CSCC Comprehensive Sickle Cell Centers

Clinical Trials Consortium

Dexamethasone for ACS

Study Information Manual V3.0

March 10, 2008

CSCC Comprehensive Sickle Cell Centers

Clinical Trials Consortium

Randomized Trial of Oral Dexamethasone for Acute Chest Syndrome
STUDY INFORMATION MANUAL

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I. INTRODUCTION

A. Comprehensive Sickle Cell Centers Clinical Trials Network Description

The Division of Blood Diseases and Resources (DBDR) of the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH), provides support to the Comprehensive Sickle Cell Centers (CSCC) to focus on multi-disciplinary programs of basic, applied, and clinical research, and also to include relevant service activities in diagnosis, counseling, and education concerning sickle cell disease and related disorders.

The NIH established the Comprehensive Sickle Cell Center Program in 1972, in response to a Presidential initiative and Congressional mandate. Following an open competitive application process, ten Centers were funded in 1972 and five additional Centers were funded in 1973. The ten Comprehensive Sickle Cell Centers funded for the current five year cycle (as of 4/1/03) are: Boston Medical Center CSCC, Albert Einstein CSCC, Children's Hospital of Philadelphia CSCC, Cincinnati Children's Hospital CSCC, Duke-UNC CSCC, Marian Anderson CSCC, Children's Hospital and Research Center at Oakland CSCC, St. Jude Children's Research Hospital CSCC, The University of Texas Southwestern CSCC, and University of Southern California CSCC.

Sickle Cell Center grants are identifiable units within sponsoring institutions that are organized around a group of investigators and other health professionals engaged in ongoing basic and clinical research and community service related to sickle cell disease. Centers provide support for multi-disciplinary programs of basic, clinical, and behavioral research; for core resources such as laboratory and data analysis; and for quality service activities including diagnosis, counseling, and education.

While a Center must devote its major effort to basic and clinical research, it must also provide supporting activities in diagnosis, education, and counseling. It is anticipated that the total program, i.e., all ten Centers combined, will achieve a mix of outstanding projects that are two-thirds research oriented and one-third devoted to supporting activities. The actual balance between research and other activities will vary from Center to Center and will depend on local circumstances and strengths.

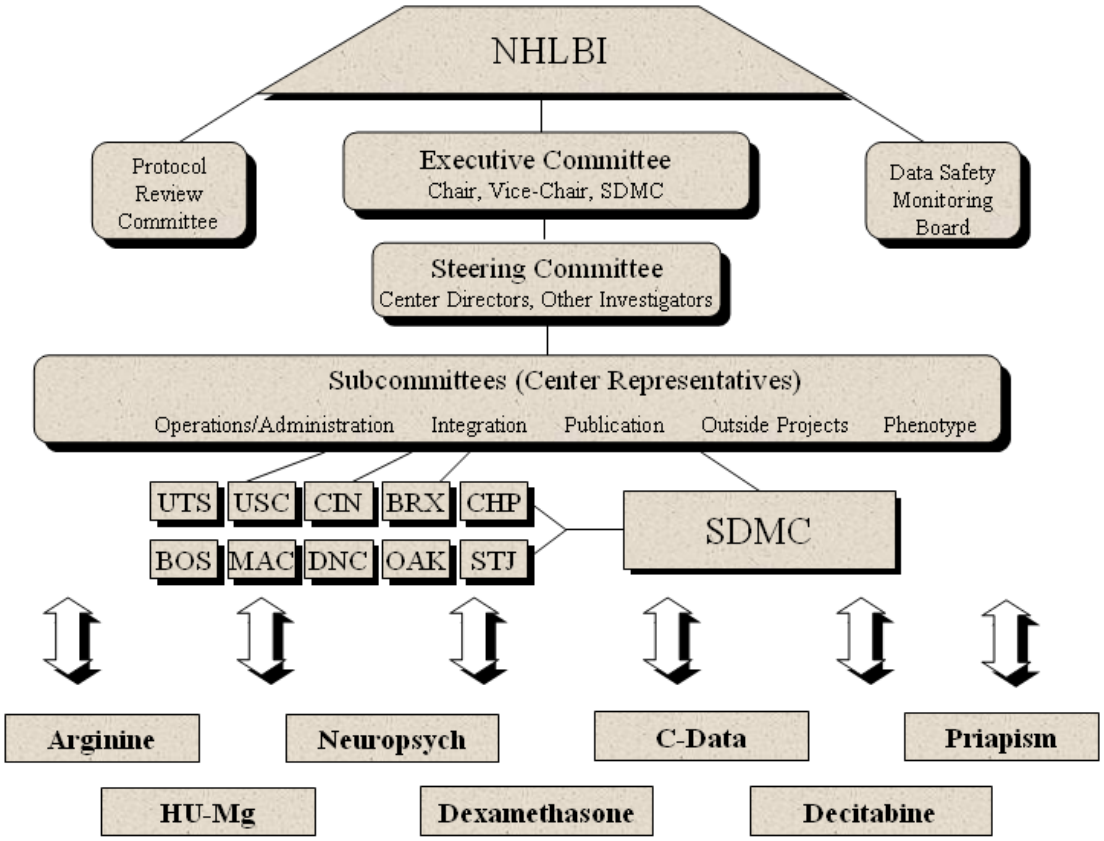
Each Comprehensive Sickle Cell Center is headed by a Program Director who is responsible for and provides leadership to all Center activities, and who may serve as principal investigator on one or more of the projects contained within the Center as well. Although individuals may enjoy a certain amount of autonomy in the conduct of a specific project, each is directly accountable to the Center Program Director, who has overall responsibility for program coordination, implementation, and evaluation.

