin Oncol. 2018;14(2):e129–37.	**RANDOMIZED CONTROL TRIAL** **Objective:** To find out whether there is any difference in hematopoietic response in patients treated with oral versus IV iron. **Methods:** A prospective single-centre open label randomized controlled phase III trial in which patients over 18 years old with malignancy requiring chemotherapy, who had haemoglobin (Hb) level <12 g/dL with at least one feature indicating iron deficiency: serum ferritin <100 mcg/mL, transferrin saturation <20% or hypochromic red blood cells >10% were recruited from the outpatient medical oncology department at Tata Memorial Hospital (TMH), India. Patients were stratified according to the type of malignancy (solid tumour *vs* haematolymphoid) and the level of Hb (≤10 g/dL *vs* >10 g/dL). Randomization was by a computer-generated schedule with block randomization, using a block size of 10. IV iron administered to patients with cancer-related iron-deficiency anaemia was hypothesised to lead to a 20%	**I**	A total of 192 patients were enrolled between March 2010 and March 2015. Median age was 51 years; male-to-female ratio was 0.68. Over 95% patients had solid tumours, most commonly gynaecologic, lung, head and neck and breast cancer. Intent of therapy was curative in 66%. The majority of patients (82%) were treated with platinum based two-drug combination chemotherapy regimen.	98 were randomized to IV iron sucrose in two divided doses, each diluted in 250 mL of 5% dextrose administered intravenously over 120 min with cycle 1 and cycle 2 of chemotherapy (three weeks apart). The dose of iron sucrose was calculated from the formula for total iron deficit: dose of iron in mg = weight in kg × Hb deficit (13-actual Hb in g/dL) × 2.4 + 500 The mean planned dose of IV iron was 869.35 mg (standard deviation [SD]: 203.1) and the mean dose received was	94 to oral ferrous sulfate capsules (100 mg) three times a day, started with cycle one of chemotherapy and continued until the end of cycle 2 (i.e., for 42 days). Oral iron could be continued beyond trial completion, if desired by the patient or the treating physician.	Week 1, 3 and 6	<u>Mortality/Survival rate:</u> At a median estimated follow-up of 24 months (95% CI: 19.5, 28.5), 78 patients (40.6%) have died, 37 in the IV iron arm and 41 in the oral iron arm. Estimated median OS for all patients was 17 months (95% CI: 10.9, 23.1). Estimated median OS for patients on IV iron was 16 months (95% CI: 7.3, 24.7) and that of patients on oral iron was 20 months (95% CI: 11.7, 28.4 months; SE:4.3 months), *P* = 0.73 by log-rank test. <u>Hypersensitivity reaction (HSR):</u> Hypersensitivity reactions (any grade) developed in five patients on IV iron, and none on oral iron, *P* = 0.059. Three of the hypersensitivity reactions (3%) were ≥ grade 3 (one was grade 4), although none were fatal. <u>Adverse events (AEs)/ adverse drug reactions (ADRs):</u> Toxicity to iron supplementation was minimal and easily manageable. Grade 3 diarrhoea occurred in 3% patients on IV iron and 7% patients on oral iron. Two percent patients on oral iron experienced grade 3 vomiting. Overall, gastrointestinal toxicity (any grade) developed in 41% patients on IV iron and 44% patients on oral iron, *P* = 1.0.	Mode of administration of iron, age, gender, intent of therapy and baseline Hb did not significantly impact response to iron therapy. True iron deficiency is defined as ferritin <15–30 mcg/mL, however in the setting of chronic inflammation and in disorders like malignancy, using a ferritin cut-off of 100 mcg/mL and a transferrin saturation <20% is widely accepted. –look for reference to include in background. Low response to iron (18.8%), given the fact that all patients included in the trial were iron deficient, based on measurement of baseline iron levels – in

	difference in hematopoietic response compared to oral iron. To prove this hypothesis with a type 1 error of 5% and a power of 80%, we needed 178 patients, assuming a binomial distribution. Accounting for an 8% rate of lost-to-follow, the final sample size was 192 patients. Patients who received blood transfusion during the 6-week study period were taken off study and their subsequent Hb values were not recorded or analysed. For patients who defaulted or died prior to completing the study and for whom the 6-week Hb value was not available were excluded from the analysis of the primary endpoint. All patients were included in the toxicity analysis, except patients who defaulted and for whom no side-effect information was available. Survival was estimated by the Kaplan–Meier method and follow-up was estimated by the reverse Kaplan–Meier technique.			760.17 mg (SD: 241.78).				patients on cytotoxic chemotherapy, this response is likely to be blunted due to the myelosuppressive effects of chemotherapy. Other possible explanations for the low observed efficacy of iron supplementation include a possibly short time to assessment of response, an inadequate dose of iron added to the myelosuppressive effects of chemotherapy and the type of malignancy. Given the lower than expected hematopoietic response to iron therapy, this trial was underpowered to assess a difference between IV iron and oral iron.

Evidence Table : Safety
Question : Is intravenous iron safe in non-dialysis chronic kidney disease patients?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
11. Agarwal R, Kusek JW, and Pappas MK. A randomized trial of intravenous and oral iron in chronic kidney disease. Kidney Int. 2015;88(4):905–14.	**RANDOMIZED CONTROLLED TRIAL** **Objective:** To compare the effect of intravenous and oral iron on kidney function in patients with moderate to severe CKD and iron deficiency anaemia. **Methods:** The study was conducted between August 2008 and November 2014 with study participants recruited from two hospitals located in Indianapolis, IN, USA. Study participants were required to be at least 18 years of age, have an estimated glomerular filtration rate (eGFR) by the 4-component MDRD formula of >20 and ≤ 60 ml/min/1.73m^2 using IDMS-calibrated creatinine, anaemia and iron deficiency. Eligible participants were randomized in a 1:1 ratio, using permuted blocks, to either oral iron or intravenous iron using concealed opaque envelopes. The randomization sequence was computer generated by a statistician.	**I-II**	A total of 136 subjects with iron deficiency anaemia and chronic kidney disease not on dialysis. Compared to the oral iron group, the intravenous iron group was younger (p=0.02), had less baseline cardiovascular disease (p=0.04), and history of hospitalization due to infection (p=0.05). Overall, the mean haemoglobin concentration at baseline was 10.6 g/dL, transferrin saturation 17.3% and serum ferritin 153 ng/mL. At baseline, erythropoiesis stimulating agents (ESA) were used by only 8.1% of the participants. Mean measured glomerular filtration rate (mGFR) was 34.5 mL/min/1.73 m^2 and proteinuria had a geometric mean of 0.5 g/g creatinine.	Iron sucrose: n=67 Dose: 200 mg intravenously over 2 hours at each of these 5 visits.	Ferrous sulfate: n=69 Dose: 325 mg three times daily for 8 weeks to provide at least the minimum dose of 200 mg elemental iron per day.	Median follow up (interquartile range) of all participants was 24.0 months (11.0–24.3) and did not differ by treatment group assignment.	<u>Mortality:</u> There were 6 deaths in the IV group and 4 in the oral iron group. A total of 104.5 patient-years (PY) of follow-up was obtained in the oral iron treatment group and 101 PY of follow up in the intravenous iron treatment group. <u>Serious adverse events:</u> Serious adverse events in the oral iron group occurred in 40 subjects who had 176 events (168.4/100 PY); in the intravenous iron group they occurred in 37 subjects who had 201 events (199/100 PY), unadjusted incidence rate ratio (IRR) 1.18 (95% CI: 0.97, 1.45, *P* = 0.106). Adjusted IRR was 1.60 (1.28, 2.00), *P* < 0.0001 <u>Adverse events:</u> Iothalamate GFR declined similarly over time in both groups (oral iron −3.6 mL/min/1.73m^2 per year, IV iron − 4.0 mL/min/1.73m^2 per year, between group difference −0.35 mL/min/1.73m^2 per year (95% CI: −2.9, 2.3; *P* = 0.79). After additional adjustment for age, sex, black race, ACE/ARB use, and cardiovascular disease, the rate of change in GFR became more similar between groups (oral iron −3.8 mL/min/1.73m^2 per year, IV iron − 3.9 mL/min/1.73m^2 per year, between group difference −0.11 mL/min/1.73m^2 per year (95% CI: −2.7, 2.5; *P* = 0.94). The small baseline difference in proteinuria was not statistically significant. There was significant increase in proteinuria over time (*P* = 0.04) in both treatment groups, however, there was no significant difference between groups. Cardiovascular events in the oral iron group occurred 36 times in 19 subjects (34.4/100	The trial was stopped early on the unanimous recommendation of the Data and Safety Monitoring Board (DSMB) based on an increase in the serious adverse event rate in participants assigned to IV iron treatment compared to oral iron therapy and little difference in mGFR between treatment groups.

