Clinical Guideline for the Use of Intravenous Iron (Ferric Carboxymaltose, Ferinject®)

This guidance does not override the individual responsibility of health professionals to make appropriate decision according to the circumstances of the individual patient in consultation with the patient and /or carer. Health care professionals must be prepared to justify any deviation from this guidance.

Introduction

The majority of patients with iron deficiency can be treated with oral iron. Patients intolerant of or who are refractory to oral iron, who have severe anaemia, who require urgent surgery or are more than 36 weeks pregnant may require treatment with intravenous iron. Treatment of iron deficiency should only very rarely be with a blood transfusion. Intravenous iron may also be used for the treatment of functional iron deficiency.

This guideline does NOT cover investigation of iron deficiency anaemia. Incidence of gastrointestinal malignancy is high among patients with iron deficiency anaemia and all patients other than menstruating women must be considered for endoscopic investigation.

This guideline is for use by the following staff groups :

Clinical and nursing staff

Lead Clinician(s)

Dr Sangam Hebballi	Consultant Haematologist
Approved by Trust Transfusion Committee on:	6th October 2021
Approved by Medicines Safety Committee on:	12th January 2022
Review Date: This is the most current document and should be used until a revised version is in place	12th January 2024

Guideline written, researched and compiled by Dr Suzy Morton Consultant Haematologist for UHB and NHSBT

Key amendments to this guideline

Date	Amendment	Approved by:
June 2018	No changes to document	Trust Transfusion Committee
July 2020	Document extended for 6 months whilst review and approval process takes place	Trust Transfusion Committee
February 2021	Document extended for 6 months as per Trust agreement 11/02/2021	Trust agreement
October 2021	Document extended for 6 months to allow for full review and approval whilst transfusion lead is redeployed	Gill Godding/ Stacey Fowler
October 2021	Addition of hyperlink to NICE guidelines	Trust Transfusion Committee

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1. Introduction

Iron deficiency is a common cause of anaemia. In the majority of patients treatment is with oral iron and treatment of the underlying cause; this is often managed in the community by general practitioners. A significant minority however are seen in the emergency department or outpatient clinics. These may primarily present with iron deficiency anaemia or may be found to have iron deficiency during investigation for other conditions.

The usual standard of care for the large majority of patients is oral iron. See https://cks.nice.org.uk/anaemia-iron-deficiency

Patients presenting to hospitals with iron deficiency may be very symptomatic of anaemia, have a very low haemoglobin level or may be intolerant of oral iron. Patients are frequently diagnosed with iron deficiency anaemia in pre-operative assessment clinics where rapid normalisation of haemoglobin is required to avoid delays to surgery. National and local audits have shown a significant rate of inappropriate blood transfusion among such patients.

In addition patients with chronic diseases may be anaemic due to functional iron deficiency; total body iron stores are sufficient but the iron is not available for erythropoiesis in the bone marrow. These patients may require intravenous iron to aid erythropoiesis.

Best practice in iron deficiency is to replace iron rather than undertake a blood transfusion unless there is significant clinical compromise. Serious adverse events occur in approximately 1 in 22,000 blood transfusions as compared to 1 in 200,000 iron infusions. Transfusion associated circulatory overload (TACO) and haemolytic transfusion reactions (HTR) are significant risks following transfusion particularly in patients with risk factors. Other risks of transfusion, including immune modulation, are more difficult to quantify.

2. Investigation of anaemia

There are multiple causes of anaemia, which are beyond the scope of this guideline. Further information can be found in the Blood Transfusion Treatment pathway Anaemia Policy and from the on call haematology registrar when required.

Patients meeting the following parameters may benefit from iron replacement (which will be oral in the first instance unless meeting the criteria described below). This list is not exhaustive and patients with chronic inflammatory disease such as inflammatory bowel disease, rheumatoid arthritis and chronic renal failure may also benefit from intravenous iron. In these cases the decision to give intravenous iron lies with the consultant in charge of the patient's care.

