Erythropoietin to Prevent Unnecessary Transfusions in Patients with Cyanotic CHD - A Prospective Control Trial

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Erythropoietin to Prevent Unnecessary Transfusions In Patients With Cyanotic Congenital Heart Disease – A Prospective Randomized Control Trial

Protocol

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A Introduction

A1 Study Abstract

Children with cyanotic heart disease, "blue babies", have chronically low oxygen levels and are at particular risk for death and poor outcomes because of their reduced ability to provide adequate oxygen to the body and brain. These infants should ideally maintain hemoglobin or red blood cell levels greater than 13 g/dL or a hematocrit >40% (Strauss 1991, Roseff 2002), to deliver adequate amounts of oxygen to the body. Healthy infants often experience a drop in their red blood cell level during their first few months of life, as part of the body's normal maturation process. Children with cyanotic heart disease experience this same phenomenon, but are also exposed to additional risks such as critical illness and surgical procedures. Thus, newborns with cyanotic heart disease may require blood transfusions as part of their care in order to provide adequate oxygen to the body. Although rare, the adverse outcomes due to transfusions can be devastating to this population. These complications include transmitted infections, transfusion reactions, additional hospitalizations, and production of antibodies that could complicate heart transplant if needed in the future. Epoetin alfa (EPO) and iron stimulate red blood cell production. Studies with EPO have been done in premature infants and children prior to surgery in order to assess the drug's ability to increase red blood cell levels [1-4]. They show that early administration of EPO has reduced the use of blood transfusions. We seek to investigate, through a prospective randomized controlled trial, if EPO and iron make a clinically significant difference in the number of transfusions given to infants with cyanotic heart disease. We hypothesize that prophylactic EPO and iron may prevent and/or decrease the amount of blood transfusions needed in this population.

A2 Primary Hypothesis

We hypothesize that prophylactic EPO and iron can prevent and/or decrease the amount of blood transfusions needed in this population.

A3 Purpose of the Study Protocol

The purpose of this study protocol is to provide a guide and timeline for the completion of this prospective randomized controlled trial.

B Background

B1 Prior Literature and Studies

We are not aware of any studies that have investigated this question in this specific population. There have been multiple studies looking at the efficacy of EPO in the premature infant population (Donato 2005). In these studies, EPO has been shown to prevent blood transfusions, however it is not necessarily clinically significant in the long term. The clinical significance is different in our study population, because blood transfusions may have significant implications for transplant candidacy in the future and transplant complications if needed. There is a study involving infants and children with

craniosynostosis showing that EPO is safe and can reduce the number of blood transfusions in a surgical group that has high risk for bleeding (Fearon 2001).

B2 Rationale for this Study

Congenital heart disease occurs in about 1% of all live births. Cyanotic cardiac lesions in particular are at risk for significant mortality and morbidity because of their reduced ability to provide adequate oxygenation to the body and the brain. Many experts believe that to ensure adequate oxygen carrying capacity these infants should ideally have a hemoglobin level greater than 13 g/dL or hematocrit >40% (Strauss 1991; Roseff 2002). Many of these patients require blood transfusions prior to surgery to provide adequate oxygenation. The cause for this is likely multifactorial including normal neonatal physiology, frequent lab draws, and co-morbidities. Although rare, the morbidity due to transfusions can be devastating to this population including transmitted infections, transfusion reactions, extra hospitalizations, and antigen sensitization that would complicate heart transplant if needed.

There are centers in the United States that have developed protocols using erythropoietin to minimize blood product transfusions before and after surgery, also referred to as "bloodless surgery"[4]. There have been retrospective studies evaluating the success of these protocols, but there are no randomized controlled prospective studies that have studied the effects of erythropoietin in patients with cyanotic heart disease in regards to transfusion prevention. There have also been multiple studies looking at the efficacy of EPO in the premature infant population (Donato 2005). In these studies, EPO has been shown to prevent blood transfusions. However, these findings did not represent a clinically significant difference for the study population in the long term. The clinical significance is enhanced in our study population, because blood transfusions may have significant implications for transplant candidacy in the future and transplant complications if needed. Last, there is a study involving infants and children with craniosynostosis showing that EPO is safe and can reduce the number of blood transfusions in a surgical group that has high risk for bleeding (Fearon 2001).

C Study Objectives

C1 Primary Aim

Congenital cyanotic cardiac patients require higher hemoglobin concentrations for optimal oxygen delivery. Prophylactic erythropoietin can prevent and/or decrease the amount of blood transfusions needed prior to surgery. We seek to investigate if erythropoietin makes a clinically significant difference in the number of transfusions given to these patients and the morbidity associated with it during the period in which the subjects will be active in the study (from baseline to 14 weeks post initial injection). The primary aim will be assessed when all subjects have completed week 14 or discontinue early.

C2 Secondary Aim

We will also look to see if administering erythropoietin makes a clinical significance in the following outcomes during the period in which the subjects will be active in the study

(from baseline to 14 weeks post initial injection): weight gain, oxygen saturations, length of initial hospital stay, and hospital readmissions (related to failure to thrive or cyanosis).

C3 Rationale for the Selection of Outcome Measures

Transfusions are currently the treatment of choice for clinically significant anemia in the cyanotic congenital heart patient. However, this therapy requires hospitalization and an intravenous line which does not come without risk, in addition to the risks associated with transfusions which include transfusion reactions from blood type incompatibility, antibody sensitization, and infections. Thus, the primary outcome will be to see if the number of transfusions can be reduced by administering erythropoietin.

Although the hemoglobin level, in and of itself, should not affect oxygen saturation measured by pulse oximetry, our anecdotal experience suggest that oxygen saturations in patients with cyanotic heart disease frequently improve after a blood transfusion to increase the amount of hemoglobin. Thus, the secondary outcome of oxygen saturation will be looked at for 2 reasons. First, to ensure that the treatment and control arms are similar at baseline to prevent bias for transfusions based on criteria set below. Second, to determine if our anecdotal experience has any validity.

The secondary outcome of weight gain is appropriate in the setting of infants as this variable has been used to monitor the ability to thrive and meet the body's metabolic demands. It is well established in pediatrics that the neonate and infant should gain 15-30 grams per day for optimal growth. Infants who are cyanotic, already have a deficiency in meeting their metabolic demands due to a reduced oxygen carrying capacity. This is further complicated in the instance of anemia. Thus, infants may have an increased ability to optimize weight gain in the setting of normal, stable hemoglobin levels which may be achieved with erythropoietin.

Often, cyanotic congenital heart defect neonates have prolonged initial hospital stays due to the inability to maintain acceptable oxygen saturations, and transition to adequate oral intake for appropriate weight gain. If the hospital stay is found to be shortened after starting erythropoietin, this may be of clinical and financial significance.

