Correction of Preoperative Iron Deficiency in Children Undergoing Elective Spinal Fusion.

A Randomised Control Trial of Intravenous Iron vs. Oral Iron Therapy.

Protocol Number: 1

Australia New Zealand Clinical Trails Network: ACTRN12618000917235p

Principal Investigator: Dr Rebecca Munk

Women's and Children's Hospital

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
Title	Improve clarity of terms	
Section 1	Clarification fo Schema	
Section 2	Expansion of study rational	
Section 2	Expanded discussion of risks/benefits	
Section 4, 6	Optimisation of drug dosing	
Section 5	Additional Exclusion Criteria	

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with National Health and Medical Research Council (NHMRC), Therapeutic Goods Administration (TGA) guidelines and International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- Ethics approval from the Women's and Children's Hospital, Adelaide, Australia
- NHRMC Trial Registration
- ANZCA Clinical Trials Network Registration

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Human Ethics Committee for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the Ethics Committee before the changes are implemented to the study. In addition, all changes to the consent form will be Ethics Committee approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

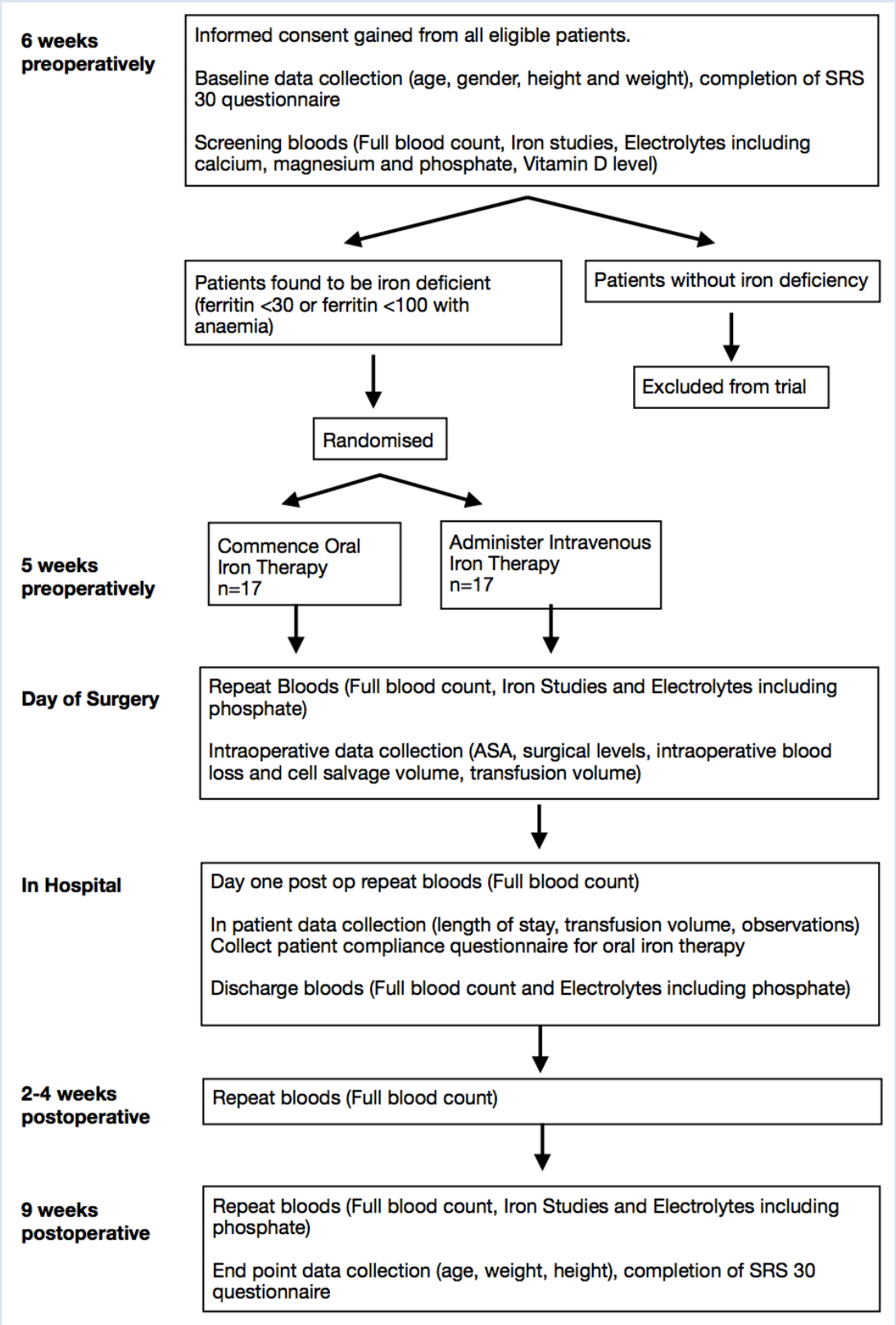
1. PROTOCOL SUMMARY

1.1. SYNOPSIS

Title:	Correction of preoperative iron deficiency in children undergoing elective spinal fusion. A Randomised control trial of intravenous iron (ferric carboxymaltose) vs. oral iron therapy.
Study Description:	This study aims to compare the efficacy of intravenous (IV) carboxymaltose iron infusion compared with oral iron therapy (ferrous fumarate or ferrous sulphate) in the correction of preoperative iron deficiency for paediatric patients presenting for spinal fusion surgery. Preoperative iron replacement using intravenous iron infusions have been demonstrated to be effective in adult patients presenting for major surgery. This research has not been conducted in perioperative paediatric patients. We hope to address the clinical question of whether to prescribe oral iron or intravenous iron therapy when patients are found to be iron deficient prior to imminent surgery (within 6 weeks). We aim to demonstrate the superiority of preoperative IV ferric carboxymaltose iron infusions over oral iron therapy in paediatric surgical patients. We expect to see a decrease in the incidence of severe anaemia at discharge, lower rates of transfusion, improved recovery and faster resolution of post operative anaemia.
Objectives:	Primary Objective: To investigate the incidence of severe anaemia (Hb< 100g/L) after spinal fusion surgery following administration of either intravenous ferric carboxymaltose or oral iron therapy.
Endpoints:	Primary Endpoint: Incidence of Hb <100g/L at time of discharge from hospital or one week post operatively (whichever is shorter). Secondary Endpoints: Incidence of blood transfusion, length of stay, haemoglobin concentration and incidence of anaemia (Hb<120g/L) at 3-5 weeks post operatively, and haemoglobin concentration and incidence of anaemia (Hb <120g/L) and iron studies at 6-12 weeks post operatively, and quality of functional recovery from surgery as measured by the SRS 30.
Study Population:	34 (17 in each arm) ASA 1 and 2 patients under the age of 18 years who present for elective spinal fusion for adolescent idiopathic scoliosis at the Women's and Children's Hospital, Adelaide Australia.
Phase:	Phase III trial - investigating effectiveness of ferric carboxymaltose in a paediatric surgical population.
Description of Sites/ Facilities Enrolling Participants:	This study will be conducted at the Women's and Children's Hospital in Adelaide, Australia. This is a 314 bed tertiary level paediatric hospital.

Description of Study Intervention:	Patients who are found to be iron deficient on preoperative screening will be randomised to receive either oral iron therapy (control) or intravenous (IV) ferric carboxymaltose iron (intervention). The dose of oral iron therapy will be 3-6mg/kg/day of elemental iron in the form of Ferrous Sulphate liquid or Ferrous Fumarate tablets administered for at least 3-5 weeks preoperatively. The dose of IV ferric carboxymaltose will be determined based on patient weight and haemoglobin (see below) this will be administered 3-5 weeks preoperatively.
Study Duration:	Estimated 36 months.
Participant Duration:	5 months

1.2. SCHEMA


6 weeks preoperatively
Informed consent gained from all eligible patients.
Baseline data collection (age, gender, height and weight), completion of SRS 30 questionnaire
Screening bloods (Full blood count, Iron studies, Electrolytes including calcium, magnesium and phosphate, Vitamin D level)
Patients found to be iron deficient (ferritin <30 or ferritin <100 with anaemia)
Patients without iron deficiency
Excluded from trial
Randomised
5 weeks preoperatively
Commence Oral Iron Therapy n=17
Administer Intravenous Iron Therapy n=17
Day of Surgery
Repeat Bloods (Full blood count, Iron Studies and Electrolytes including phosphate)
Intraoperative data collection (ASA, surgical levels, intraoperative blood loss and cell salvage volume, transfusion volume)
In Hospital
Day one post op repeat bloods (Full blood count)
In patient data collection (length of stay, transfusion volume, observations)
Collect patient compliance questionnaire for oral iron therapy
Discharge bloods (Full blood count and Electrolytes including phosphate)
2-4 weeks postoperative
Repeat bloods (Full blood count)
9 weeks postoperative
Repeat bloods (Full blood count, Iron Studies and Electrolytes including phosphate)
End point data collection (age, weight, height), completion of SRS 30 questionnaire

1.3. SCHEDULE OF ACTIVITIES (SOA)

Procedures	Enrolment/ Visit 1, Day -42 (+/- 14 days)	Group identification, Day -35 (+/- 14 days)	Study Visit 2, Day -28 (+/- 7 days)	Day Before Surgery Day -1	Day of Surgery Day 0	In hospital Days 1-5	Discharge Day 5 (+/- 2days)	Study Visit 3 Day 21 (+/-7 days)	Final Study Visit 4 Day 63 (+/-14 days))
Informed consent	X								
Demographics	X								
Medical history	X								
Baseline screening bloods	X								
Interpretation of bloods		X							
Randomization		X							
Administer study intervention - Intravenous iron therapy (IV arm only)			X						
Administer study intervention - Oral iron therapy (Oral arm only)		X————————————————X							
Vital signs	X		X		X	X	X		X
Height	X								X
Weight	X								X
SRS 30 Questionnaire	X								X
Full Blood Exam	X				X	X	X	X	X
Iron Studies	X				X				X
Electrolytes (“ELC”)	X				X				X
Vitamin D Level	X								
Surgical data - ASA, spinal levels, blood loss, cell salvage volume					X				
Transfusion volume					X	X	X		
Oral Iron Compliance Questionnaire						X			
Adverse event review and evaluation	X	X----------X							X
Data Entry	X	X	X		X	X	X	X	X

2. INTRODUCTION

2.1. STUDY RATIONALE

Posterior spinal fusion is considered major elective surgery which is associated with significant intra operative blood loss and post operative anaemia. A retrospective audit at our institution in 2016 has demonstrated that a significant number of patients were presenting for surgery with anaemia (Hb <120g/L) and over 60% of all spinal fusion patients were being discharged from hospital with severe anaemia (Hb <100g/L).

