Form FHS015: Research Protocol – Section C

South African Paediatric Surgical Outcomes Study-2 (SAPSOS-2)

A South African multi-centre pilot trial to assess the feasibility and clinical efficacy of preoperative oral iron to treat preoperative iron-deficiency anaemia in children undergoing elective noncardiac surgery

Protocol version 1.0

15 July 2022

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Patient advocate

TBC

Sponsor

University of Cape Town

Funders

None as yet

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1. List of abbreviations

DHb	Delta haemoglobin (pre-treatment haemoglobin – post-treatment haemoglobin)
Hb	Haemoglobin
IDA	Iron deficiency anaemia
SAPSOS	South African Paediatric Surgical Outcomes Study

2. Summary

Short title	SAPSOS-2: Pilot Study
Methodology	Prospective national multi-centre interventional study
Research sites	Hospitals undertaking paediatric surgery in South Africa
Objective	To evaluate the efficacy of oral iron supplementation in children diagnosed with preoperative iron-deficiency anaemia undergoing noncardiac surgery.
Primary outcome	The delta Hb (DHb) (pre-intervention Hb –post-intervention Hb)
Number of patients	420 patients
Inclusion criteria	Paediatric patients aged >6 months and <16 years admitted to participating hospitals undergoing elective non-cardiac surgery Anaemia as per WHO criteria[1]
Exclusion criteria	Patient or parent refusal Surgery planned within 6 weeks from surgical outpatient visit Known history of acquired iron overload, family history of haemochromatosis or thalassemia Known reason for anaemia (e.g. untreated vitamin B_{12} or folate deficiency or haemoglobinopathy) Treatment with oral iron, erythropoietin, IV iron therapy or blood transfusion in the previous 12 weeks Known hypersensitivity to oral iron or other contraindication to oral iron Temperature > 38.0 °C or receiving non-prophylactic antibiotics
Statistical analysis	The primary outcome measure is comparison of pre-intervention and post-intervention haemoglobin
Proposed start date	03 October 2022
Proposed end date	28 July 2023
Trial duration	Recruitment in outpatient clinic and follow-up until day of surgery

3. Introduction

Studies in both paediatric and adult patients have shown an association between preoperative anaemia and increased postoperative morbidity and mortality, and transfusion rates[2-7]. The incidence of preoperative anaemia in the secondary analysis of the SAPSOS cohort of children who underwent noncardiac surgery was 46.2%[4]. Iron deficiency anaemia (IDA) has been shown to represent up to 30% of preoperative anaemia in adults[8]. Iron deficiency and IDA are of even greater concern in children, because of the negative impact it may have on cognitive performance[9].

A recent Cochrane review on the role of preoperative iron in reducing perioperative blood transfusion in adult patients found no significant reduction in the administration of allogeneic blood transfusion in patients who had received preoperative iron compared with those who did not[10]. These findings were supported by the Preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTT) trial which found no difference in blood transfusion or death between the patients who did and did not receive intravenous iron[11]. However, these findings have generated much discussion in the literature and concerns have been raised about the clinical application of this study. The mean Hb difference between the two groups post intervention ($0.47 g.dl^{-1}$) highlights the need for greater understanding of the impact of an intervention on the absolute or relative increase in Hb when designing trials looking at the impact of iron treatment on perioperative outcomes. Dosing regimens of preoperative oral iron varies widely between studies further complicating the ability to draw conclusions of the role of oral iron in the treatment of preoperative anaemia[12-16].

In contrast with the findings of the Cochrane review and the PREVENTT trial, a meta-analysis of patient blood management programme (PBM) studies, many of which include preoperative iron treatment as a component, found that there was a reduction in exposure to red cell transfusions[17]. Although, the meta-analysis also found the implementation of PBM was not associated with a reduction on in-hospital mortality or 30-day mortality, there was no additive benefit from multiple interventions and no trial showed that PBM were cost-effective.

Not included in this meta-analysis were recently published studies on the implementation of preoperative anaemia screening clinics in adults in elective colorectal surgery and major surgery which demonstrated reductions in red cell transfusions[18,19], length of stay[18,19], and net costs[18] in patients with IDA who were treated with preoperative intravenous iron. Similarly, a large study from Western Australia reported significant reductions in cost associated with the use of blood products, and improved patient outcomes, after implementation of a PBM[20].

Studies investigating the impact of increasing preoperative haemoglobin on perioperative outcomes in children are primarily focused on blood loss and blood transfusion rates in surgery in which significant bleeding and frequent blood transfusion are anticipated and most children in these studies received preoperative erythopoeitin[21-27]. The impact of preoperative oral iron as a stand-alone intervention to increases preoperative Hb are limited to 2 studies[28,29]. A single retrospective study has reported on the impact of the introduction of preoperative oral iron without EPO in children undergoing spinal surgery[28]. They found a significant difference in intraoperative transfusion rates in patients who received a longer duration of preoperative oral iron therapy. The major limitation of the study was a lack of preintervention Hb, precluding the ability to assess the effect of iron supplementation on delta Hb.

A subsequent study reviewing the impact of preoperative oral iron in paediatric cardiac patients found that iron supplementation resulted in an increase in preoperative haemoglobin levels which was associated with reduced red blood cell transfusion volumes[29].

Given the high incidence of preoperative anaemia in children having surgery in South Africa in the public sector and its association with poorer postoperative outcomes, it is important to assess the feasibility of a pragmatic intervention to treat preoperative anaemia in the context of a resource-constrained setting. Although intravenous iron in combination with EPO may be more effective and have fewer side effects, oral iron is relatively inexpensive and widely available in South Africa. Regular deworming may also play an important role in the treatment of preoperative anaemia and has been shown to be an effective intervention to increase baseline Hb in school age children from low- and middle- income countries[30].

We hypothesise that the implementation of preoperative anaemia screening and treatment of anaemic patients with a minimum of 6 weeks supplementation with oral iron will have a clinically significant effect on increasing the haemoglobin in patients with preoperative IDA.

4. Study objectives

4.2 Primary objective

To evaluate the efficacy of oral iron supplementation in children diagnosed with preoperative IDA undergoing noncardiac surgery.

4.2 Secondary objectives

Describe the incidence of preoperative IDA.

5. Study aims

5.2 Primary outcome measure

DHb (pre-intervention Hb – post-intervention Hb)

5.2 Secondary outcome measures

Incidence of preoperative IDA in the elective paediatric surgical population in South Africa.

6. Methods

6.1 Study design

Prospective interventional quasi-experimental pre-post study across multiple hospitals in South Africa. Patients will be screened for trial eligibility at a normal routine outpatient clinic visit. Those patients with a screening Hb meeting the criteria for anaemia according to the WHO definition[30] and able to receive the oral iron for a minimum of 6 weeks prior to their planned operation, will be eligible for inclusion.

The formal laboratory blood test results will be reviewed within 48-76 hours by the research nurse to diagnose those patients who meet the pre-defined criteria for IDA. Parents & legal guardians will be contacted via telephone by the research nurse to inform them about their child's results and to instruct them to either discontinue or continue taking the oral iron supplementation dependent on whether the results meet the pre-defined criteria for iron-deficiency anaemia.

Prior to inclusion, freely given written informed consent must be obtained from all parents or legal guardians and assent from patients where appropriate.

6.2 Inclusion criteria

- Age > 6 months to <16 years
- Noncardiac surgery
- Elective surgery
- Anaemic as per WHO criteria[1]

6.3 Exclusion criteria

- Patient or parent refusal
- Unable to obtain written consent at the surgical outpatient clinic
- Surgery planned within 6 weeks from surgical outpatient visit
- Known history of acquired iron overload, family history of haemochromatosis or thalassemia
- Known reason for anaemia (e.g., untreated vitamin B_{12} or folate deficiency or haemoglobinopathy)
- Treatment with oral iron, erythropoietin, IV iron therapy or blood transfusion in the previous 12 weeks
- Known hypersensitivity to oral iron or other contraindication to oral iron
- Temperature > 38.0 °C or receiving non-prophylactic antibiotics
- Acute liver failure

6.4 Site requirements

Hospital sites will include public hospitals in South Africa performing elective paediatric surgery and each site must meet the following requirements:

1) Appointed research nurse able to obtain consent and perform finger-prick test at the surgical outpatient clinic.
2) On-site phlebotomy service.
3) On-site pharmacy able to provide the patient and parent or legal guardian with the oral iron supplementation and deworming medication where appropriate.

6.5 Research ethics and informed consent

Research ethics and regulatory approvals will be sought before starting the study at each site, in accordance with national research legislation/guidelines. Hospitals will not be permitted to record data unless ethics approval is in place.

Written informed consent (Appendix A) will be required for all study participants prior to screening haemoglobin is performed, with translators where necessary, from the primary parent or legal guardian or legally authorised representative and should include assent (Appendix B) of the child where appropriate. Two consent ± assent forms will be completed. One copy of the form(s) will be given to the parent or legal guardian to keep, and the other copy(s) will be kept in a study folder in a secure location.

The investigators will perform the study in accordance with this protocol, will obtain consent, and will report unanticipated problems involving risks to subjects or others in accordance with local ethics committee requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

6.6 Subject withdrawal

Subjects may withdraw from the study at any time without prejudice to their care and will still be treated for their anaemia in accordance with standard treatment protocols.

6.7 Recruitment and screening

Eligible subjects will be identified at routine surgical outpatient appointments. Paper informed consent will be obtained prior to a finger-prick screening haemoglobin (Hemacue) is performed, with translators where necessary, from the primary parent or legal guardian or legally authorised representative and included assent of the child where appropriate. Broadcasting through an appropriate hospital notice will inform the patients, their parents/guardians and the public that the hospital is participating in the study (Appendix C).

The total patients planned to be recruited for screening is 420 patients and these will be divided across 3 sites:

220 patients Red Cross War Memorial Children's Hospital
100 patients Site B (TBC)
100 patients Site C (TBC)

6.8 Ensuring adequate resources

To conduct a sound and valid study the investigators will ensure to the best of their ability that the following criteria are met:

1) Reasonable potential to recruit 420 individuals to the study over a cumulative 6-month period (2-month recruitment period at 3 sites).
2) An appropriate amount of time to complete recruitment, intervention, and data collection (9 months).
3) An adequate supply of suitably qualified staff at each facility including:

a) Appointed research nurse at each research site able to carry out the following responsibilities 3 days per week:

08:00 to 10:00

Checking National Health Laboratory Services Results (NHLS) for blood tests at outpatient clinic
Telephonic follow-up with recruited patients to discontinue iron supplementation if they do not meet criteria for IDA

10:00 to 16:00

Recruitment of patients for study
Obtaining written informed consent and assent where appropriate
Performing finger-prick Hb (Hemacue)
Applying EMLA for venepuncture for anaemic patients
Giving drug script signed by clinic doctor for oral iron supplementation ± deworming medication for collection at the hospital pharmacy

b) Appointed research assistant for all sites to complete weekly telephonic survey for all IDA patients assessing medical adherence and side-effects, referring onto study nurse or doctor where appropriate.