The number of hospital readmissions (related to failure to thrive or cyanosis) may imply the overall clinical stability of a patient. Because these infants are at high risk for mortality at home, there are multiple reasons why they may be admitted to the hospital including clinically significant anemia which requires blood transfusions, poor weight gain, difficulty feeding, inadequate oxygen saturations, and illnesses. Each admission is stressful to the patient and their families. Having a normal hemoglobin level may have a role in preventing several of these factors, especially regarding failure to thrive or cyanosis.

D Investigational Agent

D1 Preclinical Data

Epoetin alfa is approved for use by the US Food and Drug Administration. The current labeled use is to treat a lower than normal number of red blood cells (anemia) caused by

chronic kidney disease in patients on dialysis to reduce or avoid the need for red blood cell transfusions. It should not be used in place of emergency treatment for anemia (red blood cell transfusions). It has not been proven to improve quality of life, fatigue, or well-being.

Common side effects include joint pain, muscle pain, bone pain, fever, cough, rash nausea, vomiting, soreness of mouth, itching, headache, redness and pain in the injection site.

More serious side effects such as stroke, seizures, antibodies to Epoetin alfa, and serious allergic reactions have also been reported.

D2 Clinical Data to Date

There is no published clinical data on erythropoietin administration in the cyanotic congenital heart defect infant population that we are aware of.

D3 Claim for Exclusion of Environmental Assessment

In accordance with 21 CFR 25.31(e), I, David Werho, MD request a categorical exclusion from the requirement for an environmental assessment for the manufacture and formulation of *epoetin alfa* for use in human clinical trials under this IND #129795. All waste from the investigational drug will be properly controlled. The amount of wasted expected to enter the environment may reasonably be expected to be non-toxic. To my knowledge, no extraordinary circumstances exist.

D4 Dose Rationale and Risk/Benefits

500 units/kg/injection (SQ) and oral ferrous sulfate (iron) at 3 mg/kg/day (Donato 2005 & Maier 2002) which is an accepted treatment for anemia and prevention of anemia.

E Study Design

E1 Overview or Design Summary

The study will be a prospective randomized controlled trial, to investigate if administration of EPO and supplemental iron make a clinically significant difference in the number of transfusions given and the morbidity associated with it in infants with cyanotic heart disease. There will be 2 arms in the study, a treatment arm (EPO) and an observational control arm. The patients will be enrolled in the neonatal period after diagnosis and initial palliative procedure (surgical shunt, hybrid procedure, stent in patent ductus arteriosus or right ventricular outflow tract to ensure adequate pulmonary blood flow). They will be followed for 14 weeks from their enrollment. Clinical data will be obtained as appropriate to study the primary and secondary outcomes. The data will be analyzed with a biostatistician to reveal any statistically significant differences between the 2 arms of the study.

E2 Subject Selection and Withdrawal

2.a Inclusion Criteria

- Newborns less than 4 weeks old at diagnosis
- Gestational age ≥34 weeks
- Birth weight 2.2-4kg
- Infants with cyanotic heart disease who have had a surgical aorto-pulmonary shunt, hybrid procedure (pulmonary artery bands with a patent ductus arteriosus stent or PGE-1 to maintain ductal patency) or a catheterization intervention that is equivalent to a shunt (patent ductus arteriosus stent, right ventricular outflow tract stent).
- Baseline hematocrit to be below <40%.
- Completes at least 1 injection in the study by 8 weeks of age.

2.a Exclusion Criteria

- Infants diagnosed at greater than 4 weeks of age
- Gestation <34 weeks
- Birth weight <2.2 kg or >4kg
- Hematocrit >40%
- Newborns with acyanotic heart disease
- Infants with significant co-morbidities
    - Renal failure (Creatinine > 2 standard deviations above age adjusted norm)
    - Hepatic failure (elevated AST/ALT levels > 2 standard deviations above age adjusted norm
    - Hemolytic disease
    - Hemoglobinopathies (Sickle-cell disease, Thalassemias)

2.b Ethical Considerations

There are no ethical concerns in regards to the treatment (EPO) group as this medication has been studied for safety, approved by the FDA for use, and has been investigated in multiple patient populations including premature infants (Donato 2005) and in pediatric craniosynostosis repair (Fearon 2001). There are also no ethical concerns to withhold treatment from the control group as there is no definitive study to show clinical significance. Because the outcome of the study is not known, a randomized prospective control trial is appropriate.

2.c Subject Recruitment Plans and Consent Process

A partial HIPPA waiver will be obtained to allow for identification of potential subjects for the research study. Information to be obtained includes name, date of birth, gestational age, weight, and congenital heart diagnosis. Subjects will be identified after birth or admission to the hospital by attending physicians (cardiology, NICU, PICU, CVICU), clinical fellows (cardiology, NICU, PICU, CVICU), or nurse practitioners in the Acute Cardiac Unit. The parents of the potential subject will be approached by the research team in the Acute Cardiac Unit. All genders and ethnicities will be recruited as long as inclusion and exclusion criteria are met.

Informed consent will be obtained by one of the research study members after the initial surgical or catheterization procedure. Each member is well informed of the study objectives, procedures, risks, benefits, physiology of the disease process and mechanism of how the treatment works. The informed consent will be obtained from the patient's parent in a private setting. Details of the study will be presented, and ample time will be given to answer any questions. The parent will have until the eligibility period expires based on the exclusion criteria outlined above to be included in the study. Consent will be obtained in the primary language of the parent. English and Spanish versions of the consent documents will be available and official translators will be used as appropriate. An appropriate official translator will be used during the entire duration of the participant in the study. Informed consent and HIPPA authorization will be documented with the study forms that have been drafted and approved for use in the study and will be kept in a master research file for the duration of the study in a secure area, in a locked drawer by the study team. It will be made clear to the parents that participation in the study is voluntary and that decision to be included or excluded will not compromise the standard of care that the patient deserves. Patients who meet all inclusion criteria except the hematocrit of <40% will be approached and consented, but will not be formally enrolled and randomized into a study group (control or EPO) unless their hematocrit reaches <40% during their eligibility period.

2.d Randomization Method

Study subjects will be randomized 1 to 1 by an algorithm determined by the biostatistician involved. After a study subject has been enrolled into the study, a 2-digit number (1-60) will be assigned. Based on the subject number and predetermined randomization provided, a research pharmacist will dispense the study drug if the subject is enrolled in the intervention arm. This study will not be blinded.

2.e Risks and Benefits

There is low risk to the patient in regards to side effects of erythropoietin. In general, neonatal population studies have not shown to have significant serious side effects. Blood counts will have to be monitored to observe for polycythemia as this would increase the risk for blood viscosity and thrombosis. There are rare instances in the adult literature with development of Pure Red Cell Aplasia, which is not evident in the neonates. There is some discomfort with the injections, however this is of minimal risk. Lab draws will be done as part of a routine basis. The benefits to receiving this medication are that it may decrease the need of transfusions and hospitalizations in the period prior to a more definitive surgery.