While preoperative optimisation of red cell mass is considered standard practice in the adult perioperative setting[1] there have been few studies to assess its application in paediatric surgery. At the present time there is little preoperative screening in place for systemically well paediatric patients. Until recently patients at our institution were not undergoing routine screening bloods until the night before surgery preventing any preoperative treatment of iron deficiency or anaemia. The perioperative patient who is found to be iron deficient presents a unique challenge to surgeons and anaesthetists who are faced with balancing the desire to provide the best preoperative optimisation without delaying surgery whenever possible. Therefore this study seeks to answer the valuable question of how to best optimise our patient's iron stores in the limited pre-operative period. We aim to determine whether oral iron or intravenous iron is more effective where there is only 4-6 weeks available to achieve adequate replacement of the patients iron stores.

This study aims to assess the efficacy of preoperative screening and treatment of iron deficiency with either oral iron (ferrous sulphate liquid or ferrous fumarate tablets) or intravenous ferric carboxymaltose iron therapy in the paediatric perioperative patient.

2.2. BACKGROUND

Posterior spinal fusion for correction of adolescent idiopathic scoliosis is a major elective surgery which is associated with significant intra-operative blood loss and postoperative anaemia. The National Blood Authority describes three pillars of perioperative blood management (preoperative optimisation, minimisation of intra-operative blood loss and tolerance of postoperative anaemia) which, when utilised appropriately aim to reduce the burden of perioperative blood transfusion and postoperative anaemia.[1]

Over the last 15 years there have been significant advances in surgical and anaesthetic techniques which, along with the use of intra-operative cell salvage, have drastically reduced the requirement for perioperative blood transfusion. However, these paediatric patients are still vulnerable to high volumes of intra-operative blood loss resulting in significant postoperative anaemia.

In a recent (2016) retrospective audit at our hospital we have found that 18% of patients presenting for posterior spinal fusion are anaemic (Hb <120g/L)[1,2] preoperatively with up to 30% demonstrating blood films consistent with iron deficiency. These patients had an average intra-operative blood loss of over 500mL. At discharge 68% of patients were found to have severe anaemia (Hb <100g/L).[2] Iron deficiency is the largest contributing factor to anaemia in all paediatric age groups.[2-5] This audit demonstrated a need for further study into the effects of thorough preoperative screening and optimisation of iron and red cell stores in the paediatric surgical population.

There are two options for replacement of iron stores to correct iron deficiency. The traditional first line therapy is oral iron supplementation followed by intravenous iron therapy in those patients who fail to respond to oral iron. However, oral iron therapy takes time to work and is often poorly tolerated due to gastrointestinal side effects and for these reasons is commonly felt to not be a viable option in the preoperative patient who requires optimisation in a matter of weeks rather than months. Traditional intravenous iron preparations required up to 6 hours for safe infusion time which was a significant deterrent for many paediatric patients. However, with the new formulation of IV ferric carboxymaltose only requiring 15 minutes of infusion time and an improved risk profile, the balance of oral vs IV iron therapy is due to be revisited. Intravenous ferric carboxymaltose formulation has been demonstrated to be safe and effective in the treatment of iron deficiency due to inflammatory bowel disease in paediatric patients[6-13] but its efficacy has not been trialed in the perioperative paediatric population.

This project aims to improve perioperative blood management through optimising preoperative haemoglobin and iron stores. There is significant data supporting the use of preoperative iron infusions in adult surgical patients,[14-22] however this research has not been conducted in paediatric patients presenting for major surgery. This trial aims to assess the efficacy of preoperative intravenous (IV) ferric carboxymaltose iron infusion compared with traditional treatment of iron deficiency with oral iron therapy (ferrous sulphate liquid or ferrous fumarate tablets). If IV ferric carboxymaltose is found to be superior to oral iron therapy then it maybe that the additional cost and risk of the IV formulation can be justified for the management of preoperative iron deficiency in paediatric patients. If it is found that oral iron is as effective as IV iron then this information will help to change medical opinion of the role of oral iron in the preoperative setting.

We expect that by adequately correcting iron deficiency and thus improving the patients preoperative haemoglobin and iron stores we will see a decreased rate of severe anaemia at discharge. We also hope to see an improved recovery from surgery as is demonstrated in a decreased rate of blood transfusion, shorter length of stay, improved SRS 30 (Scoliosis Patient Questionnaire Version 30), and decreased incidence of anaemia and iron deficiency at 6-12 weeks post operatively.

2.3. RISK/BENEFIT ASSESSMENT

2.3.1. KNOWN POTENTIAL RISKS

IV Ferric Carboxymaltose
As discussed in the NPS Medicinewise RADAR “Ferric carboxymaltose (Ferinject) for iron-deficiency anaemia” (*https://www.nps.org.au/radar/articles/ferric-carboxymaltose-ferinject-for-iron-deficiency-anaemia*)

Pooled safety information for ferric carboy maltose (FCM) comprising the total short-term phase II/III database of 20 trials has recently been published, and is the largest database reported thus far for any IV iron formulation.

In this set of patients administered FCM (n = 5799), treatment-related side effects that occurred in more than 1% of the group included:

- nausea (3.1%),
- hypophosphataemia (1.9%),
    - Hypophosphataemia occurs but is transient

    - An increased risk of transient asymptomatic hypophosphataemia has been observed in trials of FCM and appears to occur more often in association with FCM than with other iron preparations.
    - Severe cases with clinical sequelae are rare. Patients at increased risk of this adverse event include those with a concomitant disorder of phosphate homeostasis such as hyperparathyroidism or vitamin D deficiency.
    - In our study we will exclude any patients who are found to have hypophosphateamia on initial screening and we will monitor phosphate levels during the followup period. We will we will screen for vitamin D deficiency and hyperparathyroidism by measuring the vitamin D levels and serum calcium levels and any patient with elevated calcium will be referred for further testing of parathyroid hormone levels.
- injection-site reactions(1.6%),
- headache (1.4%),
- hypertension (1.3%),
    - In recently completed FCM trials, protocol-defined hypertensive events have been reported to occur more frequently among FCM-treated patients compared with those receiving other iron preparations (oral and IV). Most of these events occurred during the observation period following iron injection/infusion.
    - Monitor patients closely, especially when large single doses > 200 mg iron are administered.
- dizziness (1.2%).
- anaphylaxis
    - Cardiopulmonary equipment must be available for managing anaphylaxis before administering FCM
    - All IV iron preparations carry a small risk of causing life-threatening hypersensitivity reactions.
    - In the pooled database of short-term phase II/III trials the rate of hypersensitivity or allergic reactions potentially due to FCM treatment was 0.9% (n = 51/5799) for FCM compared with 0.8% (n = 42/5272) for all comparators and 1.5% for other IV iron preparations (n = 37/2439).
    - Patients should be monitored during and immediately after infusion.
- Risk of permanent skin tattooing if FCM is injected into a dislodged cannula.
    - FCM should be administer either by slow manual push or a free hanging bag. Use of syringe drivers and pumps increases the risk of an unrecognised tissued cannula.

As per the manufactures guidelines ferric carboxymaltose is currently recommended for patients 14 year of age and older. However multiple studies have evaluated it's use in the paediatric population. It has been demonstrated to be safe and effective in the treatment of iron deficiency due to inflammatory bowel disease in paediatric patients [6-13] but its efficacy has not been trialed in the perioperative paediatric population. There are no known additional risks in children as compared to adults but there maybe further unknown risks.

<u>Oral Iron supplementation</u>
As discussed in the Australian prescriber[5]

- "Oral iron replacement is the most appropriate first-line treatment in the majority of patients. Its efficacy can be limited by poor patient compliance due to the high rate of gastrointestinal adverse effects and the prolonged treatment course needed to replenish body iron stores."

From Australian medicines handbook (AMH)[23] online the adverse effects of oral iron are:

- abdominal pain,
- nausea,
- vomiting,
- constipation,
- diarrhoea (all dose-related),
- Iron may cause your stools to turn black, but this is not harmful.
- Additional for oral liquid: temporary black discolouration of teeth

Very rarely, oral iron preparations can cause severe adverse reactions. Seek immediate medical attention if you notice any of the following symptoms:

- allergic reactions (rash; hives; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue);
- black, tarry stools;
- blood or streaks of blood in the stool;
- fever;
- Vomiting with continuing sharp stomach pain.

This is not a complete list of all possible side effects. Others may occur in some people and there may be some side effects not yet known.

2.3.2. KNOWN POTENTIAL BENEFITS

IV Ferric Carboxymaltose

As discussed in the NPS Medicinewise RADAR[24] "Ferric carboxymaltose (Ferinject) for iron-deficiency anaemia" (*https://www.nps.org.au/radar/articles/ferric-carboxymaltose-ferinject-for-iron-deficiency-anaemia*)

The efficacy of FCM for correcting IDA has been evaluated across a range of clinical conditions including inflammatory bowel disease, chronic kidney disease, chronic heart failure, menorrhagia and postpartum anaemia.

- Haemoglobin response similar to that with iron sucrose, but with fewer doses
    - Results from prospective and retrospective trials have confirmed that large doses of FCM given in fewer injections can increase Hb levels with efficacy comparable to that of multiple small dose injections of iron sucrose.
    - In the 8-week REPAIR-IDA trial, involving IDA patients with non-dialysis-dependent CKD, two doses of FCM (750 mg/dose, n = 1276) were shown to be non-inferior to a typical dosing strategy of iron sucrose (five or fewer infusions of 200 mg, n = 1285).
    - More people treated with FCM had a sustained Hb increase of ≥ 10 g/L from baseline to study end than for those given iron sucrose (48.6% vs 41.0%, 95% CI 3.6% to 11.6%).
- Mean increases in serum ferritin and transferrin saturation were also significantly greater in the FCM group compared with the iron sucrose group. The mean total iron dose received over the treatment phase was 1464 ± 158 mg in the FCM group and 963 ± 138 mg in the iron sucrose group.
    - Similarly, among patients with IDA and associated IBD, three or fewer 500–1000 mg FCM infusions showed improved efficacy compared with iron sucrose (up to 11 infusions of 200 mg iron) in the 12-week FERGIcor trial.
    - A small difference in mean total dose was reported for these treatment groups; 1377 ± 381 mg (FCM) and 1160 ± 316 mg (iron sucrose).
    - At the end of the study, 66% of the FCM cohort had experienced a ≥ 20 g/L Hb increase compared with 54% of the iron sucrose arm (p = 0.004).