3) Appropriate training on the study protocol, about any investigational product and about their duties to allow the staff to carry out their tasks safely and effectively.
4) Appropriate supervision of any individual or group to whom the investigator assigns trial-related duties at the trial site
5) Assurance that any person or party retained to perform trial-related duties is suitably qualified to perform those duties.

6.9 Criteria for iron deficiency

The patient will be allocated to iron-deficiency group if they meet one or more of the following criteria.

1. Serum Ferritin WHO Definitions[31]
2. Transferrin saturation (TSAT) <11%[32]

6.10 Supplemental iron dosing regimen

All patients diagnosed with anaemia on the point of care Hemacue test will be given an oral iron supplement to take every day prior to surgery for a maximum of 3 months.

The recommended treatment dose of elemental iron for IDA is 3-6$mg^{-1}kg^{-1}day^{-1}$ [33]. This can be increased to 12$mg^{-1}kg^{-1}day^{-1}$. The recommendation from Red Cross War Memorial Hospital Pharmacy is that iron syrup is preferred in children up to 4 years old or in older children unable to take tablets (Table 1).

Table 1. Ferrous gluconate (350mg/5ml) Elemental Iron 8mg/ml Dosing

Weight (kg)	BD dose (mL)
5	2
6	2.5
7	2.5
8	3
9	3.5
10	4
11	4
12	4.5
13	5
14	5.5
15	5.5
16	6
17	6.5
18	7
19	7
20	7.5

If the child can take iron tablets the recommendation is possible to prescribe a dose at increments of ½ tablet (37.5mg) (Table 2).

Table 2: Ferrous Fumarate/Folic acid - Elemental iron 65mg tablets Dosing

Weight Range	Tablets*
10 to 14 kg	1.0
>15 to 20 kg	1.5
>20 to 30 kg	2.0
>30kg	3.0

*Dose to be split into BD

Based on this the dose range when prescribing tablets for patient weight range 10 to 59 kg is 2.2 to 6.5 $mg^{-1}kg^{-1}day^{-1}$. The oral iron supplementation will be dispensed the same day as the outpatient clinic appointment, with clear verbal instructions on how to take the medication and potential side-effects. The parent or legal guardian will also be given a patient information leaflet, with information on anaemia, how to take the medication, potential side-effects, and who to contact should they have any further questions or concerns (Appendix D).

6.11 Empiric treatment for worms

If the patient has not been dewormed in the last 6 months, they will be administered deworming medication in the surgical out-patient clinic as per the Standard Treatment Guidelines and Essential Medicines List for South Africa Primary Healthcare Level 2020 Edition for management of anaemia in children[33].

6.12 Research procedures, data collection and collation

At recruitment phase

Eligible patients will be screened for anaemia with a finger-prick bedside Hemacue test at outpatient clinic. If the patient meets the WHO criteria for anaemia EMLA cream will be applied to potential sites for venepuncture and the patient will then be sent to the pathology laboratory for venepuncture with a request form for tests that will include laboratory full blood count (FBC), ferritin, transferrin saturation (TSAT), C-reactive protein (CRP), and reticulocyte Hb content. Patients who have not been dewormed within the last 6 months will be treated with mebendazole or albendazole as per the South African guidelines[33].

The patients age, weight, height, co-morbidities, ASA physical status, planned surgical procedure, planned date of surgery, severity of surgery, and type of surgery will be recorded. They will also be informed that they will be contacted telephonically once a week by the research assistant to enquire about compliance with the medication and enquire about any side-effects with the medication. The telephonic contact details will be confirmed by the research nurse and documented on the paper Outpatient CRF.

At home

The laboratory blood test results will be reviewed within 48 hours to diagnose those patients who meet the criteria for IDA. Any patients who do not meet the criteria will be contacted via telephone by the research nurse to instruct them to stop taking the iron supplementation and to bring the remaining iron supplementation with them to their next hospital visit. These patient folders and results for those patients not meeting the criteria for IDA will be reviewed by the appropriate surgical team to decide on appropriate ongoing management and further investigations which will be individualised to the patient.

For those patients meeting the criteria for IDA and continuing the oral iron supplementation, the parent or legal guardian will be contacted weekly to complete a short telephonic survey on compliance with the medication, side-effects, and to answer any questions or concerns they may have.

At time of Surgery

Repeat laboratory FBC at time of routine preoperative bloods if part of standard care.

Repeat ferritin, CRP, TSAT ± FBC whilst under anaesthesia prior to start of surgery.

Data collection

Each individual hospital will collect and record data on a paper case record form (CRF) for every patient recruited. These include an Outpatient Clinic CRF (Appendix E), Telephonic Survey CRF (Appendix F), and Surgical Admission CRF (Appendix G). The Outpatient Clinic CRF and the Surgical Admission CRF will be kept in a booklet in the patient folder and a sticker will be placed on the folder to identify that the patient has been recruited. All the CRFs, including the Telephonic Survey CRF will be kept in a secure study file in a locked cupboard.

Data will be anonymised by generation of a unique study code and transcribed by local investigators onto a secure, password protected internet based electronic CRF in the REDCap platform. Each patient will only be identified on the electronic CRF by their numeric code; thus, the co-ordinating study team cannot trace data back to an individual patient without contact with the local team. A participant (patient) list will be used in each hospital to match identifier codes in the database to individual patients to record clinical outcomes and supply any missing data points. Access to the data entry system will be protected by username and password delivered during the registration process for individual local investigators. All electronic data transfer between participating hospitals and the co-ordinating centre will be encrypted using a secure protocol (HTTPS/SSL 3.0 or better).

Each hospital will maintain a secure study file including a protocol, local investigator delegation log, ethics approval documentation, the participant list, and other additional documentation such as study definitions.

A final summary printout of included patients with major variables should be produced for each hospital together with final data submission to double check for completeness and accuracy.

6.13 Dataset

A realistic data set will be fundamental to the success of the investigation. This dataset will include the following:

All patients:

- Age (continuous, numerical)
- Sex (categorical, nominal)
- Weight (continuous, numerical)
- Height (continuous, numerical)
- Co-morbidities (categorical, nominal)
- Chronic medication (categorical, nominal)
- ASA Physical Status (categorical, ordinal)
- Severity of surgery (categorical, nominal)
- Type of surgery (categorical, nominal)
- Hemacue Hb

All anaemic patients

- Pre-intervention Hb (continuous, numerical)
- Pre-intervention MCV (continuous, numerical)
- Pre-intervention ferritin (continuous, numerical)
- Pre-intervention TSAT (continuous, numerical)
- Pre-intervention CRP (continuous, numerical)
- Pre-intervention reticulocyte Hb content (continuous, numerical)
- Syrup or tablet prescribed (categorical, nominal)
- Actual dose of elemental iron prescribed ($mg^{-1}.kg^{-1}.day^{-1}$)

All patients with IDA

- Post-intervention Hb (continuous, numerical)
- Post-intervention MCV (continuous, numerical)
- Post-intervention ferritin (continuous, numerical)
- Post-intervention TSAT (continuous, numerical)
- Post-intervention CRP (continuous, numerical)
- Post-intervention reticulocyte Hb content (continuous, numerical)
- Days of oral iron treatment (continuous, numerical)

6.14 Case record forms

Whole cohort (420 patients)

An Outpatient CRF will be completed for every enrolled patient (Appendix F). This will be completed by the research nurse at each site.

IDA cohort

A Telephonic Survey CRF will be completed on a weekly basis for up to 3 months for every patient (Appendix G). This will be completed by the research assistant.

A Surgical Admission CRF will be completed on admission for surgery by the surgical team (Appendix H).

6.15 Collection and storage of blood samples

EMLA will be applied by the research nurse at the outpatient clinic. These patients will then have venepuncture performed by the on-site hospital phlebotomist. These samples will include an EDTA tube for FBC, and reticulocyte Hb content, and a gold top tube (serum separator) for C-reactive protein, ferritin, and transferrin saturation content. These samples will be labelled and stored in accordance with standard operating procedure.

6.16 Monitoring medical adherence

Few validated medical adherence surveys have been developed for the paediatric population and these are limited to asthma, HIV/AIDS, epilepsy, ADHD, and diabetes[34]. Therefore, medical adherence will be defined as the following:

Number of days the patient takes the iron supplement/number of days the patient is prescribed to take the iron supplement.

This will be assessed on a weekly basis via the telephonic survey.

The parent or legal guardian will also be asked to bring any unused iron supplements when their child is admitted for surgery. A pill count and a count of remaining iron syrup will be done to cross-reference against the reported doses taken.

6.17 Safety reporting

All study participants enrolled to take oral iron supplements will be monitored via a weekly telephonic survey for adverse events (AE). The parent or legal guardian will also be given contact details for the research nurse who will be available to be contacted with any concerns.

Serious Adverse Events (SAE) including death, life-threatening, requiring inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, are extremely unlikely given the safety profile and well-established use of oral iron supplementation in the paediatric population. Should a SAE or Serious ADR occur this will be reported to the sponsor (University of Cape Town) within 24 hours, and within 7 days to the UCT HREC. SAE & Serious ADR will be collected on a specially designed form (Appendix H).

Non-serious adverse events (AE), will be documented clearly on the CRF for the telephonic surveys. Common side-effects will be asked about specifically, these include vomiting, nausea, stomach cramps or bloating, heartburn, constipation, and diarrhoea. Should the patient suffer from any of these side-effects they will be given telephonic advice on the management options as per the telephonic survey and referred to the research nurse or clinician investigators where appropriate. Any AE, illness, or clinically significant abnormal laboratory values, actions taken, and treatments provided will be clearly documented. It will also be recorded if the individual withdraws, and this will include the reason for withdrawal if the participant is willing to supply one. If the Hb <7.0g.dl^{-1} on the formal laboratory results, the parent or legal guardian must be contacted and referred for further medical investigation and treatment.