2.f Early Withdrawal of Subjects

As this is a voluntary research study, study subjects will be allowed to withdraw from the study before completion at any time. If a withdrawal occurs before initiation of the intervention, the subject will be excluded from the study.

2.g When and How to Withdraw Subjects

A family may wish to withdraw the study subject from the study at any time. When the decision to withdraw is made after discussions with the clinical staff, a member of the research team will be notified. The date, time, and reason of the withdrawal should be noted by the research member and entered into the database. Families will be approached for permission to follow the course of the patient through the proposed study period even if the intervention was stopped.

2.h Data Collection and Follow-up for Withdrawn Subjects

Families will be approached for permission to follow the course of the patient through the proposed study period even if the intervention was stopped. An intention to treat analysis will be applied to the study subject pertaining to the research arm assigned.

2.i Blood transfusion guidelines

Absolute indications:

- Hematocrit <30%

Relative Indications:

- Hematocrit <40% AND one of the following
    - Clinical acidosis
    - Low oxygen saturations (<75%) in room air
    - Requires supplemental oxygen
    - Requires respiratory support (Ventilator, positive pressure)

When a transfusion is needed, a 10 ml/kg aliquot volume should be given.

E3 Study Drug

3.a Description

Epoetin alfa is a recombinant form of human erythropoietin used to stimulate erythropoiesis. Iron then helps support proper heme formation with the production of hemoglobin. EPO is administered by injections. Iron will be administered orally or intravenously if orals are not tolerated.

3.b Treatment Regimen

Experimental: Epoetin alfa and iron supplements:

Patients in the treatment group will receive weekly erythropoietin injections for 6 weeks starting before 8 weeks of age (at least one week after their surgery) at 500 units/kg/injection (SQ or IV).(Donato 2005 & Maier 2002) Oral ferrous sulfate 3 mg/kg/day of elemental iron will be given throughout the study if enteral feeds are tolerated which is an accepted treatment for anemia and prevention of anemia. If oral iron cannot be tolerated and there is laboratory evidence of iron deficiency, intravenous iron (either Iron sucrose or Iron dextran) will be used to replace iron stores based on the calculated iron deficit: Total replacement dose (mg of iron) = 0.6 x weight (kg) x [100 -

(actual Hgb /Desired Hgb x 100)]. This will be given in 5-7 mg/kg every day until the total replacement dose is achieved.

Iron studies (Serum iron, ferritin, total iron binding capacity) will be obtained at baseline and at week 14 with the final lab draw. If intravenous iron is used for replacement, iron studies will be repeated after replacement to ensure adequate iron stores.

All injections will be administered by a member of the subject's care team (bedside nurse, nurse practitioner, or physician) with a weekly visit in the cardiology clinic or in the hospital if the infant remains hospitalized after being dispensed by the research pharmacist.

A complete blood count will be obtained in the hospital prior to initiation of treatment for baseline measurements and to confirm eligibility if not obtained within 48 hours prior to the 1st injection as a part of the patient's standard of care. It will be repeated weekly (weeks 2-7) whether inpatient or outpatient, to confirm that there is no over-shoot with a hematocrit >45%. Labs will be reviewed prior to treatment. Treatment will be held for hematocrit levels >45%. There will be another lab drawn 14 weeks after the initial injection. Outpatient visits and lab draws will be paid for by the study grant. All labs will be analyzed by the Rady Children's Hospital Laboratory. The study drug will be provided by the study grant.

Observational Control:

An observational group will be used as a control. Thus to keep the integrity of the study with minimal bias, strict adherence to the blood transfusion guidelines as listed above is required.

Patients in the control group will have no injections given. This group will receive oral ferrous sulfate 3 mg/kg/day of elemental iron for 6 weeks starting before 8 weeks of age (at least one week after their surgery).

If oral iron cannot be tolerated and there is laboratory evidence of iron deficiency, intravenous iron (either Iron sucrose or iron dextran) will be used to replace iron stores based on the calculated iron deficit: Total replacement dose (mg of iron) = 0.6 x weight (kg) x [100 - (actual Hgb /Desired Hgb x 100)]. This will be given in 5-7 mg/kg every day until the total replacement dose is achieved.

Iron studies (Serum iron, ferritin, total iron binding capacity) will be obtained at baseline and at week 14 with the final lab draw. If intravenous iron is used for replacement, iron studies will be repeated after replacement to ensure adequate iron stores.

A complete blood count will be obtained in the hospital prior to initiation of treatment for baseline measurements and to confirm eligibility if not obtained within 48 hours prior to enrollment as a part of the patient's standard of care. A repeat CBC will be obtained at week 7 and 14 of the subject's participation in the study which will be provided by the study grant. A CBC may be obtained earlier if indicated by the subject's care team as a

part of standard of care. All labs will be analyzed by the Rady Children's Hospital Laboratory.

3.c Method for Assigning Subjects to Treatment Groups

After a study subject has been enrolled, a 2-digit number will be assigned. Based on the number and a pre-randomized allocation scheme devised by the biostatistics department, the subject will be placed into the treatment arm or the control arm of the study.

3.d Preparation and Administration of Study Drug

The *epoetin alfa* that will be used in the study will be obtained through commercial means, stored, and prepared by the research pharmacist associated with the study at Rady Children's Hospital. Based on the EPO prescribing information, benzyl alcohol has been associated with severe adverse events and death especially in the pediatric population. Only benzyl alcohol-free formulations of EPO will be used (multidose vials, single-dose vials admixed with benzyl alcohol will not be used.) When it is time to administer the intervention, the clinicians will order a dose of the medication. Based on the number assigned to the patient, a dose of epoetin alfa or an empty syringe will be prepared. A dedicated administering clinician assigned will then administer the prepared syringe either in the inpatient unit or in the cardiology clinic. The pharmacy will store, handle and prepare the study drugs according to the approved package inserts. The study drug will not be diluted in this trial. Unused portions of the drug in preservative-free single use vials will be discarded.

3.e Subject Compliance Monitoring

Compliance will be documented at each visit as the intervention will be done in the hospital or in the clinic setting. A member of the research team will be at each visit to fill out the case report form including compliance of iron therapy. The research team will be in charge of overseeing that patients return at the proper time for their clinical visits as described (see **table 1** and **table 2**)

3.f Prior and Concomitant Therapy

All patients based on the inclusion criteria will have had a surgical or interventional procedure for their cyanotic heart disease. All concomitant therapy that is standard of care for the patient will be continued.

3.g Packaging

Epoetin alfa will be obtained in its normal manufacture packaging. The study interventions will be prepared in standard fashion by the pharmacy for administration.