The Statistics and Data Management Center (SDMC) located at Rho, Inc., in Chapel Hill, North Carolina, is a completely independent resource core that provides project and data management, regulatory, statistical, and other services for the CSCC Centers sharing common clinical protocols, as well as supplying statistical support for all research projects within the Comprehensive Sickle Cell Center program. The SDMC coordinates and organizes the clinical collaboration between the ten centers, and serves as the primary unit to collect, manage, statistically analyze, and store clinical data obtained from the individual Centers.

In addition to these duties, the SDMC has the responsibility of overseeing and managing all aspects of a common patient database (C-Data) that will be used as a tool for the Steering Committee to plan collaborative clinical studies during the funding cycle.

The Collaborative Data Project (C-Data) will establish a comprehensive database of individuals from participating Centers who are potentially eligible for inclusion in any sickle cell research study. Such studies include observational (incidence/prevalence, cohort, case-control, cross-sectional) as well as interventional (randomized clinical trials) investigations. Possible study endpoints include traditional clinical and therapeutic measurements, health resource utilization, and patient-reported outcomes.

B. CSCC Organizational Chart



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III. IRB PROCESS

A. SDMC 10-Step Informed Consent Approval Procedures

The informed consent form describes in non-technical language the purpose of the study, the activities and procedures involved, the expected duration, the potential risks, benefits, and discomforts of participation, and alternatives to study participation. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The table below shows the informed consent statement approval process. The SDMC will track forms through this process; sites will not be allowed to enroll study subjects until they have completed this process.

Site Consent Form Approval Process

Step	Action	Status
1	The Dexamethasone Protocol Team develops an informed consent and assent templates	Completed
2	The templates are reviewed and approved by the SDMC and Dr. Greg Evans at the NHLBI	Completed
3	A subcommittee of the Study PI, SDMC staff, and Dr. Evans develops a checklist that is used to review each site's consent forms to assure that the forms meet all regulatory requirements	Completed
4	Each site prepares a template-based consent form(s) for submission to its own IRB	

5	Using the checklist, SDMC and NHLBI staff review the consent forms:
	• Forms will be returned to the site investigator for revision if they:
	  ○ do not satisfy the requirements on the checklist
	  ○ misstate a point (e.g., underplay a potential adverse event)
	• After forms are revised by the site, they are re-reviewed by SMDC staff	

6	Following approval from the SDMC, each site submits its consent forms to its own IRB	
7	IRB-approved consent forms are sent to the SDMC and reviewed as in Step 5, to assure that none of the key elements in the consents have been removed during the IRB review process: • Forms will be returned to the investigator for revision for the same reasons listed in Step 5 • When forms are resubmitted to the IRB, changes must be discussed with the IRB • If forms are acceptable, go to Step 8	
8	Notification that the consent forms contain the required elements, and that the site has obtained IRB approval of the forms is sent from the SDMC to the sites, and is forwarded to the DSMB and NHLBI	
9	The NHLBI approves the consent form(s)	
10	Each site keeps a copy of the original, approved consent forms and sends copies of all approved forms to the SDMC	

This will be done annually if the study goes over one year.