5.10 Expected benefits to individual participants and potential societal benefits

As an individual the participant may benefit from the intervention by a direct increase in their haemoglobin levels. The impact of increased haemoglobin levels may translate to improved perioperative outcomes and reduced blood transfusion rates for the individual patient. Please note that the study is not designed to evaluate the impact of the intervention on these outcomes. The impact of treatment with iron may also have a positive impact on cognitive development, for the individual child, although again this study is not designed to assess this outcome.

The potential benefit to the wider community of children undergoing surgery in South Africa is a greater understanding of the efficacy and feasibility of oral iron as treatment for preoperative anaemia in children, and further insight into the optimal oral iron regimen.

5.10 Sample size calculation

How many patients will need to have a screening finger-prick Hb for the pilot study to be a representative of children undergoing noncardiac surgery with preoperative anaemia?

Secondary analysis of SAPSOS study found 46.2% patients were anaemic, using estimation for a single proportion with a specified precision and allowing for 10% drop out.

$n = [p(1-p)z^{2}] / d^{2}$
n: sample size
p: population proportion
z: 1.96, level of confidence, normal distribution
d: 0.05, acceptable margin of error

n = 0.46.(0.538)3.8416 / 0.0025 = 381.98
10% drop out rate: 38.2
Sample size: 382 + 38 = 420

Given a sample size of 420 patients allowing for 10% drop-out approximately how many anaemic patients will be enrolled?

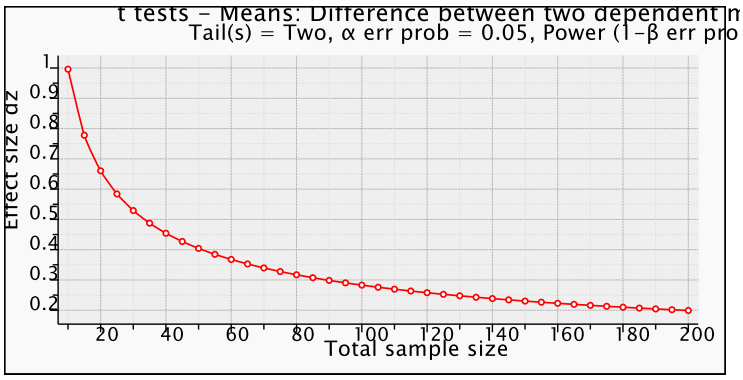
n = 420*0.90*0.462 ~ 176

5.10 Power analyses

What effect size could we expect to find statistically significant for the whole cohort given an estimated sample size of 176 patients?

Effect size for comparison between mean Hb pre and post intervention for whole cohort (matched pairs samples t-test) of 176 patients. Assuming data are normally distributed.
Sample size = 176, power = 80%, two-tailed significance 0.05

Effect size ~ 0.21



pwr.t.test(n = 176, d = NULL, sig.level = 0.05, power = 0.8,
type = "paired", alternative = "two.sided")

Paired t test power calculation

n = 176
d = 0.2123609
sig.level = 0.05
power = 0.8
alternative = two.sided

NOTE: n is number of *pairs*

What effect size could we expect to find statistically significant for the cohort of patients with IDA given an estimated sample size of 176 anaemic patients, if the incidence of IDA is unknown?**

IDA prevalence	IDA Sample size	Effect size (matched pairs samples t-test)	Effect size (Wilcoxin signed-rank test (matched pairs))
0,2	35	~0.5	~0.5
0,3	53	~0.4	~0.4
0,4	70	~0.34	~0.35
0,5	88	~0.3	~0.31

5.11 Statistical analysis

Categorical variables will be reported as number and percentage. All patient and surgical characteristics will be compared between children with and without anaemia and comparing children with IDA versus anaemia of other cause using Pearson's chi-squared or Fisher's exact tests as appropriate. These will include age groups, sex, type of surgery (general, orthopaedic, ENT, plastics, other), severity of surgery as per SAPSOS definitions (mild, moderate, severe), severity of anaemia as per WHO definitions (mild, moderate, severe).

Normal distribution of continuous variables will be determined by Shapiro-Wilk testing and summarised appropriately as means ± standard deviation or as medians ± interquartile range (IQR). All patient and surgical characteristics will be assessed with parametric testing (Student's t-test) for normally distributed data, and nonparametric testing (Mann-Whitney U test or Kruskal-Wallis test) for non-normally distributed data. These data will include pre-intervention Hb, post-intervention Hb, and duration of oral iron treatment (days).

Pre- and post-intervention Hb for the patient with IDA will be assessed by a paired t-test if data are normally distributed, and if data are not normally distributed then the data will be analyse using Wilcoxon ranked sum test.

Is there a statistically significant difference in pre and post intervention Hb in the IDA patients after adjusting for baseline haemoglobin?

The proposal is to use a mixed effect regression model. The final model will depend on the distribution of the outcome variable (post-intervention Hb). If the outcome is normally distributed, a linear mixed effect model will be used. If the outcome is not normally distributed, different approaches can be used depending on how skewed the outcome is e.g. Generalised Linear Mixed Effect Model

7. Study organisation and management

7.1 Study steering committee

The Steering Committee will be chaired by HM. The study management team will be appointed by the Steering Committee and led by HM. The duties of this team will include administration of all project tasks, communication between project partners (including funders, Steering Committee members, local coordinators, etc.), data collation and management and preparation of reports for individual study sites. The Steering Committee is responsible for the scientific conduct and consistency of the project. The Steering Committee will ensure communication between the funder(s), study management team and co-ordinators as necessary.

7.2 Patient advocate

Patient advocate(s) will be appointed who will advise the Steering Committee on possible protocol amendments if required, based on patient concerns regarding delivery of the study or communication of the study.

7.3 Local co-ordinators

Local co-ordinators in individual institutions will have the following responsibilities:

- Provide leadership for the study in their institution
- Ensure all relevant regulatory and ethics approvals are in place for their institution
- Ensure adequate training of all relevant staff prior to data collection
- Supervise daily data collection and site recruitment and follow up management
- Act as guarantor for the integrity and quality of data collected
- Ensure timely completion of electronic CRFs
- Communicate with the relevant national co-ordinator

7.4 Training of investigators

Training will be done via online virtual training sessions. Each study site will be required to complete an online questionnaire as part of the site initiation, prior to starting data collection.

8 Data management and ownership

On behalf of the Steering Committee, the Department of Anaesthesia and Perioperative Medicine, Groote Schuur Hospital and University of Cape Town will act as custodian of the data. The Steering committee will retain the right to use all pooled data for scientific and other purposes. Members of the SAPSOS-2 study group will have the right to access the pooled data for research purposes provided the research proposal has been reviewed and deemed appropriate by the Steering Committee. The primary consideration for such decisions will be the quality and validity of any proposed analysis. Only summary data will be presented publicly, and all institutions will be anonymised except in the individualised report provided to each institution at the end of the study. Individual patient data provided by participating sites remain the property of the respective institutions.

9 Publication plan

Data will be presented and disseminated in a timely manner. The Steering Committee will appoint a writing committee to draft the scientific report(s) of this investigation. The group will be known as ‘The SAPSOS-2 Investigators’. Participation and authorship opportunities will be based on contribution to the primary study. On request, hospitals will be provided with an individual report allowing comparison of their individual hospital’s summary data to that of their national cohort. In line with the principles of data preservation and sharing, the Steering Committee will, after

publication of the overall dataset, consider all reasonable requests to make the dataset available in whole or part for secondary analyses and scientific publication. The Steering Committee will consider the scientific validity and the possible effect on the anonymity of participating hospitals prior to granting any such requests. Where appropriate, a prior written agreement will set out the terms of such collaborations. The Steering Committee will consider proposals for secondary analyses on the basis of the scientific quality of the proposal. The Steering Committee must approve the final version of all manuscripts prior to submission, whether they relate to part or all of the SAPSOS-2 dataset.

10 Management of premature termination of the trial

Once the decision is taken to terminate or suspend a study, all relevant bodies should be notified as soon as possible, stating the reasons for the suspension or termination. This will include informing all participants promptly by phone, assessing treatment requirements and develop a follow-up schedule for all participants where necessary and informing the institution, sponsor (University of Cape Town), IEC/IRB and other relevant bodies involved and providing a detailed written report, as appropriate.

11 References

1. Chan M. WHO Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Geneva, Switz World Heal Organ. 2011:1-6. doi:2011

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10. Appendices

Appendix A – SAPSOS2 Parent or legal guardian informed consent form V2.0

Appendix B – SAPSOS2 Patient assent form V1.0

Appendix C – SAPSOS2 Patient information leaflet V2.0

Appendix D - SAPSOS2 Patient broadcasting poster V1.0

Appendix E – SAPSOS2 Outpatient Clinic Case Record Form V1.0

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Appendix G – SAPSOS2 Surgical Admission Case Record Form V1.0

Appendix H – Serious Adverse Event Reporting Form V1.0

Appendix I – Oral iron supplement leaflets

Appendix A

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: South African Paediatric Surgical Outcomes Study-2 (SAPSOS-2)

A South African multi-centre trial to assess the feasibility and clinical efficacy of preoperative oral iron to treat preoperative anemia in children undergoing elective noncardiac surgery

Primary Study Investigator: Dr Heidi Meyer
Red Cross War Memorial Children's Hospital
Department of Anaesthesia and Perioperative Medicine,
University of Cape Town, South Africa.
Cell: 0799988858
E-mail: heids_meyer@hotmail.com

Information:

You are being approached because your child may be able to be a part of a research study on anaemia.

The doctors that are part of this study are trying to find out if they can test children for anaemia in the hospital clinic and then treat the anaemia before the child has their operation. There will be a total of 420 children involved in this study.

What is Anaemia?

Anaemia means that the haemoglobin measured on a blood test is lower than normal. Anaemia in children having surgery is very common.

How can a Doctor tell if my child has anaemia?

This is done by pricking a finger or doing a blood test.

What causes anaemia?

There are different types of anaemia, but the commonest cause of anaemia is not enough iron in the body. This is known as iron deficiency anaemia. The doctors also want to test whether your child has anaemia because of too little iron.

Can anaemia be treated?

Yes, but at the moment the doctors only do a blood test the day before, or on the day of the operation. Unfortunately, this does not give the doctors time to treat the anaemia before your child has the operation.

Does it matter if my child has anaemia when they have their operation?