							PY); in the intravenous iron group they occurred 55 times in 17 subjects (54.4/100 PY; incidence rate ratio (IRR) 1.58 (95% CI: 1.04, 2.41, *P* = 0.033). Adjusted IRR was 2.51 (95% CI: 1.56, 4.04), *P* <0.001. Compared to the oral iron group, the incidence of hospitalized heart failure was increased about 2-fold in the intravenous iron group. Overall, gastrointestinal adverse events particularly diarrhoea were more common among participants randomized to oral iron. Gout on the other hand was more frequent among those randomized to IV iron. <u>Infection rate:</u> Serious adverse events due to infections in the oral iron group occurred 27 times in 11 subjects (25.8/100 PY); in the intravenous iron group they occurred 37 times in 19 subjects (36.6/100 PY; incidence rate ratio (IRR) 1.42 (95% CI: 0.86, 2.33, *P* = 0.17). Adjusted IRR was 2.12 (95% CI: 1.24, 3.64), *P* < 0.006. Compared to the oral iron group, the incidence of lung and skin infections were increased between 3 to 4 fold in the intravenous iron group.	

Evidence Table : Safety
Question : Is intravenous iron (sucrose/ dextran/ isomaltoside) safe in pregnant women with iron deficiency anaemia?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
12. Neogi SB, Devasenapathy N, Singh R, et al. Safety and effectiveness of intravenous iron sucrose versus standard oral iron therapy in pregnant women with moderate-to-severe anaemia in India: a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Glob Heal. 2019;7(12):e1706–1716.	**RANDOMIZED CONTROLLED TRIAL** **Objective:** To assess the safety and clinical effectiveness of intravenous iron sucrose (intervention) versus standard oral iron (control) therapy in the treatment of women with moderate-to-severe iron deficiency anaemia in pregnancy. **Methods**: Multicentre, open-label, phase 3, RCT done at four government medical college hospitals in India. Women aged 18 years and older who were between 20 and 32 weeks of gestation with MCV: RBC more than 14, randomized (1:1) to receive either intravenous iron sucrose or standard oral iron therapy using web-based random sequence generator with block sizes of six and eight, stratified by site and severity of anaemia (haemoglobin concentration ≤7 g/dL and >7 g/dL). The central randomisation procedure was implemented using an interactive voice response system managed by an independent information technology firm. All parties involved were not blinded to group assignment.	**I-II**	A total of 2018 pregnant women. Baseline information was available for 983 patients in the intravenous iron sucrose group and 1016 participants in the standard therapy group. Patient characteristics were similar in both groups (table 1). Mean age was 24·4 years (SD 3·6), and 695 (35%) women were primigravida. The mean gestational age at the time of recruitment was 27·6 weeks (SD 3·7). The baseline characteristics of women whose primary outcomes were recorded (958 [97%] in the intravenous iron sucrose group and 976 [96%] in the standard therapy group) were similar to those whose outcomes could not be obtained (25 [3%] in the intravenous iron sucrose group and 40 [4%] in the standard therapy group).	n = 999 Intravenous iron sucrose administered as 200 mg elemental iron in 100 mL 0·9% sodium chloride infusion over 30–60 min, scheduled 48 hours apart until completion of total dose; total dose was calculated based on patient's weight on first antenatal visit. No further oral iron tablets were given until 6weeks postpartum if the woman completed the required dose.	n = 1019 Oral iron tablets supplied by respective hospitals (100 mg elemental iron and 0·5 mg of folic acid per tablet), to be taken twice a day until 6 weeks postpartum. Both groups given 5 mg of folic acid daily during the trial period. When the blood picture at baseline or during follow-up was suggestive of dimorphic anaemia, vitamin B12 injections or tablets were prescribed at the discretion of the treating physician.	Up to 6 weeks post-delivery	Data of events during childbirth were available from 1943 mothers (961 [98%] in the intravenous iron sucrose group and 982 [97%] in the standard therapy group). 143 (7%) of these women delivered at home and among 1800 women who delivered in hospitals, 349 (19%) had caesarean section. <u>Serious adverse events:</u> Serious maternal adverse events: 29; one fatal and 28 non-fatal – IV: 16 of 958 (2%) vs oral: 13 of 976 (1%); 1 death in IV due to accident unrelated to the trial Postpartum haemorrhage: IV: 4/895 (<1%) vs oral iron: 4/889 (<1%); Adjusted OR: 1·01; (95% CI: 0·25, 4·05). <u>Infection rate</u>: Puerperal sepsis: IV: 13/934 (1%) vs oral: 13/947 (1%); Adjusted OR (95% CI): 1·01 (0·46, 2·22) <u>Adverse events:</u> Over the course of 4651 infusions, only one participant had an adverse event that mandated stoppage of further infusions. 13% of women reported immediate and 24% reported late self-limiting minor adverse effects. The risk of having any minor adverse effects was 22% lower in the intravenous iron sucrose group than in the oral iron group.	22 (2%) patients in the intravenous iron sucrose group and 34 (3%) patients in the standard therapy group were lost to follow-up. No withdrawals or loss to follow-up resulted from adverse events.