3.h Blinding of Study Drug

There will be no blinding in this study.

3.i Receiving, Storage, Dispensing and Return

Ordering, receiving, storage, and dispensing will be done by the pharmacy and research pharmacist per hospital standards and protocol.

F Study Procedures

F1 Screening for Eligibility

Screening for eligibility will be done on the Acute Cardiac Unit at Rady Children's Hospital. When an infant with cyanotic congenital heart disease is identified, the patient will be screened for eligibility based on the inclusion and exclusion criteria described above.

F2 Schedule of Measurements

The schedule of measurements is listed in Table 1 and Table 2. For the treatment arm, a physical exam with oxygen saturation will be recorded weekly from baseline and weeks 1-7, 14. A complete blood count will be drawn at baseline (if not already obtained for clinical use, one week post procedure and ≤ 48 hours prior to 1st injection), weekly from weeks 2-7, and at week 14. Iron studies will be drawn at baseline and week 14 unless indicated in between. All labs will be analyzed by the Rady Children's Hospital Clinical Laboratory whether inpatient or outpatient.

The control arm will have a physical exam with oxygen saturations at baseline, week 7 and 14. A complete blood count will be drawn at baseline (if not already obtained for clinical use, one week post procedure and ≤ 48 hours prior enrollment) week 7 and week 14. Iron studies will be drawn at baseline and week 14 unless indicated in between. All labs will be analyzed by the Rady Children's Hospital Clinical Laboratory whether inpatient or outpatient.

F3 Visit 1

Visit 1 will be prior to 8 weeks of age and at least 1 week post procedure while in the hospital. After confirmation of eligibility for the study, a physical exam and oxygen saturation will be obtained, and the 1st dose of the intervention will be given by the subject's care team if in the EPO arm.

F4 Visit 2 etc.

Visit 2-14 may either be obtained in the hospital or in the clinic setting. A physical exam and oxygen saturation will be obtained. A complete blood count will be obtained weekly from weeks 2-7 in the EPO arm. A complete blood count will be obtained in the control group at week 7 or earlier if indicated by the subject's care team. Study injections will be given after the lab has been reviewed and confirmed there is no overshoot (Hct >45%). There will be a final physical exam and labs at week 14 of the study, which will complete the participation of the study.

F5 Safety and Adverse Events

5.a Safety and Compliance Monitoring

Safety and Compliance Monitoring will follow standard principles as outlined below.

5.b Medical Monitoring

i Investigator

The research team will review the visits data at least once a week to monitor for adverse events, compliance, and progress of the study. The research team will meet with the Principal Investigator weekly with a report of adverse events and serious adverse events.

ii Institutional Data and Safety Monitoring Board

The UCSD Data and Safety Monitoring Board (DSMB) has been identified through the Clinical and Translational Research Institute. The DSMB is composed of experts in biostatistics, clinical trial design, and medicine. The DSMB will meet as subjects are enrolled in increments of 5 or annually (whichever is more frequent). . The DSMB will be responsible for monitoring the safety of the study.

5.c Definitions of Adverse Events

The FDA Final Rule on Investigational New Drug Safety Reporting Requirements [http://edocket.access.gpo.gov/2010/pdf/2010-24296.pdf] defines the following terms:

• Adverse Event: Any untoward (e.g. unfavorable, negative, or harmful) medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug related. An event can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the product.

• Suspected Adverse Reaction: Any AE for which there is a reasonable possibility that the drug caused the event, meaning the event is possibly, probably, or definitely related to the study drug.

• Adverse Reaction: An AE for which there is a greater degree of certainty regarding causality; meaning the event is probably or definitely related to the study drug. Adverse reactions are a subset of Suspected Adverse Reactions.

5.d Classification of Events

Monitoring adverse events requires that they be classified as to potential relationship, severity, and of the study drugs, all of which drive the reporting process.

i Relationship

Relationship assessment is required in clinical investigations to help determine which events require expedited reporting. The following criteria will be used to determine relationship:

1. Not Related: The event is clearly related to other factors, such as the subject's clinical state, or non-study drugs or interventions.

2. Possibly Related: The event follows a compatible temporal sequence from the time of administration of the study drug, but could have been produced by other factors such as the subject's clinical state or non-study drugs or interventions.

3. Probably Related: The event follows a reasonable temporal sequence from the time of drug administration, and cannot be reasonably explained by other factors such as the subject's clinical state, or non-study drugs or interventions.

ii Severity

A serious adverse event is one that:

(a) Results in death,
(b) Is life-threatening (the subject was, in the view of the Principal Investigator, in immediate danger of death from the event as it occurred),
(c) Requires inpatient hospitalization or prolongation of existing hospitalization,
(d) Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
(e) Is an Important Medical Event that may jeopardize the subject or may require medical/surgical intervention to prevent one of the serious adverse event outcomes.

iii Expectedness

The purpose of reporting is to provide new, important information on serious reactions or events previously unobserved or undocumented. Therefore, all adverse events will be evaluated as to whether their occurrence was unexpected.

1. Unexpected: An unexpected adverse event or adverse reaction is one for which the nature or severity is not consistent with information in the protocol, consent form, or product brochure. An adverse event or adverse reaction also may be categorized as unexpected if the event has not previously been observed at the same specificity and/or severity.

2. Expected: An event is considered expected if it is known to be associated with the study drugs and/or the disease state. For this protocol, expected events include at least the following and may include other symptoms included in the product brochure but not listed below:

- Injection site reactions and pain
- GI upset symptoms (nausea, vomiting)
- Fever
- Swelling
- Itching
- Heart attacks
- Strokes
- Congestive heart failure: Failure of the heart to pump with normal efficiency
- Thrombosis of vascular access: Clotting of lines placed in blood vessels
- Other blood clotting events (i.e. DVT, Pulmonary embolism)
- Tumor progression or recurrence
- High blood pressure
- Serious Allergic reactions: vomiting, low blood pressure, swelling of the tongue and face, difficulty breathing, skin rash, hives
- Pure red cell aplasia: Failure of the body to make any red blood cells

- Antibodies to EPO
- Transmission of viral disease
- Joint, muscle, or bone pain
- Dizziness
- Cough
- Soreness of mouth
- Headache
- Seizures
- Decreases or increases in the production of other blood cell types
- High blood sugar
- Insomnia
- Depression
- Trouble swallowing
- Low potassium levels
- Weight loss

5.e Grading of Adverse events

Adverse events will be graded based on the "Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0" as published by the U.S. Department of Health and Human Services, National Institute of Health, and National Cancer Institute. This can be found at: **http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf**

5.f Data Collection Procedures for Adverse Events

In this trial, a primary safety concern as well as one of the secondary end points is to capture and compare suspected adverse reactions and adverse reactions associated with epoetin alfa administration. In addition, following standard clinical trial procedures, information on other adverse events and patient-reported symptoms will be collected.