Yes, doctors think that anaemia can be a problem when a child has an operation. It may be more likely that your child will need a blood transfusion or have a problem after the operation. It is also very important to treat anaemia in children because it can cause problems with a child's development.

If I DO NOT AGREE for my child to be part of the study what will happen now?

Agreeing for your child to be part of this study is voluntary. You do not have to take part in order for your child to be treated at Red Cross War Memorial Children's Hospital. If you decide not to take part or if you change your mind later it will not change how your child would normally be looked after.

If I AGREE for my child to be part of this study what will happen now?

1. HOSPITAL CLINIC

The nurse or doctor will do a finger-prick test on your child now to check for anaemia.

What will happen if the finger-prick test shows that my child DOES NOT have anaemia?

Your child will have their surgery as planned and will not need any treatment for anaemia.

What will happen if the finger-prick test shows that my child has anaemia?

The nurse or doctor will take a blood sample to test for iron-deficiency anaemia. These tests will be sent to a laboratory to help doctors understand why your child has anaemia, and how many children having surgery in South Africa have iron deficiency anaemia.

Taking a blood sample may be uncomfortable and may cause a bruise. Before the blood sample is taken a small amount of numbing cream (EMLA) will be put on to the skin to make your child more comfortable when the sample is taken.

Will my child be treated for anaemia?

Doctors would like to treat all children with anaemia. At the moment doctors do not know for certain what is the best way to do this. The doctors want to find out if they can treat your child's anaemia by giving your child iron syrup or tablets to drink every day before their operation.

The doctors want to make sure the iron medication has the best chance of working. If your child has not been dewormed during the last 6 months, the doctor at the hospital clinic would like to give your child deworming medication.

2. AT HOME BEFORE SURGERY

The doctors would like to give you a 3-month supply of iron to take home and give to your child every day before they have their surgery.

It is very important that the iron medicine is stored in a safe place that your child, or other children cannot reach. Iron overdose can be very dangerous.

If you are worried that a child has taken an iron overdose please contact the Poison Information Helpline 24/7 emergency number 0861 555 777 immediately to find out whether you can monitor your child at home or need to take the to the clinic or hospital.

Some children may have side-effects from taking the iron medication. It is very important that you still try and give your children the medication every day, or it may not work" to "It is very important that you still try and give your child the medication and discuss how to deal with the side effects with the study team. If you are worried or want to ask any questions about the medicine or the study then please send an SMS or WhatsApp message to the research assistant (……, cell phone ……..), and they will call you back. The research assistant will also call you once a week to ask you if your child has managed to take their medication, or if there were any problems with taking the medication.

3. WHEN MY CHILD IS ADMITTED TO HOSPITAL FOR SURGERY

When your child is admitted to hospital for their surgery everything will happen like it normally would. As part of their routine care, a finger-prick or blood sample will be taken to recheck the haemoglobin. Doctors often need to know the result before the operation, but the doctors will also do the blood test when you child is asleep during the operation if it is safe to do so.

Will I find out the results of the blood tests done as part of this study?

The doctor looking after your child in hospital will be able to tell you whether your child's haemoglobin is now better, or whether your child needs further tests or medicine to treat anaemia.

Information collected

If you agree for your child to be part of this study, the doctors will collect the following information which is routinely written down as part of your child's standard patient care during the clinic visit:

- Basic information about your child including age, sex, weight and height.
- Medical information including other illnesses your child may have, if your child takes other medicine at home, the reason you child needs surgery, and the type of surgery your child will have.

This information will be kept both on paper and on computer. To protect your child's privacy, the information will be labelled in a way that will not identify your child. If the results of these studies are published, you and your child's identity will be kept confidential.

By signing this form, you are allowing the use of this information for the research study. This research project has been approved by the University of Cape Town's Human Research Ethics Committee. If you have any ethical concerns or questions about you or your child's rights or welfare as a participant in this research, the Human Research Committee can be contacted on 021 406 6338.

Please read this form carefully and ask the investigator (study doctor) to explain any words or information that are not clear to you. This will help to make sure you understand what you and your child will need to do before you agree for your child to be part of the study. You will be given a copy of this consent form to take home with you. The nurses and doctors will answer any questions you may have about this consent form and about the study.

Appendix A

CONSENT STATEMENT

I officially confirm that:

- I have read the above information form and understand that the study involves research.
- I understand that the doctors will make a copy of some of my child's routinely recorded data.
- I understand that my child will have a finger-prick to check for anaemia.
- I understand if my child's finger-prick test shows that they have anaemia that a blood sample will be taken from my child.
- I understand that my child will be given deworming medication if they have not been dewormed in the last 6 months.
- I understand that if my child has anaemia, I will be given iron and vitamin C medication for my child to take every day before surgery.
- I have had the chance to ask questions. All my questions have been answered to my satisfaction.
- I understand that any information that leaves the doctor's office will be de-identified (i.e., identifying information will be removed from the documents).
- **I understand that iron overdose is very serious and that I must phone 0861 555 777 for help immediately**

Yes ☐ No ☐

Name of child (participant) (printed)		
Parent/ Legal Representative's name (printed)	Signature	Date
Name of person obtaining consent (printed)	Signature	Date
Name of interpreter (printed)	Signature	Date

Appendix B

ASSENT FORM FOR MINORS

TITLE OF THE RESEARCH PROJECT: South African Paediatric Surgical Outcomes Study-2 (SAPSOS-2).

RESEARCHERS' NAME(S): Dr. Heidi Meyer

RESEARCHER'S CONTACT NUMBER: 0799988858

What is RESEARCH*?*
Research is something we do find **NEW KNOWLEDGE** about the way things (and people) work. We use research projects or studies to help us find out more about children and teenagers and the things that affect their lives, their schools, their families and their health. We do this to try and make the world a better place!

What is this research project all about?
When children come to hospital for an operation the nurses or doctors do a blood test. Sometimes one of the results on the blood test is lower than normal. This is called anaemia and doctors know if children have anaemia they may have more problems when they have an operation. Doctors think that it will help if they can give children medicine before they have their operation to make their blood test better.

Why have I been invited to take part in this research project?
Because you are going to have an operation.

Who is doing the research?
The doctors at the hospital.

What will happen to me in this study?
The nurse or the doctor is going to do a finger-prick test. This can be a little bit sore, but it is very quick. If the test result on the finger-prick is lower than normal, then the nurse or doctors will do a blood test. This is what happens when you have a blood test:

(1) Before the needle, a big rubber band that feels like a balloon will be wrapped around your arm. The band will feel tight like someone is squeezing your arm.

(2) The nurse or doctors will clean a small patch of skin on your arm, and this will feel cold.

(3) The needle will be put into the arm and blood will flow into the tube. You will feel a pinch or prick that can sting or hurt a little, or you may feel nothing at all.

(4) Once the blood is taken, the needle comes out and a small bandage is put on the spot where the needle was.

The nurse or doctors will then give you some medicine to take at home every day before you come to hospital for your operation.

Can anything bad happen to me?
Taking a blood sample may be sore and may cause a bruise.

Sometimes the medicine can make your tummy sore. The doctors will call on the telephone every week to ask if you are okay or if the medicine has made your tummy sore.

Appendix B

Can anything good happen to me?
Doctors think that it will help if they can give children medicine before they have their operation to make their blood test better.

Will anyone know I am in the study?
The nurses and the doctors at the hospital looking after you will know you are in the study, but there are lots of children in the study. Afterwards your name will not be used and no-one else will be able to tell you were in the study.

Who can I talk to about the study?
If you are worried or want to ask any questions about the medicine or the study then you can ask questions now or you can talk to the research assistant (TBC, cell phone TBC).

What if I do not want to do this?
Some children do not want to take part in this study, and that is okay. It is also okay to say you want to stop being in the study at any time without getting in trouble.

Do you understand this research study and are you willing to take part in it?

YES	NO

Has the researcher answered all your questions?

YES	NO

Do you understand that you can STOP being in the study at any time?

YES	NO

_____ _____

Signature of Child Date

SOUTH AFRICAN PAEDIATRIC SURGICAL OUTCOMES STUDY 2

IMPORTANT PATIENT INFORMATION

A research study is being conducted at (NAME) Hospital.
The research is being done by (Lead Investigator name) from 05 September to 28 July 2023.

What is this research project all about?
When children come to hospital for an operation the nurses or doctors do a blood test. Sometimes one of the results on the blood test is lower than normal. This is called anaemia and doctors know if children have anaemia they may have more problems when they have an operation. Doctors think that it will help if they can give children medicine before they have their operation to make their blood test better.

Why have I been invited to take part in this research project?
Because you are going to have an operation.

What will happen to me in this study?
The nurse or the doctor is going to do a finger-prick test to check for anaemia. If the test result on the finger-prick is lower than normal, then the nurse or doctors will do a blood test and you will be given an iron supplement to take at home every day before surgery.

Will this study affect my care while I am in hospital?
No. Your care will not change while you are in hospital.

Will my name or any personal details be recorded in this study?
No. Your name and personal details will not be recorded as part of this study. All information from the notes will be kept strictly confidential.

Are there any risks or benefits associated with this study?
Taking a blood sample may be sore and may cause a bruise.
Some children may become constipated, nauseous, or have a sore tummy when they take the iron supplement.

May I withdraw from this study?
Every patient has the right to withdraw from this study.

If you have questions about your rights or welfare as a research participant, please contact the UCT Faculty of Health Sciences Human Research Ethics Committee on +27 (0)21 406 6338.

Appendix D – SAPSOS-2 Patient Information Leaflet

SAPSOS-2 Research Study

Information for parents and guardians of children

This booklet explains what to expect when your child takes iron medicine as part of this study

If you are worried or want to ask any questions about the medicine or the study then please feel free to send an SMS or WhatsApp message to the research assistant (XXX, cell phone XXX), and they will call you back. The research assistant will also call you once a week to ask you if your child has managed to take their medication, or if there were any problems with taking the medication.

It is very important that the iron medicine is stored in a safe place that your child, or other children cannot reach. Iron overdose can be very dangerous. If you are worried a child has taken an iron overdose please contact the Poison Information Helpline 24/7 emergency number 0861 555 777 immediately.

Anaemia

You have been approached because your child may be able to be a part of a research study on anaemia. The doctors that are part of this study are trying to find out if they can test children for anaemia in the hospital clinic and then treat the anaemia before the child has their operation

What is Anaemia?

Anaemia means that the haemoglobin measured on a blood test is lower than normal. Anaemia in children having surgery is very common.