A template for the consent and assent forms is included in section C. These forms must be modified according to the requirements of each institution. Before submitting the informed consent to the site's Institutional Review Board (IRB), the consent must be approved by the SDMC. A copy of the approved version (with an official IRB stamp) must be provided to the SDMC after IRB approval.

Informed consent must be obtained from each patient at the first recruitment/enrollment visit (Visit 1) prior to beginning any activities with the patient. For patients under the age of 18, this consent must be obtained from the patient's legal guardian. By signing and dating the consent form, the patient (or parent/guardian) is stating that he/she understands the information and is voluntarily giving informed permission for himself/herself (or for his/her child) to participate in the study. He/She should receive a copy of the signed consent.

If the patient is under the age of 18, he/she must sign a simple version of the consent form, called the assent form, if this is your local IRB policy. If the child is unable to read, this form should be read to him/her in the presence of the legal guardian.

If the patient/guardian refuses to sign the consent or assent form, then the patient is not eligible to be in the study. If the patient is under the age of 18 and refuses to sign the assent form, the patient is also not eligible to be in the study.

Please see the attached checklist for specific requirements for the Dexamethasone informed consent.

B. Informed Consent Content Checklist

Comprehensive Sickle Cell Centers Checklist for the Randomized Trial of Oral Dexamethasone for Acute Chest Syndrome Informed Consent Materials:

According to the guidelines specified in Title 21 CFR Part 50, the consent form will contain the following required elements:

A. Basic elements of informed consent:

1. ___ A statement that the study involves medical research.
2. ___ An explanation that the purpose of the study is to test the effectiveness and safety of Dexamethasone to treat ACS.
3. ___ A statement that the expected duration of the volunteer's treatment with Dexamethasone is a tapered dosing regimen over approximately 8 days.
4. ___ A statement that the expected duration of the volunteer's participation in this trial is approximately one month after hospital discharge but no more than 60 days.
5. ___ A description of the procedures to be followed, which include screening, laboratory evaluations, physical exam, medical history and review of medical chart, chest radiograph, pulse oximetry, pain intensity ratings, randomization to Dexamethasone or placebo, administration of study drug, pulmonary function testing and two follow-up visits.
6. ___ A description of any reasonably foreseeable risks and discomforts to the subject or volunteers (includes ineffective treatment, if any). Serious risks identified in the protocol should be mentioned in the consent document.
7. ___ A description of benefits to the subjects or to others that may reasonably be expected from the study.
8. ___ A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject, together with a balanced description of their relative risks and benefits, and a statement that the alternative to participating is not to participate.
9. ___ An explicit statement describing the extent to which confidentiality of records identifying the subject will be maintained. The statement should note that i) the FDA, NHLBI, and Rho, Inc. may inspect all medical records (including identification of the patient) when needed for the purpose of verifying the accuracy of data collection; ii) all of these parties are bound by the same requirements to maintain patient privacy that apply to all medical personnel; and iii) the subject will not be identified in any publication resulting from the study.
10. ___ A statement that the results of the study will be submitted with no identifying information.
11. ___ A statement as to whether compensation or medical treatments are available if injury occurs, and, if so, what they consist of or who to contact for further information. A statement indicating that the subject has not relinquished legal rights will be included here.
12. ___ The names of persons to contact for information or questions about: i) the subject 's rights as a study participant; and ii) the study protocol. Included will be specific instruction about whom to contact in the event of a research-related injury to the subject.