Evidence Table : Safety
Question : Is intravenous safe in women with postpartum iron-deficiency anaemia?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
13. Sultan P, Bampoe S, Shah R, et al. Oral vs intravenous iron therapy for postpartum anemia: a systematic review and meta-analysis. Am J Obstet Gynecol. 2019;221(1):19-29.e3. Available from: https://doi.org/10.1016/j.ajog.2018.12.016	**SYSTEMATIC REVIEW** **Objective:** To determine whether oral iron or intravenous iron should be the primary treatment modality for women with postpartum iron-deficiency anemia. **Data sources and searches:** Searches were performed on November 6, 2017, to identify randomized trials in PubMed (includes MEDLINE) (1972-2017); Cochrane Central Register of Controlled Trials, CENTRAL (1972-2017); Cumulative Index to Nursing and Allied Health Literature, CINAHL (1972-2017); Web of Science; Excerpta Medica Database, EMBASE (1972-2017); and clinicaltrials.gov for unpublished or ongoing studies. **Quality assessment:** Quality of studies was assessed using the Cochrane Collaboration tool for evaluating the risk of bias. Data extraction was independently carried out by 5 individuals. **Data synthesis and analysis:** Quantitative data were analyzed using the Review Manager software. For pooled continuous data, mean differences with 95% confidence intervals (CIs) were calculated. For pooled	**I-II**	Fifteen randomized trials met the inclusion criteria. Study cohort comprised 2182 women, with 1001 and 1181 women receiving oral iron and IV iron therapy, respectively. Included studies used the following haemoglobin upper limit cut-off values for inclusion criteria: 8 g/dL (4 studies), 8.5 g/dL (1 study), 9 g/dL (3 studies), 10 g/dL (5 studies), and 10.5 g/dL (1 study) and one study used postpartum haemorrhage as the primary inclusion criterion. Fourteen trials consisted of 2 treatment arms (oral and IV iron). One study had 3 treatments arms; 2 arms comprised IV iron preparations (ferrous sucrose and ferrous carboxymaltose, respectively), and 1 arm comprised oral iron ascarbate. Two studies included women with other comorbid disease.	Ferric sucrose was the most common IV iron formulation (9 of 15 studies). In these studies, the total dose of ferric sucrose ranged from 300 to 600 mg. Other IV iron formulations studied were ferric carboxymaltose, iron dextran, and iron maltoside. Among the studies investigating ferric carboxymaltose, the total dose ranged from 1000 to 3000 mg. In 1 study, the total dose of iron dextran was 1000 mg. In another	Oral iron supplements studied were administered as divalent (ferrous) salts or trivalent (ferric) salts: ferrous sulphate (9 studies18,20,32-34,36,39-41), ferrous ascarbate (2 studies19,22), iron protein succinylate (2 studies35,37) and ferrous fumarate (1 study38). The oral preparation was not described in 1 study.21 Oral iron dosing regimens varied. For example, ferrous	Duration of follow-up varied from 14 days to 12 weeks, with 6 studies describing a 6-week study period.	Adherence to a medication regimen was assessed in 10 studies, but data were reported in only 3 studies. In 2 studies, adherence was higher in women receiving IV vs oral iron (98% vs 84% and 100% vs 84% respectively). In 1 study, adherence was equal (100% in both groups). Compared to oral iron, the safety profile of IV iron was reassuring, with women receiving IV iron being at lower risk for gastrointestinal related side effects. <u>Mortality:</u> There were no deaths directly attributable to iron therapy. In 1 study, 1 patient died of peripartum cardiomyopathy 13 days after vaginal delivery and 7 days after exposure to IV ferric carboxymaltose. <u>Hypersensitivity reaction:</u> Features of hypersensitivity reactions, namely urticaria and rash, occurred rarely following IV iron exposure (0.6% and 4.6%, respectively). <u>Adverse drug reaction:</u> Compared to oral iron, women receiving IV iron also had increased skin flushing (odds ratio [OR], 6.95; 95% CI: 1.56, 31.03) and decreased gastrointestinal related side effects, notably constipation (OR, 0.08; 95% CI: 0.03, 0.21), and dyspepsia (OR, 0.07; 95% CI: 0.01, 0.42). <u>Infection rate:</u> No statistically significant between-group differences were observed for other side effects, including infection risk.	Funnel plot of included studies and the Egger test demonstrated no evidence of publication bias (P= 0.09) Main findings are limited by the degree of heterogeneity between trials. This heterogeneity may be due to differences in mode of delivery, iron formulations, doses, dosing frequency, duration of drug exposure, baseline hemoglobin and iron status of study patients, and other unreported differences between study groups. There were insufficient data to

	dichotomous data, odds ratios (OR) and 95% Cis were calculated. Data were analysed using the Der-Simonian random effects model.		One study excluded women with known nutritional disorders. In 11 studies, patients were recruited within 48 hours of delivery, 2 studies recruited patients up to 10 days following delivery, and 2 studies did not state the timing of recruitment. Modest differences were observed in the baseline postpartum haemoglobin concentrations across the 4 studies: 7.4 g/ dL,32 8.8 g/dL,19 8.5 g/dL,20 and 8.1 g/dL.	study, iron maltosidase was administered as a single dose of 1200 mg.	sulphate doses ranged from 200 mg to 975 mg per day with their duration of treatment ranging from 1 month to 12 weeks.			perform sensitivity analyses, because only 4 studies reported haemoglobin concentrations at week 6 postpartum. Cost or perform cost-effectiveness analysis for different iron formulations were not examined due to the extent of study heterogeneity.