How did the Doctor find out my child has anaemia?

The blood test at the hospital clinic showed that your child has anaemia.

What causes anaemia?

There are different types of anaemia, but the commonest cause of anaemia is not enough iron in the body. This is known as iron deficiency anaemia.

Why does my child have anaemia?

The doctors do not know for certain why your child has anaemia, but they have done blood tests to see whether your child has anaemia because of too little iron.

Why would my child have too little iron?

This can happen three ways

1) Not enough food with iron
2) The body does not absorb iron
3) The body is losing iron eg. bleeding

Can anaemia be treated?

Yes. If the anaemia is caused by a not enough iron, giving iron medication will help.

Yes. If your child has worms this can cause anaemia. Treating your child with deworming medicine every 6 months can help.

When your child is admitted to hospital for surgery the doctors will be able to tell you if the test results in the hospital clinic showed that your child does not have enough iron.

If the anaemia is not because of too little iron, the iron medication will probably not help, but it is still safe for your child to take the medicine.

Can anything good happen to my child if they take the iron?

Doctors think that it will help if they can give children medicine before they have their operation to make the haemoglobin on the blood test better. This will also help them to know how best to treat other children.

At the moment the doctors only check if your child has anaemia the day before, or on the day of the operation. This means there is no time to treat the anaemia before your child has the operation.

Because you have agreed for your child to be part of this study, the doctors have already tested your child for anaemia.

This means the doctors can already try to treat the anaemia by giving your children iron syrup or tablets to drink every day before your child has their operation.

Can anything bad happen to my child if they take the iron?

Your child's poo may be black or darker in colour than usual and that this is normal/expected.

Some children may feel a bit nauseous or have tummy cramps, but this should settle within a week or so.

Constipation

Constipation can be a problem while your child takes this medicine. Fresh fruit, vegetables and high fibre breads and cereals are good foods to help avoid constipation. Make sure your child drinks lots of fluids, like fruit juices, while on the iron medication

How do I give my child the medicine?

Try to give the medicine at same time each day to help you remember to give it.

Use a spoon or a syringe.

Try to give on an empty stomach.

What do I do if my child refuses to take the medicine?

You can mix the iron in other foods such as formula milk, juice, cereal etc

Do not mix it with cow's milk as dairy stops the body absorbing iron absorption; try to wait 2 hours after giving milk before giving the iron

Try to avoid the medicine touching the teeth too much, as it can stain teeth; aim for back of mouth with spoon or syringe, or mix with water or juice. Any staining can be removed by brushing with toothpaste or sodium bicarbonate

When do I start giving my child the medicine?

Your child should take the medicine every day, starting from today.

What will happen when my child is admitted to the hospital for their surgery?

Everything will happen just like it normally would.

When your child is admitted to hospital for their surgery, as part of their routine care, a finger-prick or blood sample will be taken to recheck the haemoglobin. Doctors often need to know the result before the operation, but the doctors will also do the blood test when you child is asleep during the operation if it is safe to do so.

Will I find out the results of the blood tests done as part of this study?

The doctor looking after your child in hospital will be able to tell you whether your child's haemoglobin is better, or whether your child needs further tests or medicine for anaemia.

What happens after the surgery?

If your child still has anaemia, the doctor will tell you if your child needs to have any more tests or take any more medication.

Appendix E

South African Paediatric Surgical Outcomes Study 2
Outpatient Clinic Case Record Form V1.0

SAPSOS-2 unique patient ID: ______ - ______ **Hemacue** ______ $g.dl^{-1}$

Date of outpatient clinic ____/____/______ (DD/MM/YYYY)

Inclusion criteria (Should be *yes* to all)	Yes	No
Age > 6 months to <16 years	☐	☐
Noncardiac surgery	☐	☐
Elective	☐	☐

Exclusion criteria (Should be *no* to all)	No	Yes
Patient, parent or legal guardian refusal	☐	☐
Surgery planned within 6 weeks from surgical outpatient visit	☐	☐
Known history of acquired iron overload, family history of haemochromatosis or thalassemia	☐	☐
Known reason for anaemia (e.g., untreated vit B_{12} or folate deficiency or haemoglobinopathy)	☐	☐
Treatment with oral iron, EPO, IV iron therapy or blood transfusion in the previous 12 weeks	☐	☐
Known hypersensitivity to oral iron or other contraindication to oral iron	☐	☐
Temperature > 38.0 °C or receiving non-prophylactic antibiotics	☐	☐
Acute liver failure	☐	☐

Patient Information

Age: ______ (days) ______ (months) ______ (years) ASA-PS I ☐ II ☐ III ☐ IV ☐

Sex: Female ☐ Male ☐ Height (cm) ______ Weight (kg): ______

Comorbid disease (tick *all* that apply): ☐ Cardiac disease ☐ Cancer ☐ HIV/AIDS ☐ Neurological disorder ☐ Chronic respiratory disease

Dewormed in the last 6 months (including if treated at outpatient clinic): Yes ☐ No ☐

Surgery Information

Planned date of surgery: ____/____/______ (DD/MM/YYYY)

Planned surgical procedure: ______

Severity of surgery: ☐ Minor ☐ Intermediate ☐ Major

Type of surgery: ☐ Cardiac ☐ Thoracic ☐ ENT ☐ Burns

☐ Neurosurgery ☐ Orthopaedic ☐ Hepatobiliary ☐ Gastrointestinal ☐ Gynae

☐ Kidney/Urology ☐ Ophthalmology ☐ Plastics/cutaneous ☐ Burns ☐ Other

✂ -

Patient name: ______ Telephonic contact details ……………………

Patient hospital number : ______ **SAPSOS-2 unique patient ID:** ……………-……………

Appendix F

South African Paediatric Surgical Outcomes Study 2

Telephonic Survey Case Record Form V1.0

Good day. My name is X and I am calling you because you have agreed for your child to be part of the SAPSOS-2 study. This means your child was diagnosed with anaemia at the hospital clinic and that your child was given iron medicine to take every day at home. I would like to ask you a few questions about how well your child is managing with the iron medication.

1) In the past week how many days did your child take their iron medication?

1 2 3 4 5 6 7

2) Questions about specific side-effects

a) Did he/she vomit after the medication? Y / N

Advise to check if it was given on empty stomach, in which case rather advise giving after meal or mixed with food

b) Is he/she complaining of nausea? Y / N

Advise to give with food or after meal rather; if it persists then decrease dose e.g. to alternate days or halve dose per day

c) Any stomach cramps or bloating? Y / N

Advise to take with food, and increase water and fibre intake e.g. fruit and vegetables and unrefined carbohydrates like brown rice and brown bread instead of white

d) Any heartburn (older children)? Y / N

Avoid taking too close to bedtime; take with food

e) Is he/she struggling to pass poo, and if so, is this a new problem? Y / N

(*Advise to increase fluids, fruits and vegetables; add 5 to 10ml sorbitol once to twice a day (2.5 to 5ml <1year) if needed; if it persists despite above measures, decrease dose to alternate days or halve dose per day*) Y/N

f) Any diarrhoea? Y / N

Advise increasing fluid and fibre as above; if it persists, decrease dose to alternate days or halve dose per day)

g) Is there any red blood or severe pain with stooling? Y / N

To speak to clinic or study doctor

3) Do you have any other questions or concerns about your child taking the iron medication?

✂- -

Patient name: ______________________________ DOB | d | d | m | m | y | y | y | y |

Patient hospital number : ____________________ **SAPSOS-2 unique patient ID:** ……………**-**……………

South African Paediatric Surgical Outcomes Study 2 (SAPSOS-2)
Case Record Form (CRF): Admission for Surgery

SAPSOS-2 unique patient ID: ____________ - ____________ **Hemacue** ______ g.dl^{-1} **N/A** ☐

Date of surgical admission ______/______/______ (DD/MM/YYYY)

Pre-Intervention Laboratory Results

Hb ________ g.dl^{-1}

MCV ________ fl

Ferritin ________ mcg.L^{-1}

TSAT ________ %

Reticulocyte Hb content ________ pg

Duration of Oral Iron

Treatment commenced on ______/______/______ (DD/MM/YYYY)

Treatment finished on ______/______/______ (DD/MM/YYYY)

Treatment still ongoing Yes ☐ No ☐

Number of tablets left ____________________

Amount of syrup left ____________________

Post-Intervention Laboratory Results

Hb ________ g.dl^{-1}

MCV ________ fl

Ferritin ________ mcg.L^{-1}

TSAT ________ %

Reticulocyte Hb content ________ pg

✂ –

Patient name: ______________________________ DOB | d | d | m | m | y | y | y | y |

Patient hospital number : ____________________ **SAPSOS-2 unique patient ID:** ……………-……………

Appendix H

Serious Adverse Event (SAE)
Report Form

SOUTH AFRICAN SURGICAL OUTCOMES STUDY 2

Protocol Number:_____

Site Name:_____

Pt ID:_____

Date Participant Reported/Date of Site Awareness:

__ __ / __ __ __ / __ __ __ __
d d m m m y y y y

1. SAE Event Term (Diagnosis, ex: Stroke, Myocardial Infarction).
2. SAE onset date: ___ ___ / ___ ___ ___ / ___ ___ ___ ___
   d d m m m y y y y
3. SAE stop date: ___ ___ / ___ ___ ___ / ___ ___ ___ ___
   d d m m m y y y y
4. Location of SAE:_____
5. Was this an unexpected adverse event? ☐Yes ☐No
6. Brief description of participant with no personal identifiers:

   Sex: ☐F ☐M Age: _____

   Diagnosis for study participation:_____

   _____
7. Brief description of the nature of the SAE (attach description if more space is needed):

   _____

   _____
8. Category of the SAE:

   ☐ Date of death ___/_____/_____ (dd/mmm/yyyy)
   ☐ Life threatening
   ☐ Hospitalization – initial or prolonged
   ☐ Disability/incapacity
   ☐ Congenital anomaly/birth defect
   ☐ Required intervention to prevent permanent impairment
   ☐ Other:_____

9. Intervention type:

   ☐ Medication or nutritional supplement (specify):_____

   ☐ Device (specify):_____

   ☐ Surgery (specify):_____

   ☐ Behavioral/lifestyle (specify):_____

10. Relationship of event to intervention:

    ☐ Unrelated (clearly not related to the intervention)

    ☐ Possible (may be related to the intervention)

    ☐ Definite (clearly related to the intervention)

11. Was study intervention discontinued due to event? ☐Yes ☐No

12. What medications or other steps were taken to treat the SAE?

    _____

13. List any relevant tests, laboratory data, and history, including preexisting medical conditions.

    _____

14. Was this event a study related endpoint?

15. Type of report:

    ☐ Initial

    ☐ Followup

    ☐ Final

Signature of principal investigator: Date:

Appendix I – Drug Company Patient Information Leaflet

VITAFORCE FEROVITE

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS
Unscheduled

PROPRIETARY NAME AND DOSAGE FORM
The name of your medicine is VITAFORCE FEROVITE.
VITAFORCE FEROVITE is available in a tablet dosage form.
The VITAFORCE FEROVITE contains two active ingredients; ferrous fumarate and folic acid.