13. ___ Explicit statements that participation is voluntary and that refusal to participate will not involve a penalty or loss of benefits to which the subject is otherwise entitled.
14. ___ A statement that the subject is free to withdraw his/her consent and discontinue participation in the trial at any time without penalty or prejudice. Include the consequences of the subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject. State that it is the patient or subject's responsibility to discuss his/her future medical care with the study doctor and their regular doctor if he/she chooses to withdraw before completion of the trial.
15. ___ An explicit statement that the investigator or the NHLBI may stop the subject's participation in the trial at any time.
16. ___ Dated signatures of the volunteer and/or guardian, Investigator or authorized representative administering the consent, and a witness, if applicable.

B. Additional elements of informed consent, as indicated:
According to the guidelines specified in Title 21 CFR Part 50, the consent form will contain the following additional elements, if appropriate:

17. ___ The approximate number of subjects enrolled in the trial will be approximately 112 subjects (56 children and 56 adults) at approximately 10 centers with _____enrolled at their Center.
18. ___ A statement that participants will not be paid for participation in this trial. The trial will offer $25 compensation for time and travel to the 1st follow-up visit and $50 to the 2nd follow-up visit.
19. ___ A statement that the subject will be notified of significant new findings developed during the course of the research that may relate to the patient's or subject's willingness to continue participation in the trial.

Although some IRBs may not require assent of children as a necessary condition for proceeding with the Randomized Trial of Oral Dexamethasone for Acute Chest Syndrome, we will provide an assent form for those Centers that do require one.

20. ___ Assent form provided.

IV. DEXAMETHASONE FOR ACS PROTOCOL OVERVIEW

A. Background and Rationale

Sickle Cell Disease (SCD) is characterized by chronic anemia and episodic "vaso-occlusive" crises. Acute pulmonary disease, descriptively termed "acute chest syndrome" (ACS),[2] is one of these events.

ACS is defined clinically as a new pulmonary radiographic infiltrate and concurrent signs and symptoms of acute pulmonary disease.[3, 4] Fever and cough are common clinical findings in young children with ACS, but chest pain, shortness of breath, chills, a productive cough, and hemoptysis are more common in older individuals. About two-thirds of patients with ACS are hypoxemic, and most have an acute 1 to 2 g/dL decrease in hemoglobin concentration. The signs and symptoms of ACS may precede the appearance of an infiltrate on a chest radiograph. Lower and middle lobes are affected more often than upper lobes in adults, although upper lobe disease is more common in children. Bilateral infiltrates or involvement of multiple lobes predicts severe disease.

ACS is a common cause of hospitalization for patients with SCD, second only to painful crisis.[5,6] This complication is not always apparent at the time of admission to the hospital, however. Patients may have fever or acute pain, especially in the chest or back, but no respiratory symptoms or pulmonary infiltrates, and develop ACS two or three days later. The Cooperative Study of Sickle Cell Disease (CSSCD) showed that ACS occurs more frequently in young children and among individuals with homozygous sickle cell anemia (Hgb SS).[5] The highest incidence of ACS, 25.8 episodes per 100 patient-years, occurs in children, ages 2 to 4 years with Hgb SS, whereas the incidence is 8.8 episodes per 100 patient-years in adults with Hgb SS. The mean length of hospitalization for all patients with ACS is about 7 days, but children stay in the hospital about 3 fewer days than adults.[7] ACS is the most common cause of death due to SCD. 25% of SCD deaths are related to ACS,[7] and the death rate of ACS is 1.8% in children and 4.3% in adults.[6] Despite the gravity of this complication, the treatment of ACS is only supportive and often inadequate. Better treatments are clearly needed for this common and serious complication.

There are several presumed causes or antecedents of ACS, including infection, pulmonary fat

embolism, hypoventilation and atelectasis, pulmonary edema, pulmonary infarction, and bronchospasm.[7] Any of these may act concurrently, and the distinction of ultimate cause is difficult. Vichinsky and colleagues analyzed 671 episodes of ACS in 538 patients who underwent extensive evaluation for infection and fat embolism by bronchoscopy, serologic assays, microbiologic cultures, molecular techniques, and histologic analysis.[3] A specific etiology was identified in only 38% of episodes, although a cause was imputed in 70% of episodes for which "complete" data were available. Infections with bacterial, atypical bacterial, and viral agents were the most commonly identified cause, followed by fat embolism, either alone or in combination with infection. Over half of the episodes had no identifiable cause or were attributed to infarction by exclusion.

