Cover Page

South African Paediatric Surgical Outcomes Study 2 (SAPSOS2)

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

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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 5.0

05 August 2023

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TBC

Sponsor

University of Cape Town

Funders

Society for the Advancement of Patient Blood Management

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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	1110 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 in not less than 4 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	08 February 2023
Proposed end date	26 July 2024
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 in not less than 4 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 1110 patients and these will be divided across 7 sites:

Sites	Number of patients to be screened	Estimated number of patients with IDA
Western Cape	**460**	**18**
Red Cross War Memorial Children's Hospital	310	12
Tygerberg Hospital	150	6
KwaZulu-Natal	**250**	**10**
Inkosi Albert Luthlui Hospital	150	6
Greys Hospital	100	4
Gauteng	**400**	**16**
Steve Biko Hospital	100	4
Kalafong Hospital	100	4
Chris Hani Baragwanath Hospital	100	4
Charlotte Maxeke Johannesberg Academic Hospital	100	4
Total	**1110**	**44**

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 1110 individuals to the study over a cumulative 9-month period.

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

Table 3: Ferrous sulphate - Elemental iron 55mg tablets Dosing

Weight Range	*Dose*
20 to < 27 kg	*1 tab bd*
27 to < 37 kg	*2 tab am/1 tab pm*
37 kg and above	*2 tab 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 (1110 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 $<7.0 g.dl^{-1}$ 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?

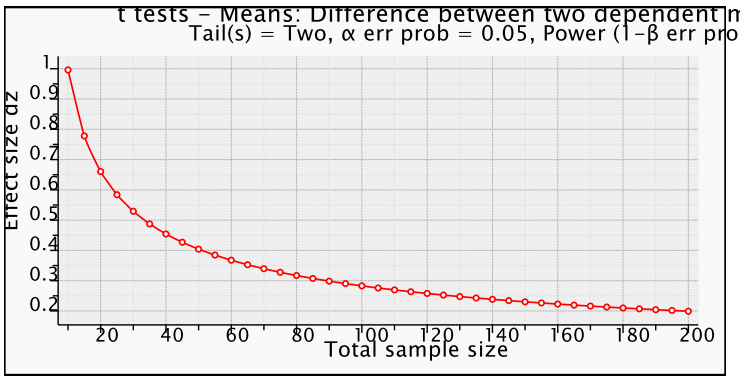
n = 420*0.90*0.462 ~ 176

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.

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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

Appendix F – SAPSOS2 Telephonic Survey Case Record Form V1.0

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