READ ALL OF THIS LEAFLET CAREFULLY BECAUSE IT CONTAINS IMPORTANT INFORMATION FOR YOU
VITAFORCE FEROVITE is available without a doctor's prescription, for you to treat a mild illness.
Nevertheless, you still need to use VITAFORCE FEROVITE carefully to get the best results from it.

- Keep this leaflet. You may need to read it again.
- Do not share VITAFORCE FEROVITE with any other person.
- Ask your health care provider or pharmacist if you need more information or advice.
- You must see a doctor if your symptoms worsen or do not improve.

WHAT VITAFORCE FEROVITE CONTAINS
Each tablet contains the following active ingredients:

Ferrous Fumarate	
(providing 65,0 mg elemental Iron)	200,0 mg
Folic Acid	100,0 µg

The tablet also contains other ingredients (inactive ingredients): microcrystalline cellulose, povidone, croscarmellose sodium and magnesium stearate.

WHAT VITAFORCE FEROVITE IS USED FOR
VITAFORCE FEROVITE is an iron and folic acid nutritional supplement to help overcome dietary deficiencies particularly during pregnancy. It is used for the prevention of iron deficiency and folate-deficient megaloblastic anaemia in pregnancy. Anaemia means that there is lower than normal number of red blood cells or quantity of haemoglobin in the blood. Iron-deficiency anaemia results from lack of iron, which is necessary for the production of haemoglobin. Folate-deficient megaloblastic anaemia results from deficiency of folate (folic acid).

BEFORE YOU TAKE VITAFORCE FEROVITE
Do not take VITAFORCE FEROVITE if:
If you are hypersensitive (allergic) to (ferrous fumarate or iron salts and folic acid or any of the other ingredients. VITAFORCE FEROVITE is not used for prophylaxis of megaloblastic anaemia associated with vitamin B_{12} deficiency. If you have haemochromatosis (a genetic disorder causing an excess iron in the body), chronic haemolysis (the abnormal breakdown of red blood cells) and frequent transfusions do not use VITAFORCE FEROVITE. If you have problems with the incorporation of iron (sickle cell anaemia - disorder caused by the presence of an abnormal form of haemoglobin), anaemia associated with lead poisoning, thalassemia (hereditary disorder in which the blood makes an abnormal form of haemoglobin), do not use VITAFORCE FEROVITE. If you have severe kidney and liver dysfunction, do not use VITAFORCE FEROVITE.
VITAFORCE FEROVITE should not be used together with iron administered as an injection. This unregistered medicine has not been evaluated by SAHPRA for its quality, safety or intended use.

SPECIAL CARE SHOULD BE TAKEN WITH VITAFORCE FEROVITE
Do not exceed the stated dose. Prolonged administration in excess of the recommended dose may result in iron overload and other side effects. Iron overloading and toxicity may occur in patients receiving both VITAFORCE FEROVITE and iron administered by injection. Care should be taken when VITAFORCE FEROVITE is used by patients with active gastrointestinal inflammation (e.g. gastritis – inflammation of the stomach lining, gastric and duodenal ulcer – ulcer in the stomach and duodenum, Crohn's disease- condition in which parts of the gastrointestinal tract become inflamed, thickened, ulcerated, and scarred or ulcerative colitis – inflammation and ulceration of the colon. Benzidine or similar tests for detection of blood in the faeces may yield false positives. VITAFORCE FEROVITE must be discontinued for 3 days prior to the planned performance of the test. A minority of pregnant women are not protected by physiological doses of folic acid

TAKING VITAFORCE FEROVITE WITH FOOD AND DRINK
Take VITAFORCE FEROVITE on an empty stomach to enhance iron absorption. The concurrent intake of products with a high content of vegetable constituents, phosphates and tannins limits the absorption of iron.
Fish and food with a high content of ascorbic acid and fruit promotes iron absorption.

PREGNANCY AND BREASTFEEDING
VITAFORCE FEROVITE is used in the prevention of iron deficient and folate deficient megaloblastic anaemia in pregnancy. If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other healthcare provider for advice before taking this medicine.

DRIVING AND USING MACHINERY
VITAFORCE FEROVITE does not interfere with your ability to drive and use machines.

IMPORTANT INFORMATION ABOUT SOME OF THE INGREDIENTS OF VITAFORCE FEROVITE
VITAFORCE FEROVITE tablets are sugar-free.

TAKING OTHER MEDICINES WITH VITAFORCE FEROVITE
Always tell your healthcare provider if you are taking any other medicines (This includes complementary or traditional medicines).
Examples of medicines that may interact with VITAFORCE FEROVITE tablets include:
Tetracyclines, administer VITAFORCE FEROVITE at least three hours before or two hours after the tetracycline.
Medicine containing calcium and magnesium bicarbonates (including antacids) as well as carbonates oxalates and phosphates and trientine. These medicines impair iron absorption by formation of insoluble complexes.
Cholestyramine prevents intestinal absorption of iron.
Avoid taking chloramphenicol and VITAFORCE FEROVITE at the same time; take them three hours apart from each other.
VITAFORCE FEROVITE can decrease the absorption of other medicines including; bisphosphonates, fluoroquinones, levodopa, methyldopa, carbidopa, entacapone, penicillamine and mycophenolate.
Sulphonamides, anticonvulsants and barbiturates impair the absorption of folic acid. Administration of VITAFORCE FEROVITE with food may impair the absorption of iron.
Tetracyclines, administer VITAFORCE FEROVITE at least three hours before or two hours after the tetracycline.

HOW TO TAKE VITAFORCE FEROVITE
Do not share medicines prescribed for you with any other person.
Always take VITAFORCE FEROVITE exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.
Adults: 18 years and older
Take 1 to 3 tablets daily or as directed by your health care provider.
Take the tablets on an empty stomach to enhance iron absorption.
Your doctor will tell you how long your treatment will last. If you have the impression that the effect of VITAFORCE FEROVITE is too strong or too weak, tell your doctor or pharmacist.

IF YOU TAKE MORE VITAFORCE FEROVITE THAN YOU SHOULD
The initial symptoms you may experience include: diarrhoea, nausea and vomiting, abdominal cramping, vomiting of blood, rectal bleeding, lack of energy and enthusiasm (lethargy) and general or specific failure of the circulation (circulatory collapse). Excess glucose in the bloodstream (hyperglycaemia) and metabolic acidosis (when the body produces too much acid or when the kidneys are not removing enough acid from the body) may occur.
In the event of over dosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.

IF YOU FORGET TO TAKE A DOSE OF VITAFORCE FEROVITE
Do not take a double dose to make up for forgotten individual doses.
Continue taking the tablets as directed on the label.
Contact your healthcare provider for further advice.

POSSIBLE SIDE EFFECTS
VITAFORCE FEROVITE can have side effects.
Stop taking VITAFORCE FEROVITE immediately and check with your doctor immediately or go to the casualty department at your nearest hospital: If you experience, rapid shallow breathing, dizziness or light-headedness, fainting, lack of concentration, cold, clammy, pale skin, fatigue, vomiting, abdominal cramping, vomiting of blood, rectal bleeding, lack of energy and enthusiasm (lethargy) and general or specific failure of the circulation (circulatory collapse).
Other side effects may occur. However check with your doctor if any of the following side effects continue or are bothersome:
Discoloured faeces, abdominal bloating, upper abdominal pain, constipation, diarrhoea, nausea and allergic dermatitis.
Not all side effects reported for VITAFORCE FEROVITE are included in this leaflet. Should your general state of health worsens while taking VITAFORCE FEROVITE, please consult your doctor, pharmacist or other healthcare provider for advice.
If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

STORING AND DISPOSING OF VITAFORCE FEROVITE
Store at or below 25 °C.
Store all medicines out of reach of children.
Store in the original package / container.
Keep the container tightly closed.
Protect from light.
Protect from moisture.
Do not store in a bathroom.
Do not use after the expiry date stated on the label.
Do not use VITAFORCE FEROVITE if you notice visible signs of deterioration.
Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

PRESENTATION OF VITAFORCE FEROVITE
White plastic container with a white plastic screw cap containing 28, 56, 84, 100, 500 or 1000 tablets

IDENTIFICATION OF VITAFORCE FEROVITE
Light brown speckled round tablet

REGISTRATION NUMBER
TBA

DATE OF REGISTRATION
TBA

PROFESSIONAL INFORMATION
For further information refer to the Professional Information of the product.

NAME AND ADDRESS OF REGISTRATION HOLDER
Ascendis Supply Chain (Pty) Ltd
1 Carey Street
Wynberg, Sandton
JOHANNESBURG
2090
+27 11 036 9420

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION
TBA

VITAFORCE FEROVITE

PASIËNTINLIGTINGSBLAADJIE

SKEDULERINGSTATUS
Ongeskeduleer

HANDELSNAAM EN DOSEERVORM
Die naam van jou medikasie is VITAFORCE FEROVITE.
VITAFORCE FEROVITE is beskikbaar in 'n tablet doseervorm.
Die VITAFORCE FEROVITE bevat twee aktiewe bestanddele; ysterfumeraat en foliensuur.

LEES DIE HELE INLIGTINGSBLAADJIE NOUKEURIG DEUR, DIT BEVAT BELANGRIKE INLIGTING VIR JOU
VITAFORCE FEROVITE is beskikbaar sonder 'n dokters voorskrif, vir jou om matige siekte te behandel.
Ongeag, jy moet steeds VITAFORCE FEROVITE versigtig gebruik om die beste resultate te verkry.

- Hou hierdie pamflet. Dit mag dalk nodig wees om dit weer te lees.
- Moet nie VITAFORCE FEROVITE met enige ander persoon deel nie.
- Vra jou gesondheidsorgverskaffer of apteker as jy meer inligting of advies benodig.
- Raadpleeg 'n dokter as jou simptome versleg of nie verbeter nie.