The final common pathway in the pathogenesis of ACS is probably pulmonary vascular occlusion and pulmonary endothelial injury. Rigid, irreversibly sickled erythrocytes may occlude the pulmonary vasculature during ACS,[8,9] but the genesis of this occlusion is likely far more complex.[10] For example, studies have shown that sickle erythrocytes bind to pulmonary endothelium via vascular cell adhesion molecule-1 (VCAM-1), whose expression is increased by hypoxia and cytokines, and this binding is not counter-balanced by cytoprotective mediators like NO.[11] Such excessive and uncontrolled adhesive interactions between erythrocytes and the pulmonary endothelium likely initiate and propagate ACS.

Pulmonary fat embolism (PFE) is one recently recognized cause of ACS.[12] Fatty bone marrow may be released into the blood as a result of bone marrow necrosis caused by a vaso-occlusive bony crisis. Embolic fat activates secretory phospholipase A_2 ($sPLA_2$), an enzyme that cleaves phospholipids and liberates free fatty acids. These fatty acids injure the pulmonary endothelium.[13] Fatty acids also increase the expression of VCAM-1 and promote the adhesion of erythrocytes to endothelium in vitro—evidence for pathologic adhesive interactions in PFE.[11] Inflammatory leukotrienes and prostaglandins are also generated when $sPLA_2$ releases arachidonic acid.[14,15] Indeed, the serum concentration of $sPLA_2$ is a laboratory marker of ACS.[16,17] Patients with ACS have an increased serum concentration of $sPLA_2$, and the concentration correlates with the severity of ACS. There is also a temporal correlation between $sPLA_2$ concentration and the time-course of ACS: $sPLA_2$ increases before ACS is clinically apparent, peaks at the onset, and declines during resolution. [16,17]

The pulmonary histopathology of SCD is characterized by intimal hyperplasia and pulmonary fibrosis.[18,19] Recurrent episodes of ACS may cause this injury.[19] Some patients consequently develop a debilitating pulmonary disease characterized by chest pain, dyspnea, chronic pulmonary infiltrates, and hypoxemia.[18, 19, 20, 21] This condition can progress to pulmonary hypertension, cor pulmonale, and even death.[21] Several investigators have used pulmonary function testing to characterize and define the frequency of pulmonary disease in SCD.[20, 22 23] These studies show that obstructive lung disease occurs frequently in this population, that it may precede restrictive lung disease,[22] and that it may be associated with prior episodes of ACS.[23] Therefore, treatments that decrease the severity of ACS might also prevent or decrease late sequelae.

ACS is the clinical manifestation of some complex combination of toxic pulmonary endothelial injury, abnormal cellular adhesive interactions, vascular occlusion, the elaboration of inflammatory cytokines, infection, and regional alveolar hypoxia. However, our limited understanding of ACS has hindered the development of specific or targeted therapies. The treatment of patients with ACS is primarily supportive, involving watchful waiting and attentive management of pain, hydration, oxygenation, and ventilation. Antibiotics are used empirically, although infectious agents are not identified in most patients.[2, 3, 24, 25, 26] Simple or exchange transfusion of packed RBCs may be beneficial for many reasons, but this therapy has not been tested in rigorous clinical trials.[27, 28, 29] Likewise, there are only anecdotal reports of the benefit of inhaled NO.[30] More effective therapy is needed.

Glucocorticoids have a potential therapeutic role because they inhibit several ostensible steps in the pathogenesis of ACS. Steroids attenuate the inflammatory process, inhibit the enzyme $sPLA_2$, and prevent cytokine-induced expression of adhesion molecules by endothelial cells.[11, 31, 32, 33] Thus, steroids could impede the process of vascular occlusion, endothelial injury, and inflammation. Further justification for the study of steroids for ACS can be inferred from related conditions. For example, pulmonary fat embolism due to trauma can be prevented, and possibly treated, with steroids.[13, 34, 35] Likewise, if there is a component of reactive airway disease to ACS, like asthma, steroids might also be beneficial.[36] Glucocorticoid therapy of ACS, therefore, deserves further investigation.