Evidence Table : Economic Evaluation
Question : Is preoperative intravenous iron cost-effective for reducing blood transfusion requirement in patient undergoing orthopaedic surgery?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
1. Basora M, Pereira A, Coca M, et al. Cost-effectiveness analysis of ferric carboxymaltose in pre-operative haemoglobin optimisation in patients undergoing primary knee arthroplasty. Blood Transfus. 2018;16(5):438–42.	**COST-EFFECTIVENESS ANALYSIS** **Objective:** To evaluate the cost-effectiveness of a preoperative haemoglobin optimisation protocol based on the administration of intravenous ferric carboxymaltose (FCM) to reduce RBC transfusion in patients undergoing primary knee arthroplasty. **Methods:** A computer simulation that modelled a hypothetical trial comparing preoperative haemoglobin optimisation with no optimisation in patients with real or functional iron-deficiency anaemia submitted to primary knee arthroplasty. A more recent cohort of 52 patients who underwent haemoglobin optimisation with FCM prior to knee arthroplasty was used to estimate data on the effectiveness of the optimisation. Probability (%) distributions used in the model to simulate dosage of intravenous FCM and subsequent increase in haemoglobin concentration, were adjusted for the presenting level of haemoglobin level prior to optimisation: <11 g/dL or ≥11 g/dL as the researchers noted from their previous study that patients with haemoglobin levels <11 g/dL have a steeper		20,000 patients were randomly assigned to the haemoglobin optimisation arm or the non-optimisation, control arm in a strict 1:1 ratio. Presenting haemoglobin levels at first visit, were adjusted to a logistic distribution (mean: 10.9 g/dL; SD: 0.5 g/dL) and truncated at 7.2 and 12.5 g/dL (no case outside this range was simulated). 80% of the hypothetical patients were in ASA category I/II. 85% of the total patients had no contraindication to tranexamic acid.	FCM	No iron treatment	-	The simulated preoperative optimisation protocol led to fewer patients being exposed to allogeneic RBC transfusion (2,212 vs 6,595 out of 10,000 patients) and a relevant decrease in the number of transfused RBC units (4,342 vs 13,336). Increased costs in the optimisation arm amounted to € 3,641,421 and were mostly associated with the outpatient day-hospital visit (54%) and the FCM treatment (40%). In the reference case scenario, the cost of one patient avoiding transfusion and one RBC unit being spared were € 831 and € 405, respectively. Sensitivity analysis 1) Cost of an outpatient day-hospital visit (may vary largely among institutions): On the assumptions of a 50% reduction and a 50% increase in the costs of the outpatient visit, the average costs per patient not exposed to allogeneic RBC were € 606 and € 1,055, respectively. With the same assumptions, the cost per RBC unit spared ranged from € 296 and € 514. 2) Probability of transfusion (impact of improvements in surgical and anaesthesia procedures): The probability randomly ranged from × 0.1 to × 1.0 the basal value according to a uniform distribution. Both costs increased exponentially as the probability of transfusion decreased. For probabilities of transfusion over 20%, there were no differences in transfusion requirements between the optimisation and control arms. <u>Summary:</u> The cost of the outpatient visit, including personnel, infusion sets and other ancillary materials, was the greatest cost component (54% of total), even higher than the acquisition	The strength of this study is that the measure of the effectiveness evaluation was RBC unit transfusion avoided rather than the cost of RBC unit, as the latter has high variability in the calculation of the transfusion cost that could imply a lack of applicability of the results. Simulation was based on a theoretical model rather than an empirical one. Despite, all variables in the model having been derived from

	increase haemoglobin concentration after FCM than those with higher levels. The probabilities of transfusion and the number of RBC units transfused were according to the immediate preoperative haemoglobin (Hb) level, the patient's American Society of Anaesthesiology (ASA) category, and whether or not he/she received tranexamic acid were derived from previous studies. Costs were derived from the clinical accounting and pharmacy records of the hospital and included only direct costs attributable to the haemoglobin optimisation. The analysis was performed from the hospital perspective and a temporal horizon limited to the length of stay in hospital. The main outcomes were the cost per unit of RBC spared and patient transfusion avoided in the optimisation arm as compared with the control arm. The simulation model was built using Excel spreadsheets and analysed with the @Risk add-in (www.palisade.com). Parameters estimated with uncertainty (e.g. probability of transfusion) were submitted to sensitivity analysis within a range of plausible values.						cost of FCM. In fact, the total cost per RBC unit spared was very sensitive to this factor, ranging from € 296 to € 514 under several realistic assumptions about the cost of outpatient visits. Cost savings were very sensitive to the proportion patients who require transfusion and fall to zero when this proportion decreases to about 18%. The costs per transfusion avoided and RBC unit spared were also very sensitive to the transfusion rate in the control arm. Costs increased exponentially with lineal reduction in the transfusion rate. <u>Authors' conclusion:</u> The theoretical model suggests that FCM-based programs of preoperative optimisation of haemoglobin concentration would be cost-effective in primary knee arthroplasty and should, therefore, be considered in patients with iron-deficiency anaemia.	observed data, some of which have been previously published, this may affect the representativeness of the results. The model did not capture the whole potential health benefits of FCM in elderly patients who may have subclinical iron deficiency.

Evidence Table : Economic Evaluation
Question : Is preoperative intravenous iron cost-effective for reducing blood transfusion requirement in patients undergoing elective abdominal surgeries ?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
2. Froessler B, Rueger AM, and Connolly MP. Assessing the costs and benefits of perioperative iron deficiency anemia management with ferric carboxymaltose in Germany. Risk Manag Healthc Policy. 2018;11:77–82.	**COST-EFFECTIVENESS ANALYSIS** **Objective:** To model the economic consequences of perioperative administration of FCM vs usual care in German hospitals (cost comparison model). **Methods:** An Excel-based model was developed to investigate the costs of FCM treatment compared with usual care in perioperative blood management in elective abdominal surgeries in Germany. The model estimates the average cost per case treated preoperatively with FCM compared with usual care (all anaemia treatment modalities as per primary care physician or surgical team) until the point of discharge. No long-term implications are considered. The model considers only the immediate outcomes and associated costs. Based on the treatment allocated, patients transitioned through the model with costs and outcomes accounted at different stages. Entering the model, patients received either FCM or usual care prior to surgery for the management of IDA.		Data utilization was based on the results of a clinical trial by Froessler et al. (2016). In this randomized controlled trial, a 60% reduction in RBC transfusion was observed in the IV iron group compared with the usual care group (31.25% vs 12.5%). Haemoglobin (Hb) values, although similar at randomization, improved by 0.8 g/dL with IV iron compared with 0.1 g/dL with usual care (P=0.01) by the day of admission. The IV iron group had higher Hb 4 weeks after discharge compared with the usual care group (1.9 vs 0.9 g/dL, P=0.01) and a shorter length of stay (7.0 vs 9.7 days, P=0.026). There was no difference in discharge Hb levels, morbidity, mortality, or quality of life.	15 mg of FCM/kg body weight to a maximum dose of 1,000 mg preoperatively and additional IV FCM post-op according to blood loss as per the protocol. The median IV iron dose administered to patients in the intervention group was 1,200 mg (interquartile range 1,088 – 1,363)	Standard therapy -Included no treatment, continued observations, oral iron recommendations, and allogeneic blood transfusion		Clinical metrics used to construct the model were based on reported transfusion rates of 12.5% in patients receiving FCM compared with 31.5% of patients receiving standard of care. The following study findings incorporated in the model: FCM patients who in addition to their IV iron treatment received RBC transfusion were administered on average 1.6 units (vs 3.2 units for non-FCM patients) and their hospital length of stay was shorter (6 vs 9 days). Hospital cost data were taken from the "LauerTaxe" (price list of the medicinal products sold in Germany; cost of FCM: €141.88/500 mg), the Department of Medical Controlling of Heidelberg University Hospital (estimated cost for 1 day of hospitalization: €350.00; and the St Marien hospital Vechta (cost of blood products: €97.00/RBC). Estimated the average cost per case treated with FCM and usual care to be €2,461 and €3,246, respectively, for resource expenses paid by the hospital per case (excluding the surgical expenses). Treatment with FCM in IDA resulted in cost savings of €786 per case in Germany based on reductions in transfusion and costs paid by hospitals for extended hospitalization. The individual costs per case were most sensitive to changes in number of patients transfused, number of units transfused and cost of RBC. Hospital length of stay and hospital cost per day, preoperative dosing and postoperative dosing had limited impact on the incremental results. <u>Authors' conclusion:</u> Preoperative correction of IDA with FCM reduces the need for blood transfusion and the length of hospital stay. Treatment with FCM in IDA resulted in cost savings of €786 per case in	Tornado diagram and description of sensitivity analysis not corresponding to each other