WAT VITAFORCE FEROVITE BEVAT
Elke tablet bevat die volgende aktiewe bestanddele:

Yster Fumeraat	
(verskaf 65,0 mg elementale Yster)	200,0 mg
Foliensuur	100,0 µg

Die tablet bevat ook ander bestanddele:
(onaktiewe bestanddele): mikrokristallyn sellulose, povidoon, kroskarmellose natrium en magnesium stearaat.

WAARVOOR VITAFORCE FEROVITE GEBRUIK WORD
VITAFORCE FEROVITE is 'n yster en foliensuur voedingsaanvulling wat help om dieetkekorte, verral tydens swangerskap, te behandel. Dit word gebruik vir die voorkoming van yster en folaat-tekort megaloblastiese anemie in swangerskap. Anemie beteken dat daar laer as die normale hoeveelheid rooibloedselle of hoeveelheid hemoglobien in die bloed is. Yster-tekort anemie kom voor as gevolg van 'n tekort aan yster, wat nodig is vir die produksie van hemoglobien. Folaat-tekort megaloblastiese anemie kom voor as gevolg van 'n tekort aan folaat (foliensuur).

VOORDAT VITAFORCE FEROVITE GEBRUIK WORD
Moet nie VITAFORCE FEROVITE neem as:
Jy hipersensitief (allergies) is vir yster fumeraat, yster-soute en foliensuur of enige van die ander bestanddele. VITAFORCE FEROVITE word nie gebruik vir die profilakse van megaloblastiese anemie wat geassosieer word met vitamien B_{12} tekort nie. As jy aan hemochromatosis ('n genetiese afwyking wat 'n oormatige hoeveelheid yster in die liggaam veroorsaak) en kroniese hemolise (die abnormale afbraak van rooibloedselle) ly of gereelde bloedoortappings kry, moet nie VITAFORCE FEROVITE gebruik nie. As jy probleme het met die insluiting van yster (sekelsel-anemie, afwyking wat veroorsaak word deur die teenwoordigheid van 'n abnormale vorm van hemoglobien), anemie geassosieer met lood-vergiftiging of tallassemia (oorerflike afwyking waar bloed 'n abnormale vorm van hemoglobien produseer) moet nie VITAFORCE FEROVITE gebruik nie. As jy ernstige nier -en lewer inkorting het, moet nie VITAFORCE FEROVITE gebruik nie. VITAFORCE FEROVITE moet nie tesamelik gebruik word moet yster wat deur inspuiting toegedien word nie. Hierdie ongeregistreerde medisyne is nie deur SAHPRA geëvalueer vir sy gehalte, veiligheid of beoogde gebruik nie.

NEEM SPESIALE SORG MET VITAFORCE FEROVITE
Moet nie die gestelde dosis oorskry nie. Verlengde toediening in oormaat, meer as die gestelde dosis mag in yster-oorlading en ander newe-effekte resulteer. *Yster-oorlading en toksisiteit mag voorkom in pasiënte wat beide VITAFORCE FEROVITE en yster wat deur inspuiting toegedien word, gebruik. Sorg moet geneem word wanneer VITAFORCE FEROVITE gebruik deur pasiënte met aktiewe gastrointestinale inflammasie (bv gastritis - inflammasie van die maagslymvlies, gastriese-en duodenale ulsers - ulsers in die maag en duodenum, Crohn se siekte - toestand waar gedeeltes van die spysverteringskaal inflammasie ontwikkel, verdik of ulseratief raak of littekens ontwikkel en ulseratiewe kolitis - inflammasie en ulserasie van die kolon. Bensidien of soortgelyke toetse vir die teenwoordigheid van bloed in feses, mag vals positiewe resultate lewer. VITAFORCE FEROVITE moet onttrek word 3 dae voor die beplande uitvoering van die toets. 'n Minderheid van swanger vroue word nie beskerm deur fisiologiese dosisse van foliensuur nie.*

NEEM VAN VITAFORCE FEROVITE MET KOS EN DRANK
Neem VITAFORCE FEROVITE op 'n leë maag op yster absorpsie te verbeter. Die gelyktydige inname van produkte met 'n hoë inhoud van groente-bestanddele, fosfate en tannoïede, beperk die absorpsie van yster.
Vis, voedsel met 'n hoë askorbiensuur inhoud en vrugte bevorder die absorpsie van yster.

SWANGERSKAP EN BORSVOEDING
VITAFORCE FEROVITE word gebruik in die voorkoming van yster en folaat-tekort megaloblastiese anemie in swangerskap.
Indien jy swanger is of borsvoed, raadpleeg jou dokter, apteker of ander gesondheidsorgpraktisyn vir advies voor die gebruik van hierdie medikasie.

DIE BESTUUR EN GEBRUIK VAN MASJINERIE
VITAFORCE FEROVITE belemmer nie jou vermoë om te bestuur of masjinerie te gebruik nie.

BELANGRIKE INLIGTING IN VERBAND MET SOMMIGE VAN DIE BESTANDDELE IN VITAFORCE FEROVITE
VITAFORCE FEROVITE tablette is suiker-vry.

AS JY ANDER MEDISYNE SAAM MET VITAFORCE FEROVITE NEEM
Raadpleeg altyd jou gesondheidsorgpraktisyn as jy enige ander medikasie gebruik (Dit sluit komplimentêre en tradisionele medikasie in).

Voorbeelde van medikasie wat interaksies met VITAFORCE FEROVITE kan hê sluit in:
Tetrasikliene, dien VITAFORCE FEROVITE ten minste drie ure voor of twee ure na tetrasikliene toe.
Medikasie wat kalsium en magnesium bikarbonaat bevat (insluitend teensuurmiddels) sowel as karbonate, oksalate, fostate en trientiene.
Hierdie medikasie kan ysterabsorpsie belemmer deur formulering van onoplosbare komplekse.
Kolestiramien voorkom die intenstinale absorpsie van yster.
Vermy die gelyktydige gebruik van chlooramfenikol en VITAFORCE FEROVITE; neem hulle drie ure weg van mekaar af.
VITAFORCE FEROVITE kan die absorpsie van ander medikasie verminder insluitend; botostonate, fluorokinolone, levodopa, metieldopa, karbidopa, entakapoon, pensiellamiene en mikofenoloaat.
Sulfoonamiede, antikonvulsante en barbiturate, inhibeer die absorpsie van foliensuur. Gelyktydige toediening van VITAFORCE FEROVITE met voedsel mag die absorpsie van yster inhibeer.
Tetrasikliene, dien VITAFORCE FEROVITE ten minste drie ure voor of twee ure na tetrasikliene toe.

HOE OM VITAFORCE FEROVITE TE GEBRUIK

Moenie jou medisyne met enige iemand anders deel nie.
Neem VITAFORCE FEROVITE altyd presies soos aanbeveel. Bevestig met jou dokter of apteker indien jy onseker is.
Volwassenes 18 jaar en ouer
Neem 1 tot 3 tablette daagliks of soos aanbeveel deur 'n gesondheidsorgpraktisyn.
Neem die tablette op 'n leë maag om yster absorpsie te verbeter.
Jou dokter sal jou adviseer oor hoe lank jou terapie sal duur. As jy onder die indruk is dat die effek van VITAFORCE FEROVITE te sterk of te swak is, raadpleeg jou dokter of apteker.

INDIEN JY MEER VITAFORCE FEROVITE GEBRUIK AS WAT JY BEHOORT

Die aanvanklike simptome wat jy mag ervaar sluit in: diarree, naarheid en braking, abdominale krampe, braak van bloed, rektale bloeding, tekort aan energie en entoesiasme (letargie) en algemene of spesifieke mislukking van sirkulasie (sirkulatoriese ineenstorting).Oormatige glukose in die bloedstroom (hiperglisemie) en metaboliese asidose (wanneer die liggaam te veel suur produseer of wanneer die niere nie genoeg suur uit die liggaam verwyder nie), mag voorkom.
In die geval van 'n oordosis, raadpleeg jou dokter of apteker. As nie een beskikbaar is nie, kontak die naaste hospitaal of gifbeheersentrum.

INDIEN JY VERGEET HET OM VITAFORCE FEROVITE TE NEEM

Moenie 'n dubbele dosis neem om vir oorgeslane dosisse te vergoed nie.
Hou aan om die tablette te neem soos aangedui word op die etiket.
Kontak jou gesondheidsorgpraktisyn vir verdere advies.

MOONTLIKE NEWE-EFFEKTE

VITAFORCE FEROVITE kan moontlik newe-effekte veroorsaak.
Staak die gebruik van VITAFORCE FEROVITE onmiddelik en raadpleeg jou dokter of gaan na die ongevalle departement van die naaste hospitaal: As jy vinnige en oppervlakkige asemhaling, duiseligheid of lighoofdigheid, floute, tekort aan konsentrasie, koue, klam en bleek vel, moegheid, braking, abdominale krampe, braking van bloed, rektale bloeding, tekort aan energie en entoesiasme (letargie) en algemene of spesifieke ineenstorting van sirkulasie (sirkulatoriese ineenstorting).
Ander newe-effekte mag voorkom. Raadpleeg egter jou dokter as enige van die newe-effekte aanhou of lastig raak: Verkleurde feses, abdominale opgeblasenheid, boonste abdominale pyn, konstipasie, diarree, naarheid en allergiese dermatitis.
Nie alle newe-effekte wat vir hierdie medisyne aangemeld is word in hierdie voubiljet genoem nie. Indien jou algemene gesondheid verswak of indien jy enige nadelige effekte ondervind terwyl jy hierdie medikasie gebruik, moet jy asseblief jou dokter, apteker of ander gesondheidsorgpraktisyn raadpleeg.
Indien jy enige newe-effekte waarneem wat nie in hierdie voubiljet genoem word nie, moet jy jou dokter of apteker daarvan vertel.

BERGING EN WEGDOEN VAN VITAFORCE FEROVITE

Bewaar teen of benede 25 °C.
Bewaar alle medikasie buite bereik van kinders.
Bewaar in die oorspronklike houer.
Maak die houer dig toe.
Beskerm teen lig.
Beskerm teen vog.
Moet nie in die badkamer stoor nie.
Moet nie gebruik na die vervaldatum wat op die etiket aangedui is nie.
Moenie VITAFORCE FEROVITE gebruik indien jy enige sigbare tekens van produkafbraak opmerk nie.
Bewaar die houer in die kartonverpakking.
Bewaar in die oorspronklike houer.