Adverse Events will be assessed at baseline and at each study visit. Subjects and families will be encouraged to report adverse events to study personnel as soon as the event occurs, rather than waiting for scheduled visits. Patient reported symptoms will be captured at each of these time points and will be documented by the study coordinators or investigators. Assessments at baseline will be obtained while the subject is not taking any study drug and is essential to accurate assessment of drug effects. Laboratory monitoring will be conducted to assess drug safety as outlined in *Table 1 and Table 2*. Abnormal values will be used to adjust study drug dosage (intervention will be held for hematocrit levels >45%), and will not be reported separately as adverse reactions or adverse events. However, analysis of safety at the end of the trial will encompass adverse reactions, other adverse events, and these laboratory abnormalities, for a comprehensive assessment of the safety profile of the study drugs.

5.g Reporting Procedures

The research investigators will report all adverse events, regardless of expectedness and relationship to the study drug according to the following timeframes:

Classification	Expectedness	Relatedness	Reporting Timeframe

Serious: Fatal life Threatening	Unexpected	Related	Within 10 calendar days of first knowledge of event to the IRB
Serious: Fatal life threatening	Unexpected or Expected	Unrelated	Within 10 calendar days of first knowledge of event to the IRB
Serious (Suspected Adverse Reactions)	Unexpected	Related	Within 10 calendar days of first knowledge of event to the IRB
Serious	Unexpected or Expected	Unrelated	Within 10 calendar days of first knowledge of event to the IRB
Not Serious	Unexpected or Expected	Unrelated or Related	Quarterly to DSMB

The Investigator or designee will report all serious adverse events to the local IRB according to local IRB policies within 10 working days.

5.h Adverse Event Reporting Period

The adverse event reporting period will begin at the baseline assessment and will continue through 30 days after exiting the study.

5.i Post-study Adverse Event

All adverse events unresolved at the time of the subject's termination from the study will be followed by the investigators until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained or has stabilized. At the last scheduled contact, the investigator will instruct each subject or parent/guardian to report any event(s) occurring in the next 30 days. Any death or other clinically serious adverse event that may be related to the study drugs and that occurs at any time after a subject has discontinued study drug or terminated study participation will be recorded and reported.

5.j Pure Red Cell Aplasia

We will be monitoring CBCs weekly. According to the prescribing information, if PRCA is suspected with severe anemia (decline in hemoglobin level >0.5 to 1 g/dL per week or transfusion requirement once a week to maintain adequate hemoglobin levels), normal platelet and white blood cell count, and low reticulocyte count (<10,000/microL) we will perform assays for binding and neutralizing antibodies in those subjects by contacting the manufacturer. All ESA administration will be permanently discontinued and the FDA will be notified within 48 hours.

Any unused blood samples from the baseline lab draw through week 14 will be banked either at UC San Diego or Rady Children's Hospital San Diego biorepositories under appropriate conditions to allow for immunogenicity testing if needed until 6 months after an individual subject has completed their last injection.

F6 Study Outcome Measurements and Ascertainment

Ascertainment of the study outcome measurements and adverse events will be obtained on a case report form by a study investigator. These will include:

- Age/adjusted age
- Weight
- Oxygen saturation
- Compliance of medication
- Complete blood count
- Transfusions needed
- Hospitalizations
- Adverse events (Severity, expectedness, and relationship)

G Statistical Plan

G1 Sample Size Determination and Power

This will be a randomized controlled single center prospective study of up to 60 patients to account for drop out rate. There will be a minimum 20 treatment patients and 20 control patients enrolled. This sample size is based on a 2 proportion population formula with the assumption that without treatment about 80% of infants need transfusions (based on our experience), and 40% of infants with erythropoietin will need transfusions.

G2 Interim Monitoring and Early Stopping

Unforeseen inaccuracies in design assumptions, in particular having to do with the number of infants who need transfusions without treatment could lead to decreases in the trial's statistical power to detect treatment effects. Accordingly, an analysis will be conducted to estimate the variance of the estimated difference, between the two arms in regards to number of transfusions. This analysis will be conducted within the intention-to-treat framework under which the primary analysis of the primary endpoint will be conducted.

To allow time for corrective action if necessary, this analysis will be performed approximately after 10 patients have been enrolled in both arms. If necessary, this method will be used to obtain a recommended increase in sample size.

An interim analysis of futility will also be performed to determine if the study should continue. This will be done when 10 subjects in each arm have completed the study. The study will be terminated if there is no absolute decrease in number of transfusions per subject.

It is possible that the DSMB may consider it necessary to stop the trial early due to safety concerns. To monitor safety, adverse event rates will be compared between the two trial arms and reported to the DSMB.

In addition, the research team will perform an analysis after the first 5 subjects have completed at least 1 intervention in the EPO arm for safety. These 5 patients will serve as a safety population study.

An interim analysis of safety will be done after 10 patients have enrolled and completed each arm to assess any differences in adverse events between the 2 arms. This will be reviewed by the DSMB who will make the determination as to whether any safety concerns mandate early trial termination.

G3 Analysis Plan

All primary analyses for efficacy will be performed on an intention-to-treat basis. All subjects will be analyzed according to their group assignment regardless of actual treatment received. In addition, both groups will be compared for safety at the end of the study by comparing adverse events and rates of adverse events. In the safety analysis, subjects will only be included if they actually received treatments in that group. (i.e. if a patient on the EPO arm did not get EPO, they should not be included in the analysis of safety in that arm).

G4 Statistical Methods

All data will only be gathered during the period in which the subjects will be active in the study (from baseline to 14 weeks post initial injection).

For the primary aim, we will compare the number of blood transfusions (one 10 ml/kg aliquot = 1 transfusion) between the two groups with a two-proportion z test. With n = 20 subjects per group, this test will have 80% power at the $\alpha = 0.05$ significance level to detect a difference. The primary aim will be assessed when all subjects have completed week 14.

We will compare weight gain and the change in oxygen saturation between baseline measurements and the 6 week follow-up with a two sample t-test. We will also use a linear mixed effects model, with a random intercept included to account for within subject correlation, to determine differences in the longitudinal trends in weight and oxygen saturation between groups. The length of the initial stay will be compared between groups with a two-sample t-test. We will treat the number of re-admissions (in regards to failure to thrive and cyanosis) as a categorical variable, and use Fisher's exact test to determine if there is a difference between EPO and control group readmission counts. We will consider the Mann-Whitney U test as a robust alternative to the two-sample t-test if the assumptions of the t-test are not met by the data.

With a sample size of n = 20 subjects per group, the t-tests described above will have 80% power at the $\alpha = 0.05$ level to detect an effect size equal to 0.91 times the common standard deviation. For weight change, assuming that the standard deviation of weights at baseline and the 6 week follow-up equal 1.22 and 1.53 (respectively), and assuming a

moderately high correlation between weight measurements within child of $\rho = 0.70$, this translates to a detectable difference of 1.00 kgs.