	Data inputs in the model are populated with information from peer-reviewed literature, publicly available data sources, and the estimations provided by clinicians. The treatment-related data input is based on the results of the clinical trial by Froessler et al. (2016) which included 72 patients with IDA prior to abdominal surgery in a university teaching hospital in Adelaide, Australia. The German hospital cost perspective, excluding labour costs, was applied to this analysis. The costs associated with administering FCM and RBC have been excluded from this analysis as administration in some cases would have been covered by the daily hospitalization cost applied in the model, thus avoiding double counting costs. The costs incurred by hospitals and the subsequent diagnostic-related group payment attributed to the surgery performed were not considered as well as they represent revenue for hospitals in relation to procedures provided, and not costs. A one-way sensitivity analysis using ±20% for all parameters except, the price of medications as these are fixed costs to the hospitals, was used to determine the impact of change in any one variable on the incremental budget impact per case.						Germany based on reductions in transfusion and costs paid by hospitals for extended hospitalization.	

Evidence Table : Economic Evaluation
Question : Is intravenous iron more cost-effective than oral iron for the treatment of iron-deficiency anaemia?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
3. Calvet X, Gené E, Àngelruíz M, et al. Cost-minimization analysis favours intravenous ferric carboxymaltose over ferric sucrose or oral iron as preoperative treatment in patients with colon cancer and iron deficiency anaemia. Technol Heal Care. 2016;24(1):111–20.	**COST-MINIMIZATION ANALYSIS** **Objective:** To compare the cost implications, using a cost-minimization analysis, of three strategies: IV FCM versus IV IS and oral iron (OI) treatment for treating iron-deficient anaemia before surgery in patients with colon cancer. **Methods:** The evaluation was performed from a third-payer perspective. Base case total costs per patient were calculated using the individual patients' data for the three different groups: patients treated with FCM, IS, or OI. The primary outcome measure was the cost of the management of each patient from diagnosis to hospital discharge. This parameter was calculated by adding the three major components of cost that were expected to be relevant for the analysis: 1) the total cost of intravenous iron infusion (including costs of the drug and direct and indirect costs of outpatient infusion in a day-care unit) in the FCM and IS groups, 2) the costs of the transfusions needed, and 3) hospitalization costs. Costs of surgery were assumed to be similar for the three groups as their clinical		Individual data of patients with colon cancer and preoperative iron-deficient anaemia treated with IV FCM were retrieved from a previous cohort study (Delgado et al., 2013). Data from patients receiving only oral iron or IV IS were collected retrospectively. All cohorts were managed in exactly the same way as the historical cohort. There were no significant differences in age, BMI and other clinical characteristics among patients in the three groups.	FCM (n=111)	1. IS (n=16) 2. Oral iron (n=155)	-	Cost-minimization analysis showed that, under baseline costs and assumptions, FCM was less costly than IS or OI. Total costs per patient (including costs of iron infusion, transfusion and hospitalization) were €1,827 for FCM, €2,312 for IS and €2,101 for OI. Therefore, baseline data cost savings for FCM treatment were €485 when compared to IS and €274 when compared to OI. The two-way sensitivity analysis shows that the most influential variable in the analysis was length of hospitalization. Baseline hospitalization reductions with FCM treatment were 2.3 days when compared to IS and 2.6 days when compared to OI resulting in respective cost savings of €485and €274. IS would need to save 0.2 days or more when compared to FCM to achieve a cost saving. FCM treatment may result in cost savings if hospitalization days saved are 1.2 or more days when compared to OI. Exclusion of hospitalization outliers (patients admitted for longer than 20 days) reduced the differences between groups, although the analysis still favoured FCM. Total costs per patient were €1,532 in the FCM group, €1,700 in the IS group and €1,693 in the OI group. The Monte Carlo simulation favoured (84.7% of the iterations) the use of FCM over IS with a mean incremental cost of €578 per patient. The study suggests that under standard conditions the savings in costs offset the higher drug cost of FCM compared with IS or OI. The results of the analysis were fairly stable and were reproduced in most of the univariate and multivariate sensitivity analyses performed. The sensitivity analysis of the study suggests that the higher the hospitalization costs, the more FCM is favoured.	Its scope is limited to direct and indirect hospital costs. Measuring and adding direct non-hospital costs – for example, workdays lost by the patient or their relatives, or the cost of transportatio n to the hospital – would have probably increased the estimated benefits of FCM.

	characteristics were not significantly different. Costs of complications were not accounted for separately but were subsumed under the total costs of hospitalization to avoid considering their effect twice. Calculations were performed using Microsoft Excel XPTM. One-way and two-way sensitivity analyses were performed by changing baseline estimates for costs within a range of potentially reasonable values and evaluating whether these changes modify the conclusions reached using baseline estimates for costs. As well as these evaluations, an additional sensitivity analysis was performed excluding outlier patients (defined empirically as those with a hospital length of stay over 20 days). Probabilistic sensitivity analysis was performed using Monte Carlo simulations for Microsoft Excel XPTM. Variables included in the analysis were cost of IS and FCM, total cost of iron infusion, cost of transfusion, cost of hospital stay, number of transfusions and days of hospitalization. These variables were tested both according to a normal distribution (number of transfusions and days of hospital stay) and a triangular distribution (for cost variables) and performing 10,000 iterations.						The study confirms that administration of larger doses of iron in a smaller number of infusions reduces costs. In the setting analysed, IS was more expensive due to the cost of repeated infusions. In addition, the total iron dose achieved with IS was lower and not related to a clear reduction in the need for transfusion or the length of hospitalization. <u>Authors' conclusion:</u> In this pharmaco-economic model, preoperative ferric carboxymaltose infusion was less costly than iron sucrose infusion or oral iron replacement and appeared to reduce the total costs in patients with iron-deficient anaemia and colon cancer.	