    - More people in the FCM treatment group experienced correction of anaemia compared with the iron sucrose group at study end (73% vs 62%, respectively, p = 0.015).
    - The simpler FCM dosing regimen was also associated with greater patient compliance compared with iron sucrose (p < 0.001).
- Improves anaemia as well as, or better than, oral iron and standard medical care
    - The efficacy of FCM for the treatment of iron-deficiency anaemia was compared with oral iron (ferrous sulphate) in several randomised open-label trials.
    - Overall, FCM (≤ 1000 mg per infusion) was at least as effective, or more effective, than oral iron (ferrous sulphate 325 mg three times daily or 100 mg twice daily) at correcting haemoglobin, ferritin and transferrin saturation levels. Perhaps not surprisingly, haemoglobin increases were more rapid with FCM than with oral iron therapy.
- The comparative effectiveness of FCM in treating iron-deficiency anaemia versus standard medical care (including IV iron formulations) has also been investigated in several randomised controlled trials.
    - Clinically meaningful improvements in haemoglobin and iron indices have been observed compared with standard medical care in patients with IDA associated with conditions such as CKD, menorrhagia, IBD and after post-bariatric surgery or delivery.
- Clinical equivalence with IV iron polymaltose is not known
    - To date, there have been no head-to-head comparisons of FCM with iron polymaltose, which is FDM's main IV iron formulation comparator in Australia.
    - Indirect comparisons between FCM and iron polymaltose, based on their efficacy relative to oral iron, are also not possible due to marked heterogeneity in patients and outcomes.

Oral Ferrous Fumarate

Oral iron therapy has been the mainstay of treatment for iron deficiency in children for many years. It is safe and when taken over several months is often effective at correcting iron deficiency with or without anaemia. It's efficacy is dependant on compliance and absorbance both of which can be affected my common side effects but it is generally well tolerated in the paediatric population.[3] It has the added benefit of being cheap and easy to administer.

2.3.3. ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Preoperative optimisation of iron stores is an important part of minimising the risk of exposing our patients to a blood transfusion and reducing the burden of post operative anaemia. At the present time there is little preoperative screening in place for systemically well paediatric patients. Until recently patients were not undergoing routine screening bloods until the night before surgery preventing any preoperative treatment of iron deficiency or anaemia. In paediatric medicine oral iron is commonly used as first line therapy to replenish iron stores in those patients who are found to be iron deficient. Oral iron is cheap, relatively safe and easy to administer to children. However, oral iron therapy is often poorly tolerated due to side effects resulting in poor compliance and it is often ineffective even when taken regularly. This study aims to demonstrate that IV ferric carboxymaltose is superior to oral iron therapy in the correction of preoperative iron deficiency and prevention of severe post operative anaemia.

We feel the risks involved in this study are outweighed by the benefits to future patients that can be achieved through effective preoperative iron replacement. If IV ferric carboxymaltose is found to be superior to oral iron therapy then it maybe that the additional cost and risk of the IV formulation can be justified for the management of preoperative iron deficiency in

paediatric patients. If IV ferric carboxymaltose is not found to be superior to oral iron supplementation then this trial will support the continued use of oral iron and it may be possible to avoid the unnecessary cost and inconvenience of an intravenous iron infusion.

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To compare the efficacy of two forms of iron replacement therapy in the prevention of severe anaemia at discharge from hospital.	The primary endpoint is the incidence of severe anaemia (haemoglobin <100g/L) the time of discharge from hospital (or one week postoperatively, whichever one is sooner).	Severe post operative anaemia is a clinically relevant method to measure the impact of preoperative iron therapy. It is simple to measure and is not subjective to bias.
Secondary		

To compare the postoperative effect of preoperative correction of iron deficiency with two different forms of iron replacement.	- Incidence of blood transfusion
	- Length of stay
	- 3-5 weeks postoperatively
	  - Haemoglobin concentration
	  - Incidence of anaemia (Hb<120g/L)
	- 6-12 weeks postoperatively
	  - Haemoglobin concentration
	  - Incidence of anaemia (Hb <120g/L)
	  - Iron studies
	  - Quality of functional recovery from surgery as measured by the SRS 30.
		These endpoints are clinically relevant markers of recovery from surgery. Post operative recovery of haemoglobin concentration is a a clinically important effect of adequate iron stores.

4. STUDY DESIGN

4.1. OVERALL DESIGN

We will be conducting a single site, randomised control trail, open label, superiority design phase III trial. The null hypothesis states that there is no difference between oral and IV iron therapy in the incidence of severe anaemia at the time of discharge following elective spinal fusion surgery.

Bias will be minimised through computer generated block randomisation, allocation concealment in opaque envelops, collecting objective data (haemoglobin and iron studies), blinding of outcome assessors and statistician.

There will be two study groups; those randomised to oral iron therapy (control group), and those randomised to IV ferric carboxymaltose (treatment group). There will be 17 patients

randomised to both the control and treatment arms. Patients will be consented and screened 6 weeks prior to their surgery and follow up will conclude at 12 weeks post operatively.

4.2. SCIENTIFIC RATIONALE FOR STUDY DESIGN

We have selected a randomised control trial comparing the efficacy of oral and IV preoperative iron therapy in order to determine if IV therapy is superior to oral therapy. At the present time oral iron is commonly used as first line therapy to replenish iron stores in those patients who are found to be iron deficient. Oral iron is cheap, relatively safe and easy to administer to children. However, oral iron therapy requires time to be effective and is often poorly tolerated due to side effects resulting in poor compliance. This study aims to demonstrate that IV ferric carboxymaltose is superior to oral iron therapy in the correction of preoperative iron deficiency and prevention of severe post operative anaemia.

If IV ferric carboxymaltose is found to be superior to oral iron therapy then it maybe that the additional cost and risk of the IV formulation can be justified for the management of preoperative iron deficiency in paediatric patients.

4.3. JUSTIFICATION FOR DOSE

Control Group:

- In accordance with current AMH guidelines [23] patients randomised to the control arm will be prescribed daily oral iron at a dose of (3-6mg/kg) elemental iron up to 200mg/day maximum.

Treatment Group:

- Those patients randomised to the treatment arm will be prescribed IV ferric carboxymaltose. The appropriate dose will be calculated using the Ganzoni equation (see section 6.1.2) which is a widely accepted method to calculate the patient's total iron deficit.[5]

4.4. END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all investigations of the study including the last visit shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5. STUDY POPULATION

5.1. INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Age <18 years
4. Diagnosed with adolescent idiopathic scoliosis

5. Requiring posterior spinal fusion surgery of greater than or equal to 6 vertebral levels or other spinal fusion surgery associated with significant blood loss as determined by the surgical team
6. Ability to take oral medication and be willing to adhere to the oral iron regimen
7. Willingness to attend hospital to undergo intravenous cannulation as required for the intravenous iron regimen
8. Agreement to adhere to Lifestyle Considerations (see section 5.3) throughout study duration

5.2. EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Any patient who is found to not be iron deficient on preoperative screening
2. Any patient who is found to have hypophosphataemia, hyperparathyroidism or low Vitamin D levels on preoperative screening
3. Current use of iron supplements
4. Pregnancy or lactation
5. Known allergic reactions to components of the IV ferric carboxymaltose or oral iron supplements
6. Significant medical co-morbidity such as neuromuscular disease, severe anaemia, cardiac disease, significant respiratory disease or impairment
7. Haematological contraindication to iron therapy such as sickle cell disease or thalassaemia
8. Significant needle phobia

5.3. LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Refrain from consumption of multivitamins or oral iron supplementation other than that prescribed in the trial from the time of enrolment until after the final investigations (12 weeks post operatively)
- Take iron supplements at least 2 hours after or 30 minutes before a meal.
- Abstain from tannin-containing products (e.g., coffee, tea, cola drinks, and chocolate) and antacids for 2 hours before taking their oral iron supplementation.

5.4. SCREEN FAILURES

Not Applicable

5.5. STRATEGIES FOR RECRUITMENT AND RETENTION

Patients routinely present to the preoperative spinal clinic at the Women's and Children's Hospital 6 weeks prior to their planned surgery date. All patients will be screened to determine their eligibility to enrol in this trial and those who meet the inclusion criteria will be approached and consented by a member of the spinal surgery team. Parents will be given information on the role of iron stores in the perioperative period and the treatment options currently available for correction of iron deficiency (see patient information sheet). They will be given an opportunity ask further questions about their participation in the study prior to signing informed consent.

As this trial focuses on the efficacy of iron therapy in the paediatric surgical patient we will be targeting young people under the age of 18 years. Information will be provided to and in addition to parental consent we will seek assent/consent from those children who are able provide such.

6. STUDY INTERVENTION

6.1. STUDY INTERVENTION(S) ADMINISTRATION

6.1.1. STUDY INTERVENTION DESCRIPTION

Intravenous Ferric Carboxymaltose (Ferinject)
Ferinject solution for injection/infusion is a colloidal solution of the iron complex ferric carboxymaltose.

The complex is designed to provide, in a controlled way, utilisable iron for the iron transport and storage proteins in the body (transferrin and ferritin, respectively). Red Cell utilisation of ^{59}Fe from radio-labelled Feinject ranged from 91% to 99% in subjects with iron deficiency and 61% to 84% in subjects with renal anaemia at 24 days post-dose. Ferinject treatment of patients with iron deficiency anaemia results in an increase in reticulocyte count and serum ferritin levels to within normal ranges.