The following suggest a diagnosis of iron deficiency

- Ferritin less than 30 micrograms/L (some sources indicate a normal range of greater than 15 mcg/L for women but in women who are anaemic with a ferritin 15-30 mcg/L and no other clear cause for anaemia, a trial of iron therapy should be given)
- Transferrin saturation less than 20% with serum iron less 12 mcg/L and TIBC (total iron binding capacity) greater than 60 micromoles/L

The following suggest a diagnosis of functional iron deficiency (see below for criteria in renal patients)

- Ferritin less than 100 mcg/L with CRP greater 30 mg/L or clinical evidence of active inflammation/chronic disease
- Fe saturation less than 20%, serum iron less than 12 mcg/L and CRP greater than 30 mg/L or clinical evidence of active inflammation/chronic disease

NB if anaemia of chronic disease is diagnosed, consideration must be given to the disease driving this process. Malignancy must be suspected and a thorough history and examination performed with appropriate investigations particularly where no other clear cause is apparent.

3. Method of Iron replacement

This may be with oral iron, IV iron or (rarely) blood transfusion, or a combination of these treatments. NB the preferred method of replacement is a clinical decision based on:

1. The severity of the symptoms of anaemia, comorbidities and the ability of the patient to tolerate anaemia
2. The cause of iron deficiency
3. The success of previous treatment.

The decision to use intravenous iron in place of oral iron should be discussed with a senior clinician experienced in the management of iron deficiency.

Haemoglobin can be anticipated to begin to increase within 1-2 weeks of IV iron treatment. If the patient is symptomatic but not compromised, and able to tolerate symptoms over a few weeks, blood transfusion is **not** indicated. Many patients' symptoms will improve even before a rise in haemoglobin is seen.

4. Indications for IV iron

IV iron should be considered in patients with demonstrated iron deficiency in **any** of the following situations**:**

- Patient intolerant of or unresponsive to oral iron
- Patient due surgery in next 6 weeks or pregnant with gestation more than 34 weeks
- Haemoglobin less than 80 g/L (if the anaemia is chronic and oral iron has not been given, a trial of oral iron is also an option)
- Patients with active inflammatory bowel disease where oral iron is likely to cause unacceptable side effects

IV iron can also be used in pre-dialysis renal patients with renal anaemia **once per month** if:

- Haemoglobin less than 120 g/L in those on erythropoiesis-stimulating agents (ESAs)
- Haemoglobin less than 110 g/L in those not on ESAs
- Functional iron deficiency with ferritin less than 200 mcg/L or ferritin less than 500 mcg/L and transferrin saturation less than 20%

5. Contraindications for use of intravenous iron

The following relate to use of **Ferric Carboxymaltose (Ferinject, FCM).** Other preparations of intravenous iron may have a higher reaction rate particularly in patients with a history of atopy. Iron dextran (Cosmofer) and iron sucrose (Venofer) may be used as an alternative.

Absolute contraindications to FCM administration

- Anaphylaxis or other significant hypersensitivity reaction to any IV iron preparation
- Current confirmed bacteraemia
- 1st trimester of pregnancy
- Iron overload

FCM should not be administered to patients with an absolute contraindication.

6. Cautions for use of FCM

In patients with the following conditions a clinical decision weighing the risks and benefits must be made. This will depend on the availability of other treatment, the chronicity, severity and impact of the anaemia and the expected duration of the relative contraindication.

Due to concern of exacerbating the condition:

- Decompensated liver cirrhosis or hepatitis
- Significant active bacterial infection

Due to increased risk of hypersensitivity reaction:

- History of atopy and/or anaphylaxis (e.g. drugs, bee stings)
- History of immune or inflammatory conditions e.g. rheumatoid arthritis

It is **not** recommended to give IV iron and a blood transfusion on the same day.