Evidence : Organizational
Question : Any organizational issue regarding preoperative intravenous iron use in colorectal cancer patients undergoing surgery?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
1. Kam PMH, Chu CWH, Chan EMY, et al. Use of intravenous iron therapy in colorectal cancer patient with iron deficiency anemia: a propensity-score matched study. Int J Colorectal Dis. 2020;35(3):521–7.	**PROSPECTIVE COHORT** **Objective:** To investigate the effect of intravenous iron therapy on haemoglobin level change and transfusion requirements among anaemic colorectal cancer patient in a tertiary hospital in Hong Kong. **Methods:** This single centre study was carried out in a tertiary centre with more than 200 elective colorectal cancer operations per year. Patients diagnosed with colorectal adenocarcinoma and found to have iron deficiency anaemia (confirmed based on blood test) preoperatively were recruited from August 2017 to March 2019. All patients were arranged to undergo intravenous iron infusion in day admission setting at least 2 weeks prior to their elective operation date. Their haemoglobin level and iron profile were recorded again during their admission for elective surgery, which was 1 day prior to the operation. The operations were performed by specialist surgeons in laparoscopic, open, or robotic method (in selected cases of	**II-2**	A total of 100 patients included in the study. There were no statistical differences between median age (70 in IVI vs. 69 in non-IVI, *P* = 0.46) and male to female ratio (50% male in both groups, *P* = 1.0). There were no statistical differences in premorbid status, medical comorbidities, or use of antiplatelet or anticoagulant. There was no difference in number of patients with red cell transfusion prior to intravenous iron (42.1% in IVI vs. 41.9% in non-IVI, *P* = 0.987). Both groups had similar proportions of patient taking oral iron supplement prior to surgery (31.6% in IVI vs. 29% in non-IVI, *P* = 0.787). Majority of patients had cancers in cecum, ascending colon, or hepatic flexure for both groups, followed by sigmoid and rectal cancers. Most patients' final pathology were stage	Iron sucrose (IS) or iron isomaltoside (IIM): n=38 IS: 500 mg in 250 ml normal saline over 210 min intravenously, with a total of two doses set at 1 week apart IIM: 1000 mg (or 20 mg/kg if bodyweight is less than 50 kg) in 100 ml normal saline over 15 min as a single dose.	No iron therapy: n=62 (after propensity score matching in a 2:1 ratio)	Not reported	The median length of stay was 8.5 (IQR 7-13.3) days in IVI group and 9 (IQR 8-14) days in non-IVI group (*P* = 0.685).	

	rectal cancer) under general anaesthesia. Patients were excluded if (1) histology of tumour was not adenocarcinoma; (2) anaemia was not due to iron deficiency; (3) no elective operation was performed (either because patient refused or was deemed unfit for surgery); and (4) only one dose of IS was given (due to incomplete IVI dosage use). The data of the historic cohort as control for matching was collected retrospectively from CDARS (Clinical Data Analysis and Reporting System). These were anaemic patients who underwent colorectal cancer surgery during the period of October 2014 to September 2017.		III disease (47.4% in IVI and 48.5% in non-IVI) and stage II disease (36.8% IVI and 30.6% non-IVI). There was no difference in median waiting time from diagnosis to operation between two groups (34.5 days in IVI and 43.5 days in non-IVI, *P* = 0.952). Propensity score matching and statistical analysis were performed on SPSS version 23 with R-extension 3.1.0 and PSMatching, using caliper 0.5. The matching criteria included first haemoglobin level, age, sex, transfusion of red cell prior to intravenous iron, use of oral iron supplement, and tumour location.					

Evidence Table : Organizational
Question : Any organizational issue regarding preoperative intravenous iron in patients undergoing cardiac surgery?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
2. Klein AA, Chau M, Yeates JA, et al. Preoperative intravenous iron before cardiac surgery: a prospective multicentre feasibility study. Br J Anaesth. 2020;124(3):243–50.	**PROSPECTIVE COHORT** **Objective:** To assess the introduction and efficacy of a preoperative IV iron pathway to treat anaemia in patients before cardiac surgery. **Methods:** The UK CAVIAR study was a multicentre, stepped, observational pilot and feasibility study comprising three groups of patients awaiting cardiac surgery. Patients were consecutively recruited between April 2016 until March 2018, but over different periods depending on the centre's progress in setting up preoperative anaemia services and availability of study teams. Sample size was calculated based on change in Hb from baseline to pre-surgery in patients who received IV iron. Assuming the SD for Hb would be 12 g/L based on national audit data, 72 patients would provide 90% power at a 5% significance level and 62 would provide 80% power (allowing for up to 10% loss to follow-up) to demonstrate a difference in the change from baseline in Hb of 10 g/L.	**II-2**	A total of 228 patients were recruited over 2 years in 11 UK cardiac centres. The baseline characteristics of the study groups varied significantly. In this study population, anaemic patients who received IV iron had a significantly higher rate of pre-existing renal impairment. There were higher rates of previously diagnosed anaemia (55% vs 30%), previous iron deficiency (39% vs 13%), and symptomatic angina (63% vs 39%) in the IV compared with the non-treated anaemic patients.	Anaemic with iron deficiency (n=64) treated with: 1. IIM (n=60): total dose calculated at 20mg/kg (mean dose of 1314 [303] mg) or, 2. Ferric carboxymaltose (FCM) [n=4]: up to a maximum of 1000mg IV iron was administered at a median (IQR [range]) of 33 (15-53 [4-303]) days before surgery. The mean (SD) dose of IV iron was 1293 (303) mg.	1. Non-anaemic: n=92 2. Anaemic with iron deficiency, but not treated: n=72	30 days	There were no statistically significant differences seen between treated and not treated with IVI groups for proportion of patients requiring readmission, days spent in intensive treatment unit (median days: 3 in IVI versus 2 in no iron group; *P* = 0.158), length of hospitalisation (median days: 10.5 in IVI versus 9 in no iron group; *P* = 0.492), as well as days alive and out of hospital (DAOH).	Excluded patients who received a large transfusion defined as four or more units of red cells). Study was not powered to demonstrate difference on transfusion rate or other patient outcomes.