Oral Iron Supplements
In this study 2 forms of oral iron supplements are available

- Ferro-tab oral iron supplements contain 200mg of Ferrous Fumarate (67.5mg of elemental iron) in a film coated tablet. Ferro-Tab tablets also contain croscarmeliose sodium, glycerol, macrogel 400 and macrocell 6000, microcrystalline cellulose, sodium laurel sulphate, sodium starch glycol late Type A, magnesium stearate, hypromellose, talc, titanium dioxide and iron oxides (black, red and yellow).
- Ferro-liquid contain ferrous sulfate 150 mg (= elemental iron 30 mg)/5 mL. Ferro-liquid also contains the following excipients: Sucrose, sodium bisulfite, propyl hydroxybenzoate, sorbitol.

6.1.2. DOSING AND ADMINISTRATION

IV Ferric Carboxymaltose
The following dosing guidelines are per the product information guide produced by the manufactures of ferric carboxymaltose.[25]

Using the Ganzoni Formula to estimate total iron deficit:

Total iron dose (mg iron) = Weight(kg) x (Target Hb* - Actual Hb)(g/L) x 0.24 + Iron for stores**

Where:
* Target Hb <35kg = 130g/L
>35kg = 150g/L

** Iron for stores <35kg = 15mg/kg
>35kg = 500mg

The above calculated dose will be administered in the Medical Day Unit according to the CMI and manufactures guidelines.

A single ferric carboxymaltose administration should not exceed 1000mg or 20mg/kg as per the manufactures recommendation. It is advised that those patients requiring larger doses receive their iron replacement in two divided doses administered 1 week apart.

Oral Iron Supplements

Dosing is based on the AMH Children's Dosing Companion Guidelines:

- 1 month – 18 years, oral 3–6 mg/kg (maximum 200 mg) daily of elemental iron

In consultation with the haematology department at the Women's and Children's Hospital the following doses of oral iron are suggested:

1. To increase tolerability and patient compliance, the iron supplementation will be started at half the recommended dose (3mg/kg/day) for 5 days.
2. Once drug tolerance is established (Day 6) the patient are will be instructed to increase to a full dose (6mg/kg/day – maximum 200mg elemental iron) to be taken until the day before surgery.

The following Dose banding has been done to achieve supplementation within 90-110% of the intended dose:

- **Prescribing of oral ferrous sulfate liquid for 12 hourly dosing:**

Ferrous sulfate 6mg/mL elemental iron – 12 hourly dosing		
Patient weight (kg)	Days 1-5 (dose in mL)	Day 6 –until surgery (dose in mL)
10	2.5	5
11	3	5
12	3	6
13	3	6
14	3.5	7
15	3.5	7
16	4	8
17	4	8
18	4.5	9
19	4.5	9
20	5	10
21	5	10
22	5.5	11
23	5.5	11
24	6	12
25	6	12
26	6.5	13

Ferrous sulfate 6mg/mL elemental iron - 12 hourly dosing		
Patient weight (kg)	Days 1-5 (dose in mL)	Day 6 –until surgery (dose in mL)
27	6.5	13
28	7	14
29	7	14
30	7.5	15
31	7.5	15
32 and above	8	16

- **Prescribing of oral ferrous sulfate liquid for 8 hourly dosing:**
  - In patients who experience gastrointestinal side effects (nausea, abdominal pain) it may be beneficial to administer the dose in 3 divided doses (8 hourly).

Ferrous sulfate 6mg/mL elemental iron - 8 hourly dosing		
Patient weight (kg)	Days 1-5 (dose in mL)	Day 6 –until surgery (dose in mL)
10	1.5	3.5
11	2	3.5
12	2	4
13	2	4
14	2.5	5
15	2.5	5
16	2.5	5
17	3	6
18	3	6
19	3	6
20	3.5	7
21	3.5	7
22	3.5	7
23	4	8
24	4	8
25	4	8
26	4.5	9
27	4.5	9

Ferrous sulfate 6mg/mL elemental iron - 8 hourly dosing		
Patient weight (kg)	Days 1-5 (dose in mL)	Day 6 –until surgery (dose in mL)
28	4.5	9
29	5	10
30	5	10
31	5	10
32	5	10
33	5.5	11
34 and above	5.5	11

- **Prescribing of oral ferrous fumarate (not to be used in children <20kg)**

Ferrous Fumarate 67.5mg/tab elemental iron		
Patient weight (kg)	Days 1-5	Day 6 –until surgery
20-27	1 tablet daily	1 tablet twice daily
27-32	1 tablet daily	1 tablet three times daily
33 and above	1 tablet twice daily	1 tablet three times daily

6.2. PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1. ACQUISITION AND ACCOUNTABILITY

Oral iron will be dispensed from the Women's and Children's Hospital Pharmacy directly to the patient. We will ask that the patients return any unused tablets or liquid for compliance monitoring.

IV ferric carboxymaltose will be dispensed from the Women's and Children's Hospital Pharmacy to the medical day unit who will prepare and administer the drug in line with the Guidelines for Paediatric Intravenous Drug Administration.

The cost of both preparations will be covered by this project's funding and there will be no out-of-pocket costs for participants in either study arm.

6.2.2. FORMULATION, APPEARANCE, PACKAGING, AND LABELLING

Both oral and intravenous iron formulations will be kept in their original packaging with labelling intact.

6.2.3. PRODUCT STORAGE AND STABILITY

Oral Iron supplementations (ferrous sulphate liquid and ferrous fumarate tablets) should be stored in a cool, dry place where temperatures stays below 25ºC. It should be stored out of the reach of children and animals.

Intravenous ferric carboxymaltose should be stored below 30ºC, it should not be refrigerated or frozen. Each vial is single use and any remainder drug should be discarded.

6.2.4. PREPARATION

Oral iron therapy requires no preparation

IV ferric carboxymaltose should be diluted with Sodium Chloride 0.9% as per the following table as per the manufactures guidelines.[25]

Ferinject Volume	Iron Dose	Sodium Chloride 0.9%	Minimum Administration Time
2-4mL	100-200mg	50mL	3 minutes
4-10mL	200-500mg	100mL	6 minutes
10-20mL	500-1000mg	250mL	15 minutes

6.3. MEASURES TO MINIMISE BIAS: RANDOMISATION AND BLINDING

We intend to minimise bias through randomisation using a computer generated randomisation sequence stored in consecutive numbered opaque envelopes. Randomisation will be revealed to the treating team upon opening of the envelope and assignment of the patient to either the control arm (oral iron therapy) or the treatment arm (IV ferric carboxymaltose).

As intravenous cannulation can be a stressful experience for some children and their families we feel it would be unethical to blind the subjects and administer a placebo injection to the patients in the oral therapy arm. Therefore the patients will be unblinded as to their allocation to either the treatment or control arms. We feel this will not significantly bias our results as we will be collecting objective data points (haemoglobin and iron studies).

We will attempt to minimise bias by blinding the outcome assessors and our statistician.

6.4. STUDY INTERVENTION COMPLIANCE

Compliance with the control arm (oral iron therapy) will be assessed two ways.

1. We will ask patients/parents to return any unused iron tablets/liquid to the orthopaedic nurse consultant who will count the remaining tablets/liquid. This will be used to estimate patient medication compliance.
2. Patients/parents will be presented with a compliance questionnaire to survey their overall usage and detail any complaints or side effects. (see Appendix E)

Compliance to the treatment arm (IV ferric carboxymaltose) will be clearly documented in the patient record of attendance at the medical day unit and the patient drug chart.

6.5. CONCOMITANT THERAPY

Not applicable

6.5.1. RESCUE MEDICINE

Not applicable

7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from oral or IV iron does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline iron studies or haemoglobin) after enrolment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Oral iron compliance questionnaire
- Documentation of side effects or adverse reactions
- Repeat haemoglobin and iron studies to advise patient of need to continue iron therapy outside of the study

7.2. PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance (refusal to undergo IV iron therapy)
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognised) that precludes further study participation
- Participant unable to receive oral or IV iron therapy at least 3 weeks preoperatively
- A patient will be discontinued from the study if they do not proceed with surgery during the required timeline from commencing iron therapy.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Iron Deficiency Case Report Form (CRF). Subjects who sign the informed consent form and are randomised but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomised and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

7.3. LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 3 consecutive scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The clinic will attempt to contact the participant and reschedule the missed visit within 1 week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. EFFICACY ASSESSMENTS

Enrolment visit - 6 weeks (+/-2 weeks) preoperative

The following will be collected:

- Informed Consent
- Full Medical History
- Collection of baseline demographics (age, gender)
- Height and weight
- SRS 30 Questionnaire
- Blood for:
    - Full Blood Exam
    - Iron Studies
    - Electrolytes including Calcium, Magnesium and Phosphate (Order "ELC")
    - Vitamin D Level

Group Identification - 5 weeks (+/-2 weeks) preoperative

The investigators will review the results of the screening blood tests (Full Blood Exam and Iron Studies) and determine whether the patient requires preoperative iron therapy.

- Those patients who have normal iron studies will be informed and require no further intervention until their day of surgery
- Those patients who qualify for preoperative iron therapy will be randomised to either the oral or intravenous group.
    - Oral Iron (standard treatment arm)
        - Patients/parents will be informed of their results and group allocation and instructed to collect the oral iron supplements from the Women's and Children's Hospital Pharmacy.
        - Included in will their tablets will be a prescription for weight appropriate dosing, a list of potential side effects and instructions on how to manage frequent side effects as well as a contact number of one of the investigators.
    - Intravenous Iron (treatment arm)
        - Patients/parents will be informed of their results and group allocation and an acceptable appointment time will be found for the patient to present

to the Medical Day unit at the Women's and Children's Hospital to undergo the intravenous iron infusion.
- At their appointment they will be provided with a list of potential side effects and a contact number of one the investigators.

Study Visit - 4 weeks (+/-1 week) preoperative

The patients will undergo their allocation treatment during this time

- Oral Iron
  - Patients will take their oral iron supplementation as prescribed starting from 3-5 weeks preoperatively until the day before surgery
- Intravenous Iron
  - Patients will appointments at the Medical Day unit (MDU) at the Women's and Children's Hospital will be made 3-5 weeks preoperatively.
  - Upon arrival at MDU patients will have a baseline set of vitals collected, they will undergo intravenous cannulation by the orthopaedic resident medical officer, and then receive the intravenous ferric carboxymaltose as described previously.
  - Following the infusion patients will remain in MDU for 45minutes where their vitals will be regularly monitored.