Dexamethasone is the first treatment shown to benefit patients with ACS in randomized, placebo-controlled trials. [47, 48] But the generalizability of these trials is limited, given that sample sizes were small, only children were studied, and individuals with severe ACS were few. The rebound effect is also worrisome. In addition, the statistical analysis and interpretation of the results was clouded because the observations were not all independent—some children with multiple episodes of ACS were included more than once in the trial.

Thus, further study of this promising treatment in a broad population is needed to clearly define its benefits and potential toxicities. This study aims to determine whether a tapered regimen of dexamethasone can both be effective and eliminate rebound VOC. The taper will follow 4 doses of the study drug as specified in the Bernini study,[47] because simply extending the duration of (un-tapered) dexamethasone to 6 doses, as in the Huh study,[48] did not prevent rebound attacks. Both adults and children who have ACS of any severity will be studied, dose modifications for marked leukocytosis will be incorporated, and individuals will participate only once. This study will also measure differences in pulmonary function at a 1-month follow-up visit, and a panel of biomarkers will be obtained at several time points during the course of study drug treatment.

Previous studies have shown that ACS is associated with endothelial activation characterized by a pathologic over-expression of proadhesive molecules, such as VCAM-1, that is not counterbalanced by cytoprotective and anti-adhesive mediators such as nitric oxide (NO).[11] Hypoxia plays a major role in endothelial cell activation and circulating blood cell-endothelial adhesion,[55,56] tissue factor expression enhancing thrombin formation (with concomitant further endothelial activation, increased permeability and heterotypic cell-endothelial interactions[57,58,59]), and the exocytosis of endothelial Weibel-Palade Bodies.[60] Weibel-Palade release of endothelial P-selectin is a crucial modulator of the early phases of polymorphonuclear adhesion to the vascular wall and leukostasis-induced pulmonary injury.[61] P-selectin also facilitates the production of monocyte-derived procoagulant and proadhesive tissue factor-positive microparticles,[62, 63] the binding of sickle red cells to the vascular endothelium [64] and the genesis of a pro-inflammatory phenotype.[65, 66] The endothelial Weibel-Palade bodies under hypoxic conditions also release high molecular weight multimers of von Willebrand factor (vWF), further recruiting platelets to areas of hypoxia-induced vascular damage. Thus, these putative metabolites or soluble plasma biomarkers that we plan to measure during ACS are mainly endothelial derived (VCAM-1, ICAM-1, P-selectin, vWF multimers and NO metabolites) or are

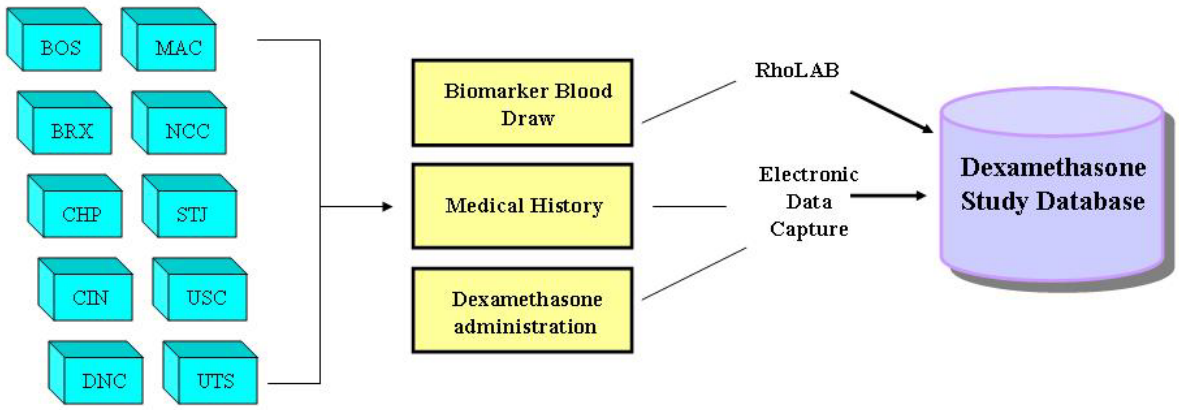
functional cell microparticles formed as a result of endothelial activation (endothelial and monocyte microparticles), with whole blood tissue factor an index of both endothelial and monocyte activation. Since ACS is a syndrome of acute pulmonary endothelial injury related to the final common pathway of hypoxia on a background of chronic endothelial activation, the evaluation of these biomarkers that have potent effects on pulmonary pathophysiology is appropriate, with precedence for their use in both SCD and other states of endothelial activation and lung injury.[67, 70]