G5 Missing Outcome Data

As this study will have an intention to treat model, missing outcome data will default to reflect that the subject has received a transfusion. In addition, there may be additional analysis only reflecting subjects who have completed the study in its entirety.

H Data Handling and Record Keeping

H1 Confidentiality and Security

All data will be kept secure through the UCSD REDCap database provided by the Clinical and Translational Research Institute. REDCap is a customizable secure Web based database. It can only be accessed with a username and password that is assigned specifically to each research member. Information entered into the data entry system will be by subject study I.D. number. Data will be checked by an automated validation tool on REDCap to ensure proper data entry. A project has been created in that database for this particular study.

H2 Training

Before the study is started, each member must complete certification requirements to conduct research and show demonstration of familiarity with study procedures, methods for endpoint measurement, use of the database management system to conduct the study.

H3 Case Report Forms and Source Documents

The case report forms (both inpatient and outpatient) will be used as the source documents. The case report form that will be used can be found in section L3.

H4 Records Retention

All data will be kept secure through the UCSD RED Cap database. Hard copies of the case report forms will be stored in binders that will be kept in secure areas in the research office.

I Study Monitoring, Auditing, and Inspecting

I1 Study Monitoring Plan, Auditing and Inspecting

Interim monitoring will be performed as outlined in section G2. In addition, throughout the entire study, data will be collected and compiled on a weekly basis. Data will be entered into the database at least monthly. The research team will review to ensure that the data is being obtained properly, entered into the database properly and to look for any missing data at least quarterly. A safety report will be submitted to the DSMB for review at least quarterly.

J Study Administration

J1 Organization and Participating Centers

University of California, San Diego
Rady Children's Hospital, Heart Institute

J2 Funding Source and Conflicts of Interest

This study is currently funded by the Academic Enrichment Grant from the Rady Children's Hospital foundation.

J3 Committees

Research team:
David Werho, MD – Principal Investigator (attending cardiologist/intensivist at RCHSD) – responsible for recruitment, data collection and analysis, as well as manuscript preparation.
Justin Yeh, MD (Attending cardiologist at Children's Hospital of Pittsburgh) – will assist in analysis of deidentified data and manuscript preparation.
Jesse Lee, MD (Attending cardiologist at Children's Hospital of San Antonio)– will assist in analysis of deidentified data and manuscript preparation.
Howaida El-Said, MD, PhD (attending cardiologist at RCHSD)– will assist in recruitment therapy administration, in data collection, analysis, and manuscript preparation.
Stephanie Moriarty RN, MSN, ACNP- (Nurse Practitioner at RCHSD) – will assist in recruitment, therapy administration, in data collection, analysis, and manuscript preparation.
Denise Suttner, MD (Attending neonatologist at RCHSD) -- will assist in recruitment therapy administration, in data collection, analysis, and manuscript preparation.
Andrew Ligsay, MD (Pediatric Resident, UCSD) –will assist in recruitment, therapy administration, data collection, analysis and manuscript preparation.
Danica Griffin, MS – Research Coordinator – responsible for all regulatory/IRB documents and communications pertaining to the study.

J4 Subject Stipends or Payments

There is no stipend or monetary benefits to the patient or their families.

J5 Study Timetable

This study is projected to take 4 years. 2 to 2.5 years for recruitment of study subjects and obtain all necessary data. 1.5 to 2 years for statistical analysis and manuscript preparation.

K Publication Plan

After the study and analysis is complete, we plan to publish the data to a journal that is well recognized in the field of congenital heart disease.

L Attachments

L1 Tables

Table 1
Treatment Group

Tests and Procedures	Baseline (one week post op/cath,≤ 48 hours prior to 1st injection)	Week 1 (1 week post op)	Week 2*	Week 3*	Week 4*	Week 5*	Week 6*	Week 7*	Week 14
Review eligibility	X								
Informed Consent	X								
Physical Exam including Saturation	X	X	X	X	X	X	X	X	X
Epogen Injection		X	X	X	X	X	X		
Iron		X and ongoing for 12 weeks							
CBC Lab Draw	X		X	X	X	X	X	X	X
Iron Studies	X	If needed after iron replacement therapy							X

***Week 2-7 visits within 5-10 days of last injection. CBC will be reviewed prior to each injection.**

Table 2
Non-Treatment (Control) Group

Tests and Procedures	Baseline (one week post op/cath, ≤ 48 hours prior to 1st injection)	Week 1 (1 week post op)	Week 2*	Week 3*	Week 4*	Week 5*	Week 6	Week 7*	Week 14
Review eligibility	X								
Informed Consent	X								
Physical Exam including Saturation	X	As indicated by subject's care team						X	X
Iron		X and ongoing for 12 weeks							
CBC Lab Draw	X	As indicated by subject's care team						X	X
Iron Studies	X	If needed after iron replacement therapy							X

***Week 7 visits +/- 1 week.**

L2 Informed consent documents

Rady Children's Hospital – San Diego
and University of California, San Diego

Parent Informed Consent

Erythropoietin to Prevent Unnecessary Transfusions In Patients With Cyanotic Congenital Heart Disease – A Prospective Randomized Control Trial

This is a research study. Research studies include only subjects who choose to take part. You are being asked to let your child take part in this study because he/she has cyanotic congenital heart disease. Please take your time to make your decision. Discuss it with your child and family. Be sure to ask any questions that you may have.

STUDY INVESTIGATOR AND SPONSOR

Investigator(s): David Werho, MD

Sponsor: Division of Cardiology, Department of Pediatrics
Rady Children's Academic Enrichment Fund

WHY IS THIS STUDY BEING DONE?

Cyanotic congenital cardiac patients require higher hemoglobin concentrations (red blood cell levels) for optimal delivery of oxygen to the body. Erythropoietin (EPO) is a hormone that the human body makes to stimulate the production of red blood cells. It has been given to help increase red blood cell levels in patients with low counts. Giving EPO and iron may prevent and/or decrease the number of blood transfusions needed in this population. We will study if giving EPO and iron is safe, tolerated, and if it decreases the need for blood transfusions.

WHAT MAKES THIS DIFFERENT FROM THE USUAL TREATMENT?

The experimental part of this study is giving EPO and iron to prevent blood transfusions. This medication has been shown in some patients to prevent blood transfusions in high risk individuals. EPO injections are FDA approved for patients with cancer and chronic renal failure, but the use in this population has not been approved. This is a randomized controlled trial.

Your child will be assigned by chance to a study group (1 group will receive the study medication, and one will be observed). Your child has an equal chance of being assigned to Group 1 or 2.