Day of Surgery

Patients will present to the Women's and Children's hospital in the usual fashion

- They will then undergo routine measure of vital signs
- Following intravenous cannulation by the attending anaesthetist blood will be collected for:
  - Full Blood Exam
  - Iron Studies
  - Electrolytes including Calcium, Magnesium and Phosphate ("ELC")
- Surgical and Anaesthetic data will be collected including:
  - ASA status
  - Estimated Blood Loss
  - Cell Salvage Volume returned to patient
  - Duration of surgery
  - Number of spinal levels fused
  - Transfusion volume and product type

In hospital - Day 1 Postoperative

Patients will undergo routine:

- Measure of vital signs
- Collection of blood for Full Blood Exam
- Documentation of any transfusion

Prior to discharge - Day 5 (+/-2 days) Postoperative

Patients will undergo routine:

- Measure of vital signs
- Collection of blood for Full Blood Exam

- This will occur one day prior to discharge or at 7 days postoperatively (whichever is sooner)
- Documentation of any transfusion
- Patients will be asked to complete their oral iron therapy compliance questionnaire

Wound review visit 3 weeks (+/-1week) Postoperatively

Patients will present to Women's and Children's hospital for routine wound review by their surgeon. At this appointment we will collect:

- Collection of blood for Full Blood Exam

Final Study visit 12 weeks (+/- 4 weeks) Postoperatively

Patients will present to Women's and Children's hospital for routine follow up by their surgeon. At this appointment we will:

- Measure vitals
- Document height and weight
- Collection blood for Full Blood Exam, Iron Studies and Electrolytes including Calcium, Magnesium and Phosphate ("ELC")
- Collect follow up SRS 30 Questionnaire

8.2. SAFETY AND OTHER ASSESSMENTS

Intravenous Carboxymaltose

Patients presenting for their infusion of IV ferric carboxymaltose will have a baseline set of vital signs recored by the MDU nurses. They will continue to have their vitals monitored during and for 45 minutes following the infusion.

Any vitals outside the acceptable range (according to the age appropriate RDR chart) will result in the infusion being stopped and the orthopaedic resident medical officer or medical emergency team being contacted for further advise. Any evidence or report of difficulties breathing or a developing rash will result in the immediate discontinuation of the infusion and the medical emergency team will be called to review the patient.

Patients and their parents will be provided with a contact number for one of the investigators and encouraged to report any adverse events/side effects.

All adverse events will be recorded on the patient data sheet and immediately feedback to the investigators.

Oral Iron Therapy

When patients or their parents collect their oral iron tablets they will be given an information sheet containing potential side effects as well as advise on how to manage these. These forms will contain the contact details of one of the investigators and patients are encouraged to report any adverse events.

8.3. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1. DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

8.3.2. DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or treating clinician, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalisation or prolongation of existing hospitalisation, or a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered serious when, based upon appropriate medical judgment, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dycrasias or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse.

8.3.3. CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1. SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2. RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate aetiology has been established.

8.3.3.3. EXPECTEDNESS

The principle investigators will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or

frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4. TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate data collection form. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilisation of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterised as intermittent require documentation of onset and duration of each episode.

Investigators will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of iron therapy. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilisation.

8.3.5. ADVERSE EVENT REPORTING

All adverse events will be recorded and collated by the investigators. The data will be collected from each participants data sheet that is completed at each of their study visits. The incidence of expected adverse events will be reported in the published data along with the occurrence and incidence of unexpected adverse events.

8.3.6. SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the Women's and Children's Health Network Human Research Ethics Committee (HREC) any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the TGA.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the therapeutic substances committee and will be provided as soon as possible.

8.3.7. REPORTING EVENTS TO PARTICIPANTS

Participants will be invited to inquire about the results of the trial and incidence and nature of adverse effects after the completion of the trial.

8.3.8. EVENTS OF SPECIAL INTEREST

Not applicable

8.3.9. REPORTING OF PREGNANCY

If patients are found to be pregnant prior to undergoing spinal fusion surgery they will be excluded from the trial as their surgery date will be postponed until following completion of their pregnancy. If a patient is found to be pregnant from any time after their surgical date they will continue to be included in the trial and their data collected in the usual fashion.

8.4. UNANTICIPATED PROBLEMS

8.4.1. DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated problems involving risks to participants or others include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given
  - (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and
  - (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research; and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognised.

8.4.2. UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Drug and Therapeutics Committee (DTC) and lead principal investigator. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the HREC within 1 week of the investigator becoming aware of the event.
- Any other UP will be reported to the DTC within 1 month of the investigator becoming aware of the problem.

8.4.3. REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Participants will be invited to inquire about the results of the trial and incidence and nature of unanticipated problems after the completion of the trial.

9. STATISTICAL CONSIDERATIONS

9.1. STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):
  - Incidence of severe anaemia (Hb <100g/L)at time of discharge from hospital or 7 days postoperatively (whichever is sooner)
  - This trial is designed to demonstrate superiority of IV iron therapy over traditional oral iron therapy.

- Secondary Efficacy Endpoint(s):
  - Incidence of blood transfusion
  - Length of stay
  - Haemoglobin concentration and incidence of anaemia (Hb<120g/L) at 3 weeks postoperatively
  - Haemoglobin concentration and incidence of anaemia (Hb <120g/L) and incidence of iron deficiency (ferritin <30mcg/L) at 9 weeks postoperatively
  - Quality of functional recovery from surgery as measured by the SRS 30 at 9 weeks postoperatively

9.2. SAMPLE SIZE DETERMINATION

The null hypothesis states that there is no difference between oral and IV iron therapy in the incidence of severe anaemia at the time of discharge following elective spinal fusion surgery. The primary outcome measure is the Incidence of severe anaemia (Hb<100g/L) at discharge from hospital.

Previous audit of 16 spine patients demonstrated a mean discharge Hb of 96g/L, with a standard deviation of 15.2. Haematocrit was not recorded.

Intravenous iron sucrose has been proven to increase Hb in adults with iron deficiency anaemia of various aetiologies that is non-responsive to oral iron by up to 50% (85.4g/L to 121 g/L) [26].

Whilst the figures for paediatric surgical patients' responsiveness to IV iron are not known (hence the development of the proposed study); it has been postulated that this may be likely to be similar to adults. Thus these preexisting findings in adults allow for an extrapolation of data to enable power calculation for the proposed study. Namely, that of the of patients being discharged with severe anaemia (Hb<10 g/dL) after spinal surgery - which currently number 68% of patients - should be able to be halved (50% decrease) through judicious and appropriate IV iron therapy.

In view of the lack of previously defined population characteristics, power calculations have been done using:

- a two study group design (Population rates of Discharge Hb<100 of 68.75% observed previously, compared to the expected post iron-infusion rates of Discharge Hb<100 of 34.38%, a figure chosen for reasons outlined above.)
- Further, while data will be collected in a continuous manner, it will be analysed as dichotomous, binomial data (two outcomes only: Hb >10 g/dL or Hb <10g/dL.) to reduce the number of patients required for the study.
- Assumption of alpha of 0.05, as per current medical research convention [27]
- Assumption of power (1-beta) of 0.8 as per current medical research convention [27]

This will result in an expected sample size of approximately 14 patients in the treatment group.

This figure has been reached using the following equation (fig. 1), which was selected to meet the above criteria [28]. The calculation was performed using the on-line tool at http://clincalc.com/stats/samplesize.aspx.

This power calculation remains a guide, and will be subject to formal review by a statistician. Further recruitment may be required in the event of patient drop-out, the rates of which are difficult to predict. Anticipating a 10% attrition rate we will aim to recruit 34 patients (17 in each treatment arm).

$$N = \frac{p_0 q_0 \left\{ z_{1-\alpha/2} + z_{1-\beta} \sqrt{\frac{p_1 q_1}{p_0 q_0}} \right\}^2}{(p_1 - p_0)^2}$$

$$q_0 = 1 - p_0$$

$$q_1 = 1 - p_1$$

$$N = \frac{0.6875 * 0.3125 \left\{ 1.96 + 0.84 \sqrt{\frac{0.3438 * 0.6562}{0.6875 * 0.3125}} \right\}^2}{(0.3438 - 0.6875)^2}$$

$$N = 14$$

p_0 = proportion (incidence) of population
p_1 = proportion (incidence) of study group
N = sample size for study group
α = probability of type I error (usually 0.05)
β = probability of type II error (usually 0.2)
z = critical Z value for a given α or β

Figure 1.

9.3. POPULATIONS FOR ANALYSES

We will use an intention to treat analysis and consider all randomised patients who present for surgery within the timeframe outlined in the exclusion criteria.

9.4. STATISTICAL ANALYSES

9.4.1. GENERAL APPROACH

Advise from a biostatistician will be sought prior to data analysis.

9.4.2. ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Primary Endpoint: Severe anaemia at the time of discharge from hospital

Advise from a biostatistician will be sought prior to data analysis.

9.4.3. ANALYSIS OF THE SECONDARY ENDPOINT(S)

Advise from a biostatistician will be sought prior to data analysis.

9.4.4. SAFETY ANALYSES

This study is not powered to demonstrate safety of either oral or IV iron therapy.

9.4.5. BASELINE DESCRIPTIVE STATISTICS

Advise from a biostatistician will be sought prior to data analysis.

9.4.6. PLANNED INTERIM ANALYSES

Not-applicable.

9.4.7. SUB-GROUP ANALYSES

Advise from a biostatistician will be sought prior to data analysis.

9.4.8. TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual data will not be provided.

9.4.9. EXPLORATORY ANALYSES

None

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1. INFORMED CONSENT PROCESS

10.1.1.1. CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol:

- Patient information sheet
- Informed consent

10.1.1.2. CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Human Ethics Committee approved and the participant will be asked to read and review the document. The investigator will explain the research study to the patient and parent and answer any questions that may arise. A verbal explanation will be provided in terms suited to the patient and parent comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The patient and/or parent will sign the informed consent document prior to any procedures being done specifically for the study. Patient and parents must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the patient for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the patient undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasising to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2. STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, therapeutic substance committee, and human ethics committee. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the therapeutic substance committee, and human ethics committee and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping

- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the therapeutic substance committee, TGA and human ethics committee.