Reference should be made to the summary of product characteristics for full details of relative contraindications.

7. Patient information

If a decision is made to give IV iron, the patient's clinical team should discuss the decision with the patient, including side effects of IV iron. The most common reported side effect is nausea (3.1%). Less than 1% of patients can be expected to experience a hypersensitivity reaction which is mild in the majority; between 0.01 and 0.1% patients will experience an anaphylactoid reaction. Patients may also experience myalgia and should be alerted to the risk of extravasation which can cause pain and tissue discolouration.

Information on anaemia and the NHSBT Iron in your diet leaflets (both available online) should be given to the patient.

Reference should be made to the summary of product characteristics for FCM for full details of side effects.

Alternative strategies for treatment of anaemia and the risks and benefits associated with these should also be discussed with the patient.

8. Prescription of FCM

The prescription of FCM should be written on an intravenous fluid chart.

The individual iron need for repletion using Ferinject is determined based on the patient's body weight and haemoglobin (Hb) level.

Table 1: Determination of the iron need

Hb (g/L)	Patient body weight		
	below 35 kg	35 kg to less than70 kg	70 kg and above
less than 100	500 mg	1500 mg	2000 mg
100 to less than 140	500 mg	1000 mg	1500 mg
greater than or equal to 140	500 mg	500 mg	500 mg

Iron deficiency must be confirmed by laboratory tests.

Calculation and administration of the maximum individual iron dose(s)

Based on the iron need determined above the appropriate dose(s) of Ferinject should be administered taking into consideration the following:

A single Ferinject administration should not exceed

- 15 mg iron/kg body weight (for administration by intravenous injection) or 20 mg iron/kg body weight (for administration by intravenous infusion)
- 1000 mg of iron (20 mL Ferinject)

The maximum recommended cumulative dose of Ferinject is 1000 mg of iron (20 mL Ferinject) per week.

Some patients will require 2 doses of FCM. Depending on factors affecting anticipated red cell improvement (e.g. whether definitive management of the iron deficiency has been undertaken, whether the patient is able to tolerate oral iron) the remaining dose may be administered after 1 week.

In patients expected to have on-going need for intravenous iron therapy a decision may be made to replace 1000mg at regular intervals. This will be at the discretion of the treating clinician.

Oral iron should be stopped for 5 days before and after administration of intravenous iron.

Post-iron repletion assessments

Re-assessment should be performed by the clinician based on the individual patient's condition. The Hb should be re-assessed no earlier than 4 weeks post final Ferinject administration to allow adequate time for erythropoiesis and iron utilisation. (NB ferritin levels

checked before that time will likely be very high, which does not indicate iron overload). In the event the patient requires further iron repletion, the iron need should be recalculated using Table 1 above.

Patients with haemodialysis-dependent chronic kidney disease

A single maximum daily injection dose of 200 mg iron should not be exceeded in haemodialysis-dependent chronic kidney disease patients.

Procedure for administration of IV iron

Please see Medusa for administration details.
FCM may be given as an inpatient or outpatient. It should be given in an area where facilities for resuscitation are present. If the patient attends as an outpatient or day case, observations should be taken before and after administration of the drug, and the patient should remain in the clinical area for 30 minutes following the administration.

The cannula should be flushed with 10 ml 0.9% sodium chloride following administration.

9. Adverse reactions

Procedure for management of anaphylaxis
In the event of anaphylactic reaction follow the Anaphylaxis Policy see Resuscitation Policy Pathway (Treatment pathway).

Hypersensitivity reactions
If the patient experiences any of the following signs, the infusion should be stopped immediately and a full set of observations performed.