Evidence Table : Organizational
Question : Any organizational issue regarding preoperative intravenous iron use in women undergoing abdominal hysterectomy?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
3. Diez-Lobo AI, Fisac-Martín MP, Bermejo-Aycar I, et al. Preoperative intravenous iron administration corrects anemia and reduces transfusion requirement in women undergoing abdominal hysterectomy. Transfus Altern Transfus Med. 2007;9(2):114–9.	**PROSPECTIVE COHORT** **Objective:** To investigate the utility of preoperative IV iron treatment to increase Hb levels and reduce the need for allogeneic blood transfusion (ABT) in women undergoing elective abdominal hysterectomy. **Methods:** All women with ID or IDA who scheduled for elective abdominal hysterectomy from January 2004 to June 2006 were enrolled. The presence of ID was defined by two of the following conditions: serum ferritin < 30 ng/mL, serum iron < 50 µg/dL or transferrin saturation index < 20%.9 The presence of preoperative or postoperative anaemia was defined according to World Health Organization criteria as Hb < 12 g/dL. They were assigned by the anaesthesiologist to one of the two groups depending on the time between preoperative assessment and surgery. The transfusion trigger was set at Hb < 8 g/dL.	**II-2**	A total of 75 women were included in the study. Most women (63/75, 84%) were already on oral iron, as prescribed by their gynaecologist or family doctor. There were no statistically significant differences between the two groups in terms of weight or age, type of procedure, prevalence of anaemia, estimated blood loss, length of hospital stay, Hb levels or iron laboratory parameters at baseline.	Iron sucrose (IS): n=31 Administered for 2–4 preoperative weeks, at doses of 200 mg in 200 mL saline every 48–72 hours, with a maximum of 600 mg/week, according to total iron deficit calculation (760 ± 290 mg; range: 300–1400 mg) Assigned to - women having their surgical procedure at least 1 month after preoperative assessment	Oral iron: n=44 (Assigned to women having their surgical procedure within a few days after preoperative assessment	Postoperative day 21	In addition, the length of hospital stay was longer in women receiving allogeneic blood transfusion (ABT) (n=14) than in women receiving no ABT (n=61) (6.9 ± 2.3 days vs. 5.8 ± 1.0 days, respectively; $P < 0.01$). Whereas, the length of stay in the IVI group per se was 5.6 ± 0.8 days, however compared to the control group this difference was not statistically significant, $P = 0.083$.	

Evidence Table : Organizational
Question : Any organizational issue regarding the use of postoperative intravenous iron in patients undergoing cardiac surgery?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
4. Xu H, Duan Y, Yuan X et al. Intravenous iron versus placebo in the management of postoperative functional iron deficiency anaemia in patients undergoing cardiac valvular surgery: a prospective, single-blinded, randomised controlled trial, J Cardiothorac Vasc Anesth. 2019;	**RANDOMIZED CONTROLLED TRIAL** **Objective:** to compare the safety and efficacy of intravenous iron versus placebo to correct postoperative anaemia in patients undergoing cardiac valvular surgery. **Methods:** A prospective, single-blind, randomised controlled trial at a hospital in China from March 2018 to October 2018. Eligible patients aged 20-70 years who agreed to participate were randomly assigned (1:1) to either the treatment (intravenous iron) group or the control (placebo) group using Excel 2010 (Microsoft, Redmond, WA, USA) To ensure allocation concealment, treatment codes were located in a central site, the pharmacy department. This department was not involved in any collection of trial data, follow-up, or patient activity to avoid possible bias. Randomisation allocation was delivered by pharmacy in sealed numbered opaque envelopes that were opened consecutively after informed consent was obtained. All intravenous solutions were presented in disguised form by the pharmacy department and assigned to patients according to the random numbers list.	**I**	A total of 150 patients were recruited: 75 were randomized to intravenous iron group and 75 were randomized to placebo group. There were no differences in demographic variables, preoperative Hb levels and postoperative parameters.	Iron sucrose (IS): n=75 weight-based calculated dose of iron sucrose administered with the dose of 200mg over 30 min on the day after surgery and maintained this dose every other day until the total iron deficiency was achieved. (794.8 ± 173.7mg)	Saline solution: n=75	0,4, 14 days after surgery	There were no significant differences in proportion of patients requiring ventilator time > 24 hours (13 [17.3%] in IVI versus 14 [18.7%]; *P* = 0.832) and postoperative hospital stay >10 days (13 [17.3%] versus 10 [13.3%]; *P* = 0.497) between the two groups.	

Evidence Table : Organizational
Question : Any organizational issue regarding perioperative intravenous iron use in patients undergoing orthopaedic surgery?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
5. Shin HW, Park JJ, Kim HJ et al. Efficacy of perioperative intravenous iron therapy for transfusion in orthopedic surgery: A systematic review and meta-analysis. PLoS ONE. 2019; 14(5): e0215427.	**SYSTEMATIC REVIEW** **Objective:** To evaluate the efficacy of IVIT with respect to details of transfusion and recovery profiles, such as length of hospital stay (LOS), rate of post-operative infection, and mortality among patients undergoing orthopedic surgery. **Data sources and searches:** PubMed, Embase, Cochrane Central, KoreaMed, and Google Scholar databases up to September 2017, with no language restrictions. **Quality assessment:** Two authors independently evaluated the quality of clinical trials using the Cochrane Risk-of-Bias tool to assess the quality of randomized controlled trials (RCTs) and the Newcastle-Ottawa scale to assess the quality of non-randomized controlled studies [case-controlled studies (CCSs)] in the meta-analysis. **Data synthesis and analysis:** Authors attempted to contact the authors of studies with insufficient or missing data. If this was impossible, they extrapolated data from the figures to obtain the target information. The values for units	**II-2**	A total of 12 clinical studies, comprising 4 RCTs with 616 patients and 8 CCSs with 1,253 patients*. 2 RCTs (n=227) and 5 CCSs (n=947) have used iron sucrose in the studies. * only results from RCTs were included in this review Countries: Australia, Republic of Korea, Spain and Canada	IV iron sucrose (IS) & IV ferric carboxymaltose (FCM)	No iron therapy		Combined results from RCTs and CCSs: IVIT therapy shortened length of stay (LOS; days) (MD, −1.60; 95% CI: −2.52, −0.68; I^2 = 66%; P = 0.0006). However, IVIT in the group of RCTs alone (MD, −0.98; I^2 = 38%; P = 0.21 / RR,0.61, I^2 = 71%; P = 0.31) did not.	

	of RBCs transfused and LOS were converted to units per patient or days per patient, and the proportion of patients who received transfusion, the rate of postoperative infection, and the mortality were reported as the number of patients per total patients. Statistical analysis was performed using RevMan version 5.3 (Cochrane Collaboration, London,U K). The mean difference (MD) with its 95% confidence interval (CI) was calculated for continuous variables, and the relative risk (RR) with its corresponding 95% CI was obtained for dichotomous outcome data. Due to the relatively small number of clinical trials and the resulting clinical heterogeneity in the meta-analysis, the Mantel–Haenszel test or inverse-variance random-effects model was used instead of the fixed-effects model. To assess the heterogeneity of outcomes, a sensitivity analysis was performed to evaluate the influence of a single study on the overall effect estimated by excluding one study at a time.							