10.1.3. CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorised third party.

All research activities will be conducted in as private a setting as possible.

Human Ethics Committee, Therapeutic substances committee or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for 15 years.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will stored at the on the intranet at the Women's and Children's Hospital. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Women's and Children's Hospital.

10.1.4. FUTURE USE OF STORED SPECIMENS AND DATA

Not applicable

10.1.5. KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Dr Rebecca Munk	*Dr Scott Ma*
Women's and Children's Hospital	*Women's and Children's Hospital*
72 King William Road, North Adelaide	*72 King William Road, North Adelaide*
0420 638 893	*0420 883 888*
munk.rebecca@gmail.com	*scott.ma@sa.gov.au*

10.1.6. SAFETY OVERSIGHT

Safety oversight will be under the direction of the Human Research Ethic Committee (HREC) at the Women's and Children's Hospital. Dr Scott Ma, consultant paediatric anaesthetist will act as a medical monitor for this trial. All adverse effects and complications will be reported to him for review and presentation to the HREC. Dr Ma is independent from the study conduct and free of conflict of interest. The investigators will immediately report any serious adverse events (SAE) to the HREC and all adverse events (AE) will be presented at least semiannually to assess safety and efficacy data on each arm of the study.

10.1.7. CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- The orthopaedic research scientist will conduct monthly centralised review of data collection to ensure completeness and accuracy.

10.1.8. DATA HANDLING AND RECORD KEEPING

10.1.8.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff under the supervision of the principle investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic database derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the adverse event data base. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.8.2. STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 30 years after completion the study intervention. These documents should be retained for a longer period, however, if required by local regulations.

10.1.9. PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the principle investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity.

10.1.10. PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Health and Medical Research Council (NHMRC) Public Access Policy, which ensures that the public has access to the published results of NHMRC supported research. It requires scientists to submit final peer-reviewed journal manuscripts t to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NHMRC Data Sharing Policy and Policy on the and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at nhmrc.gov.au, and results information from this trial will be submitted to nhmrc.gov.au. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 15 years after the completion of the primary endpoint by contacting the principle investigator or a representative at the Women's and Children's Hospital.

10.1.11. CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the Women's and Children's Hospital Ethics Committee has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2. ADDITIONAL CONSIDERATIONS

Not Applicable

10.3. ABBREVIATIONS

AE	Adverse Event
ANZCA	Australia and New Zealand College of Anaesthetists
ASA	American Society of Anaesthesiology Score - global score which assesses the physical status of patients before surgery
CRF	Case Report Form
CKD	Chronic Kidney Disease
DTC	Drug and Therapeutics Committee
FCM	Ferric Carboxymaltose
Fe	Elemental Iron
Hb	Haemoglobin concentration
ICH-GCP	International Conference on Harmonisation Good Clinical Practice
IDA	Iron Deficient Anaemia
IBW	Ideal Body Weight
IV	Intravenous
MDU	Medical Day Unit
NHMRC	National Health and Medical Research Council
NPS	National Prescriber System
PI	Principal Investigator
RDR	Rapid Detection and Response Paediatric Observation Chart
SAE	Serious Adverse Event
SRS30	Scoliosis Questionarie Version 30
TGA	Therapeutic Goods Administration
WCH	Women’s and Children’s Hospital

10.4. PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.1	28/3/2018	Preliminary Protocol	
1.2	30/5/2018	Revised Protocol	Changes made in response to feedback from DTC ethics committee.
1.3	31/7/2018	Revised Protocol, patient information sheet, and ferrous sulphate patient information sheet	Changes made in response to feedback from HREC and DTC ethics committees.

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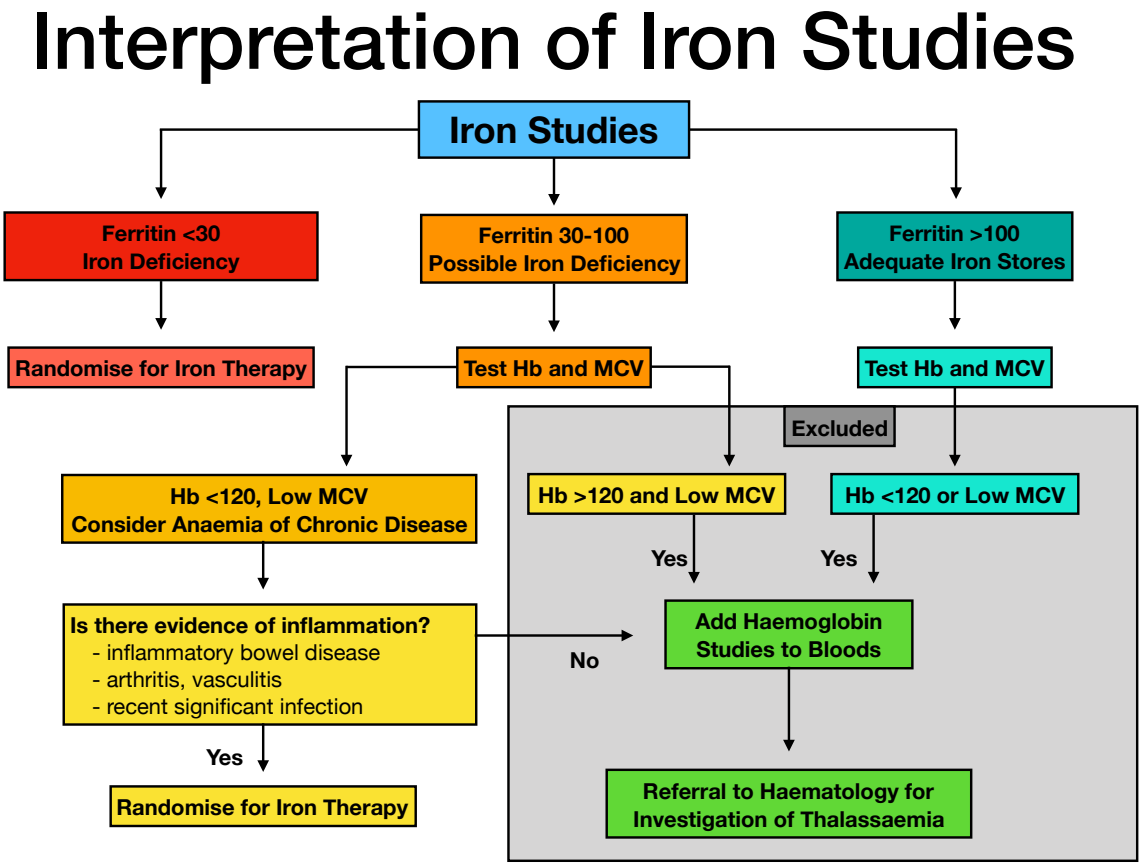
12. APPENDIXES

APPENDIX A - INTERPRETATION OF IRON STUDIES



APPENDIX B - PARTICIPANT INFORMATION SHEET

PATIENT RESEARCH INFORMATION:

Women's & Children's Hospital ADELAIDE

Correction of preoperative iron deficiency in children undergoing elective spinal fusion.
A randomised control trial of intravenous iron vs. oral iron therapy.

Purpose of the study
To determine the effectiveness of preoperative intravenous iron infusion compared to traditional oral iron supplements in reducing anaemia after spinal surgery in children.

Who is doing this research? Who do I contact if I have any questions or concerns about this study?
Dr Rebecca Munk, Paediatric Anaesthesia Consultant, Tel: 08 8161 7231
Kory Horwood, Orthopaedic Nurse Consultant, Tel: 08 8161 7219

What is iron deficiency?
Iron deficiency results from an inadequate dietary intake or absorption of iron. It is common in children and often has no symptoms. However, if iron deficiency is severe or your child experiences major bleeding, such as can occur during surgery, the iron stores may be inadequate to make new red blood cells. When this occurs, anaemia (low blood counts) can result.

How do we currently manage iron deficiency?
There is currently no clear protocol for the screening and management of iron deficiency in children presenting for major surgery at the Women's and Children's Hospital. Therefore this project will be an adjunct to the standard care received by our patients. All other aspects of your child's care will follow the standard protocol for patients undergoing spinal fusion surgery.

The currently accepted standard of care in paediatric medicine is to treat iron deficiency with oral iron supplements. This has been demonstrated over time to be a safe but often ineffective treatment due poor patient compliance and variable absorption. Additionally, many medical practitioners feel that oral iron therapy takes too long to replenish iron stores and given the short time (6-8 weeks) between booking and surgical dates doctors are hesitant to delay surgery for an adequate time period to ensure full correction of their patients' iron stores. Intravenous iron replacement with ferric carboxymaltose is a relatively new treatment option for children with iron deficiency. It has been trial and found to be safe and effective in children with iron deficiency secondary to bowel disease.

Why should my child consider participating in this study?
Anaemia after spinal surgery is common and may affect your child's energy levels, their ability to participate in physiotherapy and exercises, and prolong their return to school and normal activities. It is believed that children who are iron deficient are slower to recover from anaemia after surgery. At this time there has been no research yet in the use of intravenous iron in children undergoing surgery. As such it is still unclear whether intravenous iron therapy before surgery is more effective than oral iron therapy before surgery for reducing anaemia and the need for blood transfusion in children after spinal surgery. If one treatment proves to be better, it is possible that this form of treatment will be made available to all children with iron deficiency having spinal surgery on a routine basis in the future.

Which children are eligible to participate?
If your child is having spinal surgery at the Women's and Children's Hospital, he or she may be eligible.
Which children are not eligible to participate?
Those children with thalassaemia, sickle cell anaemia, hypophosphataemia or complex medical conditions.

How will this study be conducted?
Study participants will undergo routine screening blood tests as is our current practice. Those found to be iron deficient will be divided by chance (randomised) into two different groups.

One group will be prescribed an oral iron supplement to be taken from 3-5 weeks before surgery until the day before surgery. These children will have the option of taking either a liquid or tablet form or iron supplements.

The other group will receive a preoperative intravenous iron infusion which will entail one extra visit to the hospital 2-4 weeks prior to surgery. An iron infusion is a liquid form of iron which can be administered directly into the blood stream resulting in a rapid replacement of your child's iron stores.