- Breathlessness
- Dizziness
- Wheezing
- Cough
- Urticaria
- Back, chest and/or joint pains

If there is **no evidence** of

- hypo/hypertension
- tachycardia
- wheeze
- chest pain
- extravasation

the infusion may be restarted at a slower rate. If symptoms are persistent or any of these features are present, the patient should be assessed medically and treated with intravenous hydrocortisone 100mg and 10 mg intravenous chlorphenamine. If the symptoms are mild and settle quickly, the infusion can be restarted at half the previous rate. If symptoms recur, no further FCM should be given and this must be recorded as an allergy on the patient's record. Progressive symptoms or anaphylaxis must be treated as per the Trust anaphylaxis guideline.

If extravasation occurs the infusion should be stopped, the cannula aspirated and cold packs applied to the site. Extravasation does not usually cause tissue injury but there will be discolouration of the skin at the affected site which may be long-lasting. This is due to iron deposition in the skin and subcutaneous tissues.

Ferric carboxymaltose is known to be commonly associated with hypophosphatemia as per MHRA Drug Safety Update. Please see: Ferric carboxymaltose (Ferinject▼): risk of symptomatic hypophosphataemia leading to osteomalacia and fractures - GOV.UK (www.gov.uk)

Monitoring

Page/ Section of Key Document	Key control:	Checks to be carried out to confirm compliance with the Policy:	How often the check will be carried out:	Responsible for carrying out the check:	Results of check reported to: *(Responsible for also ensuring actions are developed to address any areas of non-compliance)*	Frequency of reporting:
	WHAT?	**HOW?**	**WHEN?**	**WHO?**	**WHERE?**	**WHEN?**
All	Audit of the use of IV iron	Audit	2 yearly	Transfusion practitioners	Trust Transfusion Committee	Quarterly

References

Ferric carboxymaltose: Summary of Product Characteristics.
http://www.medicines.org.uk/emc/medicine/24167/SPC

Contribution List

Guideline written by Dr Suzy Morton UHB and NHSBT

Contribution List

This key document has been circulated to the following individuals for consultation;

Designation
Consultant Haematologist
Consultant Urgent care
Consultant Specialised medicine
Consultants Women's and Children's
Consultant SCSD
Consultant Surgery
Blood Bank Manager
Community IV team lead
Private Hospital lead
Deputy Chief Nurse
Transfusion practitioner

This key document has been circulated to the chair(s) of the following committee's / groups for comments;

Committee
Trust Transfusion Committee
Medicines Safety Committee
Clinical Governance Group

Supporting Document 1 - Equality Impact Assessment Tool

. To be completed by the key document author and included as an appendix to key document when submitted to the appropriate committee for consideration and approval.

Please complete assessment form on next page;

NHS Worcestershire Acute Hospitals NHS Trust

Herefordshire & Worcestershire STP - Equality Impact Assessment (EIA) Form
Please read EIA guidelines when completing this form

Section 1 - Name of Organisation (please tick)

Herefordshire & Worcestershire STP		Herefordshire Council		Herefordshire CCG	
Worcestershire Acute Hospitals NHS Trust	✓	Worcestershire County Council		Worcestershire CCGs	
Worcestershire Health and Care NHS Trust		Wye Valley NHS Trust		Other (please state)	

Name of Lead for Activity	

Details of individuals completing this assessment	**Name**	**Job title**	**e-mail contact**
	Gill Godding	**Lead Transfusion practitioner**	**gilliangodding@nhs.net**
Date assessment completed			

Section 2

Activity being assessed (e.g. policy/procedure, document, service redesign, policy, strategy etc.)	**Title: Clinical Guideline for the Use of Intravenous Iron (Ferric Carboxymaltose, Ferinject®)**			
What is the aim, purpose and/or intended outcomes of this Activity?	To promote patient Blood management within Worcestershire acute hospitals trust			
Who will be affected by the development & implementation of this activity?	✓ ✓ ❑ ❑	Service User Patient Carers Visitors	✓ ❑ ❑ ❑	Staff Communities Other _____
Is this:	✓ Review of an existing activity ❑ New activity ❑ Planning to withdraw or reduce a service, activity or presence?			