Group 1 (treatment group):

- Patients in the treatment group will receive weekly EPO injections and iron supplementation for 6 weeks starting before 8 weeks of age, 1 week after their first procedure (surgery or heart catheterization). They will be followed for 14 weeks.

Group 2 (control group):

- Patients in the treatment group will not receive any extra intervention outside of standard of care. They will receive iron supplementation for 6 weeks starting before 8 weeks of age, 1 week after their first procedure (surgery or heart catheterization). They will be followed for 14 weeks.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

We will be enrolling up to 60 subjects to be in this study with a minimum of 20 subjects in each group.

HOW LONG WILL YOUR CHILD BE IN THE STUDY?

Your child will be in the study for 14 weeks.

You can stop your child's participation at any time. However, if you decide to stop your child from participating in the study, we encourage you to talk to the research doctor.

WHAT IS INVOLVED IN THE STUDY?

This is what will happen if your child participates in this study:

Group 1 (treatment group):

- Patients in the treatment group will receive weekly EPO injections for 6 weeks starting before 8 weeks of age (at least one week after their surgery) at 500 units/kg/injection (SQ) and oral ferrous sulfate (iron) at 3 mg/kg/day of elemental iron, which is an accepted treatment for anemia and prevention of anemia.
- All injections will be administered with a weekly visit in the cardiology clinic or in the hospital if the infant remains hospitalized by a member of the care team.
- A complete blood count will be obtained prior to initiation of treatment, after the 1st dose and weekly during weeks 2 through 7 of the study (to confirm that there is no over-shoot, i.e. that the hemoglobin is increased to an abnormally elevated level), and week 14. They will be assessed at these time intervals. You will not be billed for clinic visits and laboratory tests performed as part of the research study.
- Any unused blood samples from the baseline through week 14 draw of the study will be banked for antibody testing if needed.

Group 2 (non-treatment group):

- Patients in the non-treatment group will not receive injections. They will be started on oral ferrous sulfate (iron) at 3 mg/kg/day of elemental iron.
- They will be assessed at baseline for enrollment in the study, at week 7 and 14 after enrollment. A complete blood count (lab draw or heel stick) will be obtained at these intervals for comparison with the treatment group.
- Additional visits and labs will be done only as indicated by the clinician primarily taking care of the infant.
- Any unused blood samples from the baseline through week 14 draw of the study will be banked for antibody testing if needed.

WHAT ARE THE RISKS OF THE STUDY?

The most common side effects seen with erythropoietin injections per the prescribing information are:

- Injection site reactions and pain
- GI upset symptoms (nausea, vomiting)
- Fever
- Swelling
- Itching

Over 2200 neonates have been a part of studies involving EPO. No significant adverse events have been reported in the literature with neonates receiving EPO.

Some possible adverse effects for neonates include:

- ✓ Iron deficiency (which can be prevented by ensuring adequate supplementation).
- ✓ Low white blood cell counts (self-correcting after stopping treatment) may occasionally occur.
- ✓ Low platelet counts
- ✓ High platelet counts
- ✓ High blood pressure
- ✓ Early use has been associated with more severe eye disease (retinopathy of prematurity) if given in extreme premature neonates.

Side effects seen less often (in adults) are:

- "Over-shoot" of target red blood cell levels (Abnormally elevated number of red blood cells)
- Decreases or increases in the production of other blood cell types
- High blood pressure
- Cough
- Soreness of mouth
- Headache

- Dizziness
- Low potassium levels
- Weight loss
- Transmission of viral disease
- Joint, muscle, or bone pain
- Seizures
- High blood sugar
- Insomnia
- Depression
- Trouble swallowing
- Heart attacks
- Strokes
- Congestive heart failure: Failure of the heart to pump with normal efficiency
- Thrombosis of vascular access: Clotting of lines placed in blood vessels
- Other blood clotting events (i.e. DVT, Pulmonary embolism)
- Tumor progression or recurrence
- Serious Allergic reactions: vomiting, low blood pressure, swelling of the tongue and face, difficulty breathing, skin rash, hives
- Pure red cell aplasia: Failure of the body to make any red blood cells
- Antibodies to EPO

If your child has any illness or discomfort as a result of using the study drug call your study doctor immediately. If necessary, the study drug may be stopped and other therapy may be started.

Your child will be assigned to a study group at random (by chance). Your child's assignment is based on chance rather than a medical decision made by the researchers. The study group to which your child is assigned to might not be the group you would prefer your child to be in. It might also prove to be less effective or have more side effects than the other study group(s), or other treatments available for your child's condition.

Possible side effects from blood drawing or heel stick include:

- Faintness
- Irritation of the vein, such as redness or swelling
- Pain
- Bruising or bleeding at the blood draw site.
- There is also a slight possibility of infection.
- Need for blood transfusions because of more frequent lab monitoring

If your child uses the numbing cream for blood draws there may be skin irritation, the skin may temporarily turn red, white or develop a rash.

Other risks in this study include the following:

- Your child's condition may not improve; it may stay the same; or it may worsen while participating in this study.

- There may be side effects or discomforts associated with this study, which are not yet known.
- The researchers in this study have determined to target a red blood cell level (hematocrit) that is higher than the recommended amount of 33% as listed in the prescribing label for EPO. The EPO prescribing information is based on and includes data of various adult populations which suggest that targeting a hematocrit level above 33% is associated with increased severe adverse events. Specifically, when higher targets of hematocrit levels of 42% were used in clinical trials, the risk of death, blood clotting events, and other adverse events were seen in the higher target groups, in adult patients with chronic kidney disease as well as cancer. This has not been replicated in pediatric studies especially neonates. There are some studies in pediatric patients showing that a higher hematocrit level may not be necessary to ensure adequate oxygen delivery to the body, however given what we know about "blue" (cyanotic) heart conditions, these patients require a hematocrit level of 40-45% to ensure adequate delivery of oxygen to the body. A blood transfusion is often considered when the hematocrit level is below 40% in this population in our practice. EPO has been used safely in premature infants, however safe hematocrit target levels in pediatric patients has not been well studied or well established. We will be targeting a hematocrit level between 40-45%.
- Possible risk of loss of confidentiality associated with participant study data. The study doctor and the study staff will take care to de-identify any information about your child, including using a subject number rather than your child's name, as one of the ways that his/her personal information will be protected.

For more information about these risks and side effects, ask your child's study doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

There may or may not be any direct benefit to your child by participating in the study. However knowledge can be obtained to help infants in the future as well as provide a platform for more research in this area.

WHAT OTHER OPTIONS ARE THERE?

The alternative to study participation is to not be included in the study. Your child will continue to have standard of care treatment without erythropoietin which may include blood transfusions, but will not be included in the study data. Your child's care will not be compromised.

WHAT ABOUT CONFIDENTIALITY?