Currently at WCH there is no standard protocol for preoperative management iron deficiency. Other than the treatment of iron deficiency your child will receive standard care in relation to their preoperative, surgical and postoperative care (no additional tests or hospital visits are required).

What will my involvement in the trial be if I choose to participate?
1. We will ask all parents of children who agree to participate in this trial for permission to access their medical records for research purposes. We will record basic data such as age, height and weight as well as data relating to their surgery and hospital stay. We will also access all blood test results relevant to this study.
2. For half the children one extra hospital visit will occur which will last approximately 2 hours in total. During this visit your child will have observations recorded and an intravenous cannula will be inserted. Your child will then receive an infusion of iron which will last 15-30 minutes. After completion of the infusion your child will be monitored for a short time before going home. This visit will take 1-2 hours. For some children who have significant iron deficiency your child may be required to undergo a second iron infusions one week after the initial infusion.
3. For the other half of children they will be prescribed oral iron supplementation to be taken daily from the time of prescription until the day before surgery. This prescription may be made for either the liquid or tablet form of iron.
4. Two additional blood tests will be taken at the follow up appointments (one at 2-4 weeks and one at 6-12 weeks) after the surgery to monitor your child's blood count and iron levels.
5. Your child will be given a short questionnaire to complete once before and once after their surgery to explore their overall quality of recovery.
6. All other care will be as per usual with children undergoing this surgery.

Are there any risks associated with this trial?
There are some risks documented with intravenous iron infusions. Nausea, dizziness, headache, flushing, high blood pressure may occur. Rarely, an allergic reaction or shortness of breath may occur. Anaphylaxis or other life threatening reaction is rare. Permanent skin tattooing (brown discolouration) may occur due to leakage of iron into the tissues around the infusion site. This is not common but the stain can be long lasting or permanent and may require laser treatment to remove. Inform the doctor or nurse straight away of any discomfort, burning, redness or swelling at the infusion site.

Currently this medication is not approved for use in children under the age of 14. This is common for many medications used in paediatrics due to the ethical considerations of testing new mediations on children. However, ferric carboxymaltose has undergone numerous studies in the paediatric population in children as young as 2 years of age and has been found to be safe and well tolerated.

Oral iron supplements may be associated with changes in bowel habit, stomach upset or nausea, and dark stools. Occasionally temporary black discolouration of the teeth may occur. Rarely allergic reactions or bleeding from the bowels may occur.

As with any possibly effective intervention there is the possibility of unknown side effects.

What are the possible benefits of participating in this study?
Any child who choses to participate will be screened for iron deficiency. All children who are found to be iron deficient will receive one form of iron therapy (either oral supplements or IV infusion). We feel that by treating iron deficiency children may have less severe anaemia and improved recovery after surgery, however, we don't know.

Is it OK to leave the trial after signing a consent form to participate?
Yes, you may leave the trial at any time and your ongoing care will continue as normal.

Is there any payment involved in participating?
No, you will not receive any payment for your participation.

Is there any cost involved in participating?
No, the cost of both treatments will be covered by research funding.

Are all of my personal details confidential?
Your information will remain confidential except in the case of a legal requirement to pass on personal information to authorised third parties. This requirement is standard and applies to information collected both in research and non-research situations. Such requests to access information are rare; however we have an obligation to inform you of this possibility.

Ethics Approval
The study has been given approval by the Women's & Children's Hospital's Ethics Committee. All researchers involved in have received formal training in Iron administration. Please contact the Secretary of the Committee (Mr Luke Fraser, Research Secretariat, ph 8161 6521) if you wish to discuss the approval process, or have any concern or complaint.

APPENDIX C - INFORMED CONSENT FORM

WOMEN'S & CHILDREN'S HEALTH NETWORK (WCHN)

CONSENT FORM

I, _____ *(Parents name)*

hereby consent to my child's involvement in the research project entitled:

"**Correction of preoperative iron deficiency in children undergoing elective spinal fusion. A Randomised control trial of intravenous ferric carboxymaltose vs. oral iron therapy."**

1. The nature and purpose of the research project described on the attached Information Sheet has been explained to me. I understand it and agree to (my child**) taking part.
2. I understand that I (my child**) may not directly benefit by taking part in this study.
3. I acknowledge that the possible risks and/or side effects, discomforts and inconveniences, as outlined in the Information Sheet, have been explained to me.
4. I understand that I can withdraw (my child**) from the study at any stage and that this will not affect medical care or any other aspects of my (my child's**) relationship with this healthcare service.
5. I understand that there will be no payment to me (my child**) for taking part in this study.
6. I have had the opportunity to discuss taking part in this research project with a family member or friend, and/or have had the opportunity to have a family member or friend present whilst the research project was being explained by the researcher.
7. I am aware that I should retain a copy of the Consent Form, when completed, and the Information Sheet.
8. I agree to the accessing of my (my child's) medical records for the purpose of this study.
9. I understand that my (my child's) information will be kept confidential as explained in the information sheet except where there is a requirement by law for it to be divulged.

Signed:……

Relationship to Patient: ……

Full name of patient: ……

Dated:……

I certify that I have explained the study to the parent (**patient)(**and/or child) and consider that he/she understands what is involved.

Signed: …….. Title: ……..

Dated: ……

APPENDIX D - DATA COLLECTION FORMS

CORRECTION OF PREOPERATIVE IRON DEFICIENCY IN CHILDREN UNDERGOING ELECTIVE SPINAL FUSION.

BASELINE DATA SHEET

6 weeks preoperative

URN:_____

Date of Birth:____/____/_____

Gender: _____

Today's Date: ____/____/_____

Date of surgery (if known): ____/____/_____

Baseline Data	
Height (cm)	
Weight (kg)	
Heart Rate (bpm)	
Blood Pressure (mmHg)	
Saturations	
History of Thalasseamia, Inflammatory Bowel Disease, Arthritis, or Vasculitis?	Yes / No

Paperwork	Completed
Patient Information Sheet Provided to Patient	☐
Informed Consent	☐
SRS 30	☐
Bloods Requested:	
Full Blood Count	☐
Iron Studies	☐
Group and Hold	☐
Electrolytes	☐

1

CORRECTION OF PREOPERATIVE IRON DEFICIENCY IN CHILDREN UNDERGOING ELECTIVE SPINAL FUSION.

REVIEW OF BASELINE RESULTS

URN:_____
Date of Birth:____/____/_____

Today's Date: ____/____/_____

Date of surgery (if known): ____/____/_____

5 weeks preoperative

Blood Results	
Haemoglobin	
MCV	
Blood Film Comment	
Ferritin	
Iron	
Transferrin	
Transferrin Saturation	
Phosphate	
Serum Calcium	
Vitamin D Level	

Does Patient meet exclusion criteria? (see protocol)

Yes - Please list: _____

Does Patient Qualify for Iron therapy? (Use the Interpretation of Iron Studies Flow Chart)

No - Inform patient/parent of results and the need for no further treatment before surgery

Yes - Randomise patient then inform patient/parent of results and arrange appointments as required by randomisation.

Group Allocation: (circle one)

Oral Iron Therapy **IV Iron Therapy** **Excluded**

CORRECTION OF PREOPERATIVE IRON DEFICIENCY IN CHILDREN UNDERGOING ELECTIVE SPINAL FUSION.

INTRA-OP

Day of Surgery

URN:_____

Date of Birth:____/____/_____

Date of surgery: ____/____/_____

Please send blood for Full Blood Count, Iron Studies, and Electrolytes at induction PRIOR to fluid administration

Admission Data	
Height (cm)	
Weight (kg)	
Heart Rate (bpm)	
Blood Pressure (mmHg)	
Saturations	
ASA	

Intra operative	
Spinal Levels Fused	
Duration of Surgery	
Estimated Blood Loss	
Cell Salvage Volume	
Volume of Crystalloid	
Volume of Colloid	
Volume and type of Transfusion	

CORRECTION OF PREOPERATIVE IRON DEFICIENCY IN CHILDREN UNDERGOING ELECTIVE SPINAL FUSION.

IN PATIENT DATA SHEET

URN:_____

Date of Birth:____/____/_____

Date of surgery: ____/____/_____

Date of discharge: ____/____/_____

0-7 days postoperative

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Haemoglobin							
Transfused (yes/no)							
Observations stable (yes/no)							
Phosphate Level							
Day of discharge							

Please complete a Full Blood Examination on Day 1-2 and Day 5-7 and at least one test of Electrolytes including Calcium Magnesium and Phosphate "ELC" prior to discharge

If randomised to oral iron therapy:

- **Please collect the patient compliance survey**
- **Count any remaining doses. Remaining Tablets/Volume:_____**

If patient was transfused please detail the indications:

_____

_____

_____

If patient was not discharged prior to day 7 please detail the indications for increased duration of admission:

_____

_____

_____

CORRECTION OF PREOPERATIVE IRON DEFICIENCY IN CHILDREN UNDERGOING ELECTIVE SPINAL FUSION.

POST OPERATIVE DATA SHEET

URN:_____
Date of Birth:____/____/_____
Date of surgery: ____/____/_____

6-12 weeks postoperative

Study Conclusion Data		Date
Height (cm)		
Weight (kg)		
Heart Rate (bpm)		
Blood Pressure (mmHg)		
Saturations		
SRS 30 Completed	☐	

Blood Results	2-4 weeks post-op	6-12 weeks post-op
Date of Test		
Haemoglobin		
MCV		
Blood Film Comment		
Ferritin		
Iron		
Transferrin		
Transferrin Saturation		
Phosphate		

APPENDIX E - PATIENT COMPLIANCE QUESTIONNAIRE

CORRECTION OF PREOPERATIVE IRON DEFICIENCY IN CHILDREN UNDERGOING ELECTIVE SPINAL FUSION.

ORAL IRON QUESTIONNAIRE

Collect While Inpatient

URN:_____
Date of Birth:____/____/_____
Date of surgery: ____/____/_____

Iron Dosing Data	Liquid	Tablets
Date Iron Initiated		
Dose Prescribed	_____mL/day	_____Tabs/day
Typical Dose Taken	_____mL/day	_____Tabs/day

How many days per week did your child take the oral iron supplements?