AANBIEDING VAN *VITAFORCE FEROVITE*

Wit, plastiek houer *met 'n wit pastiek skroefprop wat 28, 56, 84, 100,* 500 of 1000 tablette *bevat.*

IDENTIFIKASIE VAN VITAFORCE FEROVITE

Ligbruin, gespikkelde, ronde tablet

REGISTRASIENOMMER

TBA

DATUM VAN REGISTRASIE

TBA

PROFESSIONELE INLIGTING

Verwys na die voubiljet met professionele inligting vir meer inligting.

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE REGISTRASIESERTIFIKAAT

Ascendis Supply Chain (Pty) Ltd.
1 Carey Straat
Wynberg, Sandton
JOHANNESBURG
2090
+27 11 036 9420

DATUM VAN PUBLIKASIE VAN DIE PROFESSIONELE INLIGTING

TBA

VITAFORCE FEROVITE

PROFESSIONAL INFORMATION

SCHEDULING STATUS

Unscheduled

PROPRIETARY NAME AND DOSAGE FORM

VITAFORCE FEROVITE, tablet

COMPOSITION

Each tablet contains:

Ferrous Fumarate (providing 65,0 mg elemental Iron)	200,0 mg
Folic Acid	100,0 µg

Inactive ingredients: Microcrystalline cellulose, povidone, croscarmellose sodium and magnesium stearate.
Sugar free

PHARMACOLOGICAL CLASSIFICATION

A 8.3 Erythropietics (haematinics)

PHARMACOLOGICAL ACTION

Folic acid in the body is reduced to tetra hydrofolate, a co-enzyme for various metabolic processes. Ferrous fumarate is a source of iron for iron deficiency anaemia.

INDICATIONS

VITAFORCE FEROVITE is an iron and folic acid nutritional supplement to help overcome dietary deficiencies particularly during pregnancy. It is indicated for the prophylaxis of iron deficiency and folate-deficient megaloblastic anaemia in pregnancy.
VITAFORCE FEROVITE is not intended to the treatment of megaloblastic anaemia in pregnancy, only for its prevention and it's not indicated for the prevention or treatment of anaemia in men, non-pregnant women, or children.

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients. Megaloblastic anaemia associated with vitamin B_{12} deficiency. Iron overload (haemochromatosis, chronic haemolysis, frequent transfusions). Problems with incorporation of iron (sickle cell anaemia, anaemia associated with lead poisoning, thalassemia). Severe renal and hepatic dysfunction. Do not use in conjunction with parenteral iron formulations.

WARNINGS AND SPECIAL PRECAUTIONS

Do not exceed the stated dose. Prolonged administration in excess of the recommended dose may result in iron overload and other adverse reactions. Iron overloading and toxicity may occur in patients receiving both VITAFORCE FEROVITE and parenteral administration of iron (see CONTRAINDICATIONS).
Gastrointestinal Inflammation: Care should be taken when administering VITAFORCE FEROVITE to patients with active gastrointestinal inflammation (e.g. gastritis, gastric and duodenal ulcer, Crohn's disease or ulcerative colitis).
Stool darkening: VITAFORCE FEROVITE may lead to darkening of the stool, giving the appearance of a tarry stool.
Investigation: Benzidine or similar tests for detection of faecal occult blood may yield false positives. VITAFORCE FEROVITE must be discontinued for 3 days prior to the planned performance of the test.
A minority of pregnant women are not protected by physiological doses of folic acid.
The development of anaemia despite prophylaxis with VITAFORCE FEROVITE calls for investigation and appropriate therapy.
Ability to perform tasks that require judgement, motor or cognitive skills: No effect on the ability to drive and use of machines was observed.
This unregistered medicine has not been evaluated by SAHPRA for its quality, safety or intended use.

INTERACTIONS

The absorption of iron salts and tetracyclines is diminished when taken concomitantly. If treatment with both VITAFORCE FEROVITE and a tetracycline is required, the iron salt should be administered at least three hours before or two hours after the tetracycline. Medicine containing calcium and magnesium bicarbonates (including antacids) as well as carbonates oxalates and phosphates and trientine, impair iron absorption by formation of insoluble complexes.
Cholestyramine inhibits intestinal absorption of iron.
The concomitant administration of chloramphenicol may delay the therapeutic action of VITAFORCE FEROVITE.
VITAFORCE FEROVITE can decrease the absorption of other medicines including; bisphosphonates, fluoroquinones, levodopa, methyldopa, carbidopa, entacapone, penicillamine and mycophenolate.
Sulphonamides, anticonvulsants and barbiturates impair the absorption of folic acid. Administration of VITAFORCE FEROVITE with food may impair the absorption of iron.
The concurrent intake of products with a high content of vegetable constituents, phosphates and tannins limits the absorptions limits the absorption of iron, while fish and food with a high content of ascorbic acid and fruit have the opposite effect.

HUMAN REPRODUCTION

PREGNANCY: VITAFORCE FEROVITE is indicated for the prevention of iron deficiency anaemia in pregnancy.

LACTATION: Folic acid is excreted in breast-milk. The amount of iron and folic acid which is transferred from VITAFORCE FEROVITE to breast-milk has not been determined and it is not known if adverse effects occur in the breastfed infants of mothers who receive VITAFORCE FEROVITE treatment.

DOSAGE AND DIRECTIONS FOR USE

Adults 18 years and older:
Take 1 to 3 tablets daily or as directed by your health care provider.
Tablets to be taken on an empty stomach to enhance iron absorption.

SIDE EFFECTS

Gastrointestinal disorders:
Frequent: faeces discoloured, abdominal bloating, upper abdominal pain, constipation, diarrhoea, nausea.
Skin and subcutaneous tissue disorder:
Less frequent: allergic dermatitis.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Signs and symptoms:
Initial symptoms of iron overdosage include nausea, vomiting, diarrhoea, abdominal pain, haematemesis, rectal bleeding, lethargy and circulatory collapse. Hyperglycaemia and metabolic acidosis may occur.
In severe cases after visible transient improvement, relapse may occur after 24-48 hours manifested by hypotension, coma, hypothermia, hepatocellular necrosis, renal failure, pulmonary oedema, circulatory failure, convulsions, coma and death.
Chronic overdosage may present as haemosiderosis or haemochromatosis. This is especially likely if anaemia resistant to treatment is erroneously diagnosed as iron deficiency.
Ingestion of a large of overdosage of VITAFORCE FEROVITE requires emergency treatment.
Treatment:
The treatment of mild to moderate poisoning is based on the induction of emesis. It should be borne in mind that perforation may occur in patients, in whom the gastric wall is already damaged. In severe cases of poisoning, particularly if the serum iron concentration exceeds the total iron binding capacity, desferroxamine, an iron-chelating agent, should be administered orally or parenterally as a specific antidote. A solution of 10 g desferroxamine in 50 ml of water should be left in the stomach. Alternatively, a 1 % solution of sodium bicarbonate may be employed, some of which should be left in the stomach. Also give 2 g desferroxamine in 10 ml water for injections by intramuscular injection. Exchange transfusion and surgical treatment must be considered if a potentially lethal dose of VITAFORCE FEROVITE has been ingested and cannot be removed from the gastrointestinal tract with the methods described above. Treatment also includes monitoring of the status of the circulation through standard examination and observation of the other signs, particularly fluid balance and acid-base imbalance. Fluid replacement is essential.

IDENTIFICATION

Light brown speckled round tablet.

PRESENTATION

White plastic container with a white plastic screw cap containing 28, 56, 84, 100, 500 or 1000 tablets.

STORAGE INSTRUCTIONS

Store at or below 25 °C.
Protect from light.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

TBA

DATE OF REGISTRATION

TBA

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Ascendis Supply Chain (Pty) Ltd.
1 Carey Street
Wynberg, Sandton
JOHANNESBURG
2090.
+27 11 036 9420

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION

TBA

842650/02

vitaforce

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Pro-Print

SCHEDULING STATUS: S0

PROPRIETARY NAME (and dosage form):

RESMED FERROUS GLUCONATE SYRUP

COMPOSITION: Each 5 ml contains:

Ferrous Gluconate 350 mg

Preservatives:

Sodium benzoate 0,1% m/v

Methyl hydroxybenzoate 0,2% m/v

Propyl hydroxybenzoate 0,02% m/v

Contains TARTRAZINE

PHARMACOLOGICAL CLASSIFICATION:

A 8.3 Erythropoietics (Haematinics).

PHARMACOLOGICAL ACTION:

Ferrous Gluconate is absorbed from the stomach and small intestine and combines with apoferritin to form ferritin which is stored in the liver, spleen, red bone marrow and intestinal mucosa.

INDICATIONS:

Iron deficiency anaemia.

CONTRA-INDICATIONS:

Ferrous Gluconate should not be given to patients receiving repeated blood transfusions, or in cases of existing haemochromatosis, haemosiderosis or other anaemic conditions, unless accompanied by iron deficiency. It should not be administered concomitantly with parenteral iron.

DOSAGE AND DIRECTIONS FOR USE:

Children under 2 years: 5 - 10 drops

2 to 5 years: 10 - 20 drops

5 to 12 years: 2 - 2,5 ml

Adults & children older than 12 years:

1 - 2 medicine measures

three or four times daily after meals or as directed by the physician.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

The oral administration of iron preparations sometimes produces gastrointestinal irritation, abdominal pain, nausea and vomiting. These irritant adverse effects are usually related to the amount of elemental iron taken rather than the type of preparation. Other gastrointestinal effects may include either diarrhoea or constipation. Adverse effects may be reduced by giving it with or after food rather than on an empty stomach or by beginning therapy with a small dose and increasing gradually. The faeces of patients taking iron salts may be coloured black.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdosage may be fatal, especially in small children. Seek medical attention immediately.

IDENTIFICATION:

A brown liquid.

PRESENTATION:

100 ml amber plastic bottles.

STORAGE INSTRUCTIONS:

Store at or below 25°C. Protect from light. Keep well closed.

KEEP OUT OF REACH OF CHILDREN

REFERENCE NUMBER: H880 (Act 101/1965)

NAME AND BUSINESS ADDRESS OF APPLICANT:

Resmed Healthcare,

71 Rochdale Road,

Springfield Park, Durban, 4051

DATE OF PUBLICATION OF THIS PACKAGE INSERT: 08/12/1974