Your child will be given a study identification (ID) number. All study records and questionnaires will be labeled with this number and not your child's name or other personal data. This information will be kept on a password-protected

computer, will be kept separately from the study data, and will not be shared with researchers outside the study center.

While your child is in this study all related records may be made available to:

- The UCSD Institutional Review Board (for the protection of human subjects in research)
- Other regulatory agencies responsible for overseeing research, such as the federal Office for Human Research Protections
- The Food and Drug Administration (FDA)

A copy of this permission form, and the HIPAA authorization form that you will sign, will be placed in your child's medical record. Your child's records and information will not be released without your permission unless required by law.

Under California law, we must report information about known or reasonably suspected incidents of abuse or neglect of a child including physical, sexual, emotional, and financial abuse or neglect. If any investigator has or is given such information, he or she may be required to report such information to the appropriate authorities.

If the study results are published or presented, your child will not be identified.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Website will not include information that can identify your child. At most the Website will include a summary of the results. You can search this Website at any time.

WHAT ARE THE COSTS?

Labs (CBC) during an inpatient hospitalization are a part of acceptable standard of care and you or your health plan/insurance company will have to pay for these. Outpatient clinic visits and labs (i.e. CBC) that are not considered part of acceptable standard of care and pertain to this research will be covered by the research study funds. You will not be billed for clinic visits and laboratory tests performed as part of the research study. The study drug erythropoietin will be supplied at no cost while your child takes part in this study

You and/or your health plan/insurance company will need to pay for all of the other costs of your child's condition not specifically related to the research.

WHAT IF YOUR CHILD IS INJURED IN THE STUDY?

If your child is injured as a direct result of participation in this research, Rady Children's Hospital – San Diego or the University of California will provide any medical care needed to treat those injuries. Neither Rady Children's Hospital – San Diego nor the University

will provide any other form of compensation to you if your child is injured. You may call the Human Research Protections Program Office at (858) 246-4777for more information about this, to inquire about your child's rights as a research subject or to report research-related problems.

WILL YOU OR YOUR CHILD BE COMPENSATED?

There is no compensation for participation and completion of this study.

WHO DO YOU CALL IF YOU OR YOUR CHILD HAS QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury during business hours, contact the research coordinator:

David Werho, MD
(858) 966-5855

For questions after normal business hours or on weekends, please call **(858) 576-1700** and ask for the cardiology physician on call.

WHAT ARE YOUR CHILD'S RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is voluntary. You may choose not to let your child take part or you or your child may choose to leave the study at any time. Your decision will not result in any penalty or loss of benefits to which your child is entitled. If you have questions about your child's rights you may call:

University of California, San Diego
Human Research Protections Program
(858) 246-4777

You will be told about any new information that may affect your child's health, welfare, or willingness to stay in this study.

SIGNATURE AND CONSENT TO BE IN THE STUDY:

Your signature below means that you have read the above information about the study and have had a chance to ask questions to help you understand what your child will do in this study and how your child's information will be used.

You or your child can change your minds later if you want to. You will be given a copy of this consent form and a copy of the Subject's Bill of Rights. By signing this consent form you are not giving up any of your or your child's legal rights.

You agree to allow your child to participate in this research study.

NAME OF PARTICIPANT AGE

PRINTED NAME OF PARENT OR GUARDIAN

SIGNATURE OF PARENT OR GUARDIAN DATE

PRINTED NAME OF WITNESS (person explaining this form)

SIGNATURE OF WITNESS (person explaining this form) DATE

SUBJECT'S BILL OF RIGHTS

It is important that the purpose and procedures of the research study are fully understood and that consent is offered willingly. A subject in a research study or someone, who is asked to give consent on behalf of another person for such participation, has the right to the following:

1. Be informed of the nature and purpose of the research.

2. Be given an explanation of all procedures to be followed and of any drug or device to be used.

3. Be given a description of any risks or discomforts, which can be reasonably expected to result from this research study.

4. Be given an explanation of any benefits, which can be reasonably expected to the subject as a result of this research study.

5. Be informed of any appropriate alternative procedures, drugs, or devices that may be advantageous and of their relative risks and discomforts.

6. Be informed of any medical treatment, which will be made available to the subject if complications should arise from this research.

7. Be given an opportunity and encouraged to ask any questions concerning the study or the procedures involved in this research.

8. Be made aware that consent to participate in the research may be withdrawn and that participation may be discontinued at any time without affecting continuity or quality of medical care.

9. Be given a copy of the signed and dated written consent form.

10. Not be subjected to any element of force, fraud, deceit, duress, coercion, or any influence in reaching the decision to consent or to not consent to participate in the research.

If you have any further questions or concerns about your child's rights as a research subject, please contact your research doctor or the UCSD Human Research Protections Program at (858) 246-4777.

L3 Case report form

Erythropoietin to Prevent Unnecessary Transfusions In Patients With Congenital Cyanotic Heart Disease – A Prospective Control Trial

Patient ID: _____ Date of Visit: _____

Trial Week (circle one): 1 2 3 4 5 6 7 8 9 10 11 12 13 14

Cardiac diagnosis/Surgical history:

_____

_____

_____

Age: _____ Adjusted Age: _____ Weight: _____(kg) SpO2 _____%

Injection dose: # 1 2 3 4 5 6 **Iron Sulfate**:_____(mg) ; _____(mg/kg);

Is patient compliant ? Y/N

Other medications:_____

CBC: WBC _____ HgB _____ Hct _____ Plt _____

Transfusions needed (circle one): YES / NO

If Yes, # units/ml and date: _____

Hospitalization needed **(circle one):** YES / NO **# of Days:** _____

If Yes, Dates and Primary reason:

_____

_____

Adverse events: Check off if subject has the following since the last visit

- Injection site reactions and pain
- GI upset symptoms (nausea, vomiting)

- Fever
- Swelling
- Itching
- Heart attacks
- Strokes
- Congestive heart failure: Failure of the heart to pump with normal efficiency
- Thrombosis of vascular access: Clotting of lines placed in blood vessels
- Other blood clotting events (i.e. DVT, Pulmonary embolism)
- Tumor progression or recurrence
- High blood pressure
- Serious Allergic reactions: vomiting, low blood pressure, swelling of the tongue and face, difficulty breathing, skin rash, hives
- Pure red cell aplasia: Failure of the body to make any red blood cells
- Antibodies to EPO
- Transmission of viral disease
- Joint, muscle, or bone pain
- Dizziness
- Cough
- Soreness of mouth
- Headache
- Seizures
- Decreases or increases in the production of other blood cell types
- High blood sugar
- Insomnia
- Depression
- Trouble swallowing
- Low potassium levels
- Weight loss
- "Over-shoot" of target red blood cell levels (Abnormally elevated number of red blood cells)
- Other Adverse Events: _____

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