Dosing	Everyday (7days)	Most Days (5-7days)	Some Days (3-4days)	Rarely (1-2days)	None (0days)
First Week					
Second Week					
Third Week					
Fourth Week					
Fifth Week					

Please list any reasons why your child was unable to take the iron supplements daily:

_____

_____

_____

How many days per week did your child experience the following symptoms?

Side Effects	Everyday (7days)	Most Days (5-7days)	Some Days (3-4days)	Rarely (1-2days)	None (0days)
Nausea					
Constipation					
Diarrhea					
Abdominal Pain					
Other					

APPENDIX F - FERROUS SULPHATE LIQUID PATIENT INFORMATION SHEET

TRIAL information for parents and carers Ferrous Sulfate

This leaflet has been written specifically about the use of this medicine in children. The information may differ from that provided by the manufacturer. Please read this leaflet carefully. Keep it somewhere safe so that you can read it again.

Name of drug: Ferrous Sulfate

Brand Name: ferro-liquid oral liquid solution

Why is it important for my child to take this medicine?

Anaemia is a blood condition where there is a lack of a protein called haemoglobin. Haemoglobin is needed to carry oxygen in the blood and transport it around the body. Children with anaemia are often pale, feel tired, have little energy, and may not grow or develop properly. Ferrous sulfate is a form of iron that can be taken by mouth. It helps the body to make more haemoglobin and so treat the anaemia. It can also be used to prevent anaemia in children who are at risk of it or, for example, before surgery.

Name of drug: Ferrous Sulfate

What is ferrous sulfate available as?

- Oral liquid: (6 mg of elemental iron in 1 mL)

When should I give ferrous sulfate?

For treatment of anaemia, it is usually given twice or three times each day.

- **Twice a day:** this should be once in the morning and once in the evening. Ideally, these times are 10-12 hours apart, for example sometime between 7 and 8am, and between 7 and 8 pm.
- **Three times a day:** this should be once in the morning, once in the early afternoon and once in the evening. Ideally, these times are at least 6 hours apart, for example 8 am, 2 pm and 8 pm.

Give the medicine at about the same time(s) each day so that this becomes part of your child's daily routine, which will help you to remember.

How much should I give?

Your doctor will work out the amount of ferrous sulfate (the dose) that is right for your child. The dose will be shown on the medicine label. The dose may be given as millilitres (mL).

How should I give it?

Oral liquid: Measure out the right amount using an oral syringe. You can get these from your pharmacist. Do not use a kitchen teaspoon as it will not give the right amount. Ferrous sulfate works best when given on an empty stomach. Try to give it 30 minutes before or 2 hours after food. However, if this upsets your child's stomach, give it with a little food.

When should the medicine start working?

Ferrous sulfate takes some time to work. If it is being used to treat anaemia, you might notice an improvement in your child when they have been taking the medicine for 3-4 weeks. They may be less pale, have more energy and have less shortness of breath. Your child will need to take ferrous sulfate until the planned procedure

What if my child is sick (vomits)?

- If your child is sick less than 30 minutes after having a dose of ferrous sulfate, give them the same dose again.
- If your child is sick more than 30 minutes after having a dose of ferrous sulfate, you do not need to give them another dose. Wait until the next normal dose.

What if I forget to give it?

If you usually give it once a day: Give the missed dose when you remember, as long as this is at least 8 hours before the next dose is due. You do not need to wake up a sleeping child to give a missed dose.

If you usually give it twice a day: If you remember up to 4 hours after you should have given a dose, give your child the missed dose. For example, if you usually give a dose at about 7 am, you can give the missed dose at any time up to 11 am. If you remember after that time, do not give the missed dose. Give the next dose as usual.

If you usually give it three times a day: Do not give the missed dose. Give the next dose as usual.

- Never give a double dose of ferrous sulfate. If you are not sure whether to give a missed dose, don't give it. Giving an extra dose of ferrous sulfate by mistake is more likely to do harm than missing a dose.

TRIAL information for parents and carers Ferrous Sulfate

What if I give too much?

It may be dangerous to give too much ferrous sulfate.

Never give your child more than the doctor has advised.

If your child has one or more of the following symptoms, they may have had too much ferrous sulfate:

- stomach pains
- being repeatedly sick (vomiting)
- diarrhoea
- their vomit or stools (poo) are blood stained, or green or grey.

Children who have had too much ferrous sulfate might not show any symptoms, or only have mild symptoms. If you think your child has had too much ferrous sulfate, contact your doctor or take your child to hospital.

If your child appears very unwell or drowsy call for an ambulance straight away.

Take the medicine container or packaging with you, even if it is empty. This will be useful to the doctor. Have the medicine or packaging with you if you telephone for advice.

Are there any possible side-effects?

We use medicines to make our children better, but sometimes they have other effects that we don't want (side-effects).

- Your child may feel sick or be sick. It may help to give Ferro-liquid after some food.
- Your child might get indigestion, constipation (difficulty doing a poo) or diarrhoea/loose stools (poo).
- Temporary black discolouration of the teeth - this can be minimised by using a straw.

If these side-effects are a problem or do not wear off, the WCH, as they may suggest a different iron preparation or a lower dose. Do not reduce the dose without discussing it with your doctor first.

There may, sometimes, be other side-effects that are not listed above. If you notice anything unusual and are concerned, contact WCH.

Can other medicines be given at the same time as ferrous sulfate?

- You can give your child medicines that contain paracetamol, unless your doctor has told you not to.
- Ferrous sulfate should not be taken with some medicines that you get on prescription. Tell your doctor and pharmacist about any other medicines your child is taking before giving ferrous sulfate.
- If your child needs to take any medicines for indigestion, do not give these with ferrous sulfate. Give the two medicines at different times of the day.
- Check with your doctor or pharmacist before giving any other medicines to your child, other products that contain iron, and any products that contain zinc or magnesium. This includes multivitamin preparations and herbal or complementary medicines.

Is there anything else I need to know?

General advice about medicines

- Try to give medicines at about the same time(s) each day, to help you remember.
- Only give this medicine to your child. Never give it to anyone else, even if their condition appears to be the same, as this could do harm.
- If you think someone else may have taken the medicine by accident, contact your doctor straight away.
- Make sure that the medicine you have at home has not reached the 'best before' or 'use by' date on the packaging. Give old medicines to your pharmacist to dispose of.

Where should I keep this medicine?

- Keep the medicine in a cupboard, away from heat and direct sunlight. It does not need to be kept in the fridge.
- Make sure that children cannot see or reach the medicine.
- Keep the medicine in the container it came in.

Who to contact for more information?

- Ulrik Lorenzen, Clinical Pharmacist, WCH
  - Ph: 08 8161 8781
- Kory Horwood - Orthopaedic CN Nurse, WCH
  - Ph: 08 8161 7000
- Dr Rebecca Munk - Anaesthetic Consultant
  - Ph 08 8161 7121

APPENDIX G - FERROUS FUMARATE TABLETS PATIENT INFORMATION SHEET

TRIAL information for parents and carers Ferrous Sulfate

This leaflet has been written specifically about the use of this medicine in children. The information may differ from that provided by the manufacturer. Please read this leaflet carefully. Keep it somewhere safe so that you can read it again.

Name of drug: Ferrous fumerate

Brand Name: ferro-tab

Why is it important for my child to take this medicine?

Anaemia is a blood condition where there is a lack of a protein called haemoglobin. Haemoglobin is needed to carry oxygen in the blood and transport it around the body. Children with anaemia are often pale, feel tired, have little energy, and may not grow or develop properly. Ferrous sulfate is a form of iron that can be taken by mouth. It helps the body to make more haemoglobin and so treat the anaemia. It can also be used to prevent anaemia in children who are at risk of it or, for example, before surgery.

Name of drug: Ferrous fumerate

What is ferrous sulfate available as?

- Tablet:200mg –equivalent to elemental iron 65.7mg

When should I give ferrous fumerate?

For treatment of anaemia, it is given twice each day.

- **Twice a day:** this should be once in the morning and once in the evening. Ideally, these times are 10–12 hours apart, for example sometime between 7 and 8am, and between 7 and 8 pm.

Give the medicine at about the same time(s) each day so that this becomes part of your child's daily routine, which will help you to remember.

How much should I give?

Your doctor will work out the amount of ferrous fumerate (the dose) that is right for your child. The dose will be shown on the medicine label.

How should I give it?

Tablets should be swallowed with a glass of water or juice, but not milk. Your child should not chew the tablet. Do not crush the tablets.

Ferrous fumerate works best when given on an empty stomach. Try to give it 30 minutes before or 2 hours after food. However, if this upsets your child's stomach, give it with a little food.

When should the medicine start working?

Ferrous fumerate takes some time to work. If it is being used to treat anaemia, you might notice an improvement in your child when they have been taking the medicine for 3–4 weeks. They may be less pale, have more energy and have less shortness of breath. Your child will need to take ferrous sulfate until the planned procedure

What if my child is sick (vomits)?

- If your child is sick less than 30 minutes after having a dose of ferrous fumerate, give them the same dose again.
- If your child is sick more than 30 minutes after having a dose of ferrous sulfate, you do not need to give them another dose. Wait until the next normal dose.

What if I forget to give it?

If you usually give it once a day: Give the missed dose when you remember, as long as this is at least 8 hours before the next dose is due.

You do not need to wake up a sleeping child to give a missed dose.

If you usually give it twice a day: If you remember up to 4 hours after you should have given a dose, give your child the missed dose. For example, if you usually give a dose at about 7 am, you can give the missed dose at any time up to 11 am. If you remember after that time, do not give the missed dose. Give the next dose as usual.

What if I give too much?

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If your child has one or more of the following symptoms, they may have had too much ferrous fumerate:

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TRIAL information for parents and carers Ferrous Sulfate

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If your child appears very unwell or drowsy call for an ambulance straight away.

Take the medicine container or packaging with you, even if itis empty. This will be useful to the doctor. Have the medicine or packaging with you if you telephone for advice.

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If these side-effects are a problem or do not wear off, the WCH, as they may suggest a different iron preparation or a lower dose. Do not reduce the dose without discussing it with your doctor first. There may, sometimes, be other side-effects that are not listed above. If you notice anything unusual and are concerned, contact WCH.

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