What information and evidence have you reviewed to help inform this assessment? (Please name sources, eg demographic information for patients / services / staff groups affected, complaints etc.	NHS BT British Society for haematology guidelines Blood safety and Quality regulations NPSA safer practice notice No:14 MHRA Serious hazards of transfusion Serious adverse blood reactions and events
Summary of engagement or consultation undertaken (e.g. who and how have you engaged with, or why do you believe this is not required)	
Summary of relevant findings	

Section 3

Please consider the potential impact of this activity (during development & implementation) on each of the equality groups outlined below. **Please tick one or more impact box below for each Equality Group and explain your rationale**. Please note it is possible for the potential impact to be both positive and negative within the same equality group and this should be recorded. Remember to consider the impact on e.g. staff, public, patients, carers etc. in these equality groups.

Equality Group	Potential positive impact	Potential neutral impact	Potential negative impact	Please explain your reasons for any potential positive, neutral or negative impact identified
Age		✓		This policy will have neutral impact on all equality groups.
Disability		✓		
Gender Reassignment		✓		
Marriage & Civil Partnerships		✓		
Pregnancy & Maternity		✓		
Race including Traveling Communities		✓		
Religion & Belief		✓		
Sex		✓		
Sexual Orientation		✓		
Other Vulnerable and		✓		This policy will have neutral impact on all equality groups.

Equality Group	Potential positive impact	Potential neutral impact	Potential negative impact	Please explain your reasons for any potential positive, neutral or negative impact identified
Disadvantaged Groups (e.g. carers; care leavers; homeless; Social/Economic deprivation, travelling communities etc.)				
Health Inequalities (any preventable, unfair & unjust differences in health status between groups, populations or individuals that arise from the unequal distribution of social, environmental & economic conditions within societies)		✓		

Section 4

What actions will you take to mitigate any potential negative impacts?	Risk identified	Actions required to reduce / eliminate negative impact	Who will lead on the action?	Timeframe
	None	.		
How will you monitor these actions?				
When will you review this EIA? (e.g in a service redesign, this EIA should be revisited regularly throughout the design & implementation)				

Section 5 - Please read and agree to the following Equality Statement

1. Equality Statement

1.1. All public bodies have a statutory duty under the Equality Act 2010 to set out arrangements to assess and consult on how their policies and functions impact on the 9 protected characteristics: Age; Disability; Gender Reassignment; Marriage & Civil Partnership; Pregnancy & Maternity; Race; Religion & Belief; Sex; Sexual Orientation

1.2. Our Organisations will challenge discrimination, promote equality, respect human rights, and aims to design and implement services, policies and measures that meet the diverse needs of our service, and population, ensuring that none are placed at a disadvantage over others.

1.3. All staff are expected to deliver services and provide services and care in a manner which respects the individuality of service users, patients, carer's etc, and as such treat

them and members of the workforce respectfully, paying due regard to the 9 protected characteristics.

Signature of person completing EIA	Gill Godding
Date signed	28/09/21
Comments:	
Signature of person the Leader Person for this activity	Dr Sangam Hebballi
Date signed	28/09/21
Comments:	none

Supporting Document 2 – Financial Impact Assessment

To be completed by the key document author and attached to key document when submitted to the appropriate committee for consideration and approval.

	Title of document:	**Yes/No**
1.	Does the implementation of this document require any additional Capital resources	no
2.	Does the implementation of this document require additional revenue	no
3.	Does the implementation of this document require additional manpower	no
4.	Does the implementation of this document release any manpower costs through a change in practice	no
5.	Are there additional staff training costs associated with implementing this document which cannot be delivered through current training programmes or allocated training times for staff	no
	Other comments:	none

If the response to any of the above is yes, please complete a business case and which is signed by your Finance Manager and Directorate Manager for consideration by the Accountable Director before progressing to the relevant committee for approval.