Evidence Table : Organizational
Question : Any organizational issue regarding intravenous iron use in critically-ill patients with iron deficiency anaemia?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
6. Pieracci FM, Stovall RT, Jaouen B, et al. A multicenter randomized clinical trial of IV iron supplementation for anemia of traumatic critical illness. Crit Care Med. 2014;42(9):2048–57.	**RANDOMIZED CONTROLLED TRIAL** **Objective:** To evaluate the efficacy of IV iron supplementation of anaemic, critically ill trauma patients. **Methods:** This was a multicentre, randomized, single-blind, placebo-controlled trial involving four state-verified, American College of Surgeons–certified, level I trauma centres in the US. Eligible patients included those admitted to the ICU with a primary diagnosis of trauma. The inclusion criteria were 1) anaemia (latest haemoglobin concentration < 12 g/dL); 2) age 18 years old or older); 3) less than or equal to 72 hours from ICU admission; and 4) expected ICU length of stay (LOS) more than or equal to 5 days. Study group assignment was unblinded to both subjects and healthcare providers who administered the study drug and blinded to the research team abstracting and analysing the data. Randomization was accomplished by the investigational pharmacy at each satellite site using a computer-generated block pattern. The randomization was unblinded to		A total of 150 patients were randomised. There was no difference between groups in enrolment site (P = 0.63), age (P = 0.71), mechanism of injury (P = 0.73), comorbidity score (P = 0.15), Injury Severity Score (ISS) (P = 0.28), time from ICU admission to study enrolment (P = 0.12), In the iron group as compared with the placebo group, there was a significantly increased proportion of male patients (77.3% vs 61.3%, P = 0.03), a significantly greater baseline estimated blood loss (EBL) (196 mL vs 57 mL, respectively, P = 0.02), and a significantly greater EBL/study day (75.9 mL vs 53.6 mL, respectively, P = 0.04). Both iron and hematologic markers for the sample at baseline suggested functional iron deficiency. The median baseline	n=75 Iron sucrose 100 mg IV thrice weekly for up to six doses or until ICU discharge, whichever occurred first.	n=75 IV placebo thrice weekly for up to six doses or until ICU discharge, whichever occurred first.	Subjects were followed for 42 days or until Hospital discharge, whichever occurred first.	Length of stay in hospital: Neither ICU LOS (mean days [range], 10 [2–47] in IIVI versus 11 [2–37] in placebo; P = 0.53) nor hospital LOS (14 [2–62] in IVI versus 16 [2–65] in placebo); P = 0.50) differed between study groups.	Study limitation: 1) trial was limited by baseline differences in groups despite randomization, practice variability between centres, and generalizability outside of the critically ill trauma patient. 2) Only single blinding could be achieved reliably due to the colour of iron sucrose. 3) Hepcidin concentration was not measured due to prohibitive cost; thus, any correlation between hepcidin concentration, degree of functional iron deficiency, and response to iron supplementation could not be addressed. 4) Enrolment was 75% of the

	the investigators only after completion of data accrual. Data are expressed as median (range) or number (%). Differences in the medians of continuous variables were assessed using the Wilcoxon rank test. An a priori analysis of iron markers at baseline, day 7, and day 14 was planned, thus no post hoc adjustment for multiple comparisons was applied.		serum iron concentration was 18 ug/dL (range, 5–137), and 134 subjects (89.3%) were hypoferremic. The median baseline ferritin concentration was 247.0 (range, 18.0–967.0), and 51 subjects (34.0%) were hyperferritinemic. Only two subjects (1.3%) were hypoferritinemic at baseline (serum ferritin concentration, < 28 ug/mL) The median baseline transferrin saturation was 8% (range, 2–58%), and 133 subjects (88.7%) had a low transferrin saturation. Approximately one half of subjects had received at least one packed RBCs transfusion prior to study entry (*n* = 43 [57.3%] iron vs 37 [49.3%] placebo, *P* = 0.34).					target sample size of 200. 5) The proportion of subjects enrolled from each study centre was not equal, although the same number of subjects per group was enrolled from each centre.

Evidence Table : Organizational
Question : Any organizational issues regarding intravenous iron use in pregnant women with iron deficiency anaemia?

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (If Applicable)	Outcome Measures/Effect Size	General Comments
6. Neogi SB, Devasenapathy N, Singh R, et al. Safety and effectiveness of intravenous iron sucrose versus standard oral iron therapy in pregnant women with moderate-to-severe anaemia in India: a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Glob Heal. 2019;7(12):e1706–1716.	**RANDOMIZED CONTROLLED TRIAL** **Objective:** To assess the safety and clinical effectiveness of intravenous iron sucrose (intervention) versus standard oral iron (control) therapy in the treatment of women with moderate-to-severe iron deficiency anaemia in pregnancy. **Methods**: Multicentre, open-label, phase 3, RCT done at four government medical college hospitals in India. Women aged 18 years and older who were between 20 and 32 weeks of gestation with MCV: RBC more than 14, randomized (1:1) to receive either intravenous iron sucrose or standard oral iron therapy using web-based random sequence generator with block sizes of six and eight, stratified by site and severity of anaemia (haemoglobin concentration ≤7 g/dL and >7 g/dL). The central randomisation procedure was implemented using an interactive voice response system managed by an independent information technology firm. All parties involved were not blinded to group assignment.	**I-II**	A total of 2018 pregnant women. Baseline information was available for 983 patients in the intravenous iron sucrose group and 1016 participants in the standard therapy group. Patient characteristics were similar in both groups. Mean age was 24·4 years (SD 3·6), and 695 (35%) women were primigravida. The mean gestational age at the time of recruitment was 27·6 weeks (SD 3·7). The baseline characteristics of women whose primary outcomes were recorded (958 [97%] in the intravenous iron sucrose group and 976 [96%] in the standard therapy group) were similar to those whose outcomes could not be obtained (25 [3%] in the intravenous iron sucrose group and 40 [4%] in the standard therapy group).	n = 999 Intravenous iron sucrose administered as 200 mg elemental iron in 100 mL 0·9% sodium chloride infusion over 30–60 min, scheduled 48 hours apart until completion of total dose; total dose was calculated based on patient's weight on first antenatal visit. No further oral iron tablets were given until 6weeks postpartum if the woman completed the required dose.	n = 1019 Oral iron tablets supplied by respective hospitals (100 mg elemental iron and 0·5 mg of folic acid per tablet), to be taken twice a day until 6 weeks postpartum. Both groups given 5 mg of folic acid daily during the trial period. When the blood picture at baseline or during follow-up was suggestive of dimorphic anaemia, vitamin B12 injections or tablets were prescribed at the discretion of the treating physician.	Up to 6 weeks post-delivery	Data of events during childbirth were available from 1943 mothers (961 [98%] in the intravenous iron sucrose group and 982 [97%] in the standard therapy group). 143 (7%) of these women delivered at home and among 1800 women who delivered in hospitals, 349 (19%) had caesarean section. Median duration of hospital stay for vaginal deliveries was 2 days (IQR 1–2) and 4 days (3–5) in caesarean deliveries. Prolonged hospital stays due to maternal causes (>3 days for normal delivery and >7 days for lower segment Caesarean section (LSCS) delivery): IV: 59/885 (7%) vs oral iron: 68/879 (8%); Adjusted* odds ratio (95% CI): 0.85 (0.59,1.22) Intensive care unit (ICU) admission or referral to higher centres: IV: 2/895 (< 1%) vs oral iron: 1/889 (< 1%)	