During the early rolling phase of the inflammatory cascade, shedding of L-selectin occurs from the activated polymorphonuclear surface, with elevated levels of plasma sL-selectin noted in some reports of patients with SCD.[75, 76] Since dexamethasone modulates white cell activation, it is also possible that an additional effect of glucocorticoids may be mediated via modulation of polymorphonuclear leucocyte and monocyte activation, with concomitant effects on sL-selectin and whole blood tissue factor expression respectively.

Glucocorticoids not only attenuate the inflammatory response,[71] but also inhibit the cytokine-induced surface expression of proadhesive endothelial molecules and activate NO synthase.[31,72,73] These may be the mechanisms of the beneficial therapeutic effects of glucocorticoids for ACS, and these effects will be identified in our study. However, the rebound phenomenon is troublesome. The occurrence of rebound VOC suggests a perturbation in homeostatic mechanisms related to adhesion and coagulation. Evidence for such a possibility has been recently provided by Belcher et al. who have demonstrated that in sickle cell transgenic mice expressing human α, β^S and $\beta^{S\text{-Antilles}}$ globins, dexamethasone pretreatment for 3 days inhibited inflammation, leukocyte rolling and vaso-occlusion in a reperfusion injury model (hypoxia-reoxygenation) concomitant with a decrease in endothelial cell nuclear factor kappa B (NF_KB), intercellular adhesion molecule-1 (ICAM-1), and VCAM-1 levels in lungs and skin.[74] VCAM-1 or ICAM-1 blockade with monoclonal antibodies mimicked dexamethasone by inhibiting vaso-occlusion and leukocyte adhesion in the sickle mice, demonstrating that endothelial activation with VCAM-1 and ICAM-1 expression are necessary for hypoxia-induced vaso-occlusion. However, following steroid discontinuation, reperfusion injury in the steroid-treated mice resulted in a dramatic increase in NF_KB activation with increased levels of ICAM-1 and VCAM-1 concomitant with vascular stasis and venular occlusion. These data strongly argue

that proadhesive and also perhaps procoagulant molecules (such as tissue factor, which is partially under NFκB regulation), may increase markedly after steroid withdrawal and possibly mediate rebound vaso-occlusion. As such, a tapered regimen is included in this trial of dexamethasone for ACS.

B. Project Flow Diagram



C. Protocol Overview

The primary objective of the Randomized Trial of Oral Dexamethasone for Acute Chest Syndrome study is to determine whether dexamethasone decreases the duration of signs and symptoms of ACS. The duration of ACS will be assessed by structured discharge criteria (Appendix 2) that incorporate the resolution of tachypnea, hypoxemia, increased work of breathing, and thoracic pain as well as the cessation of medical interventions to support respiration. We predict that dexamethasone will decrease the time to pulmonary recovery.

Secondary Objectives:

To determine whether dexamethasone reduces morbidity associated with ACS.

To determine whether a tapered regimen of dexamethasone prevents rebound VOC.

To determine whether dexamethasone modulates the endothelial phenotype to a less proadhesive and procoagulant state, and to determine whether the discontinuation of dexamethasone will be associated with a rebound in the expression of endothelial activation markers of adhesion and coagulation.

To determine whether dexamethasone prevents subacute adverse effects of ACS on pulmonary function.

To determine whether dexamethasone modulates white cell activation and whether the discontinuation of dexamethasone will be associated with a rebound in white cell activation.

Primary and Secondary Endpoints

The primary endpoint is the duration of signs and symptoms of ACS or the duration of hospitalization, whichever is less. The duration of signs and symptoms of ACS is defined as the interval between study entry and the time at which the elements of the structured discharge criteria are satisfied. The structured discharge criteria incorporate assessments of tachypnea, hypoxemia, work of breathing, thoracic pain, and medical interventions to support respiration (Appendix 2). The time of study entry is defined as the time of the first administration of the

study drug. The elements of the structured discharge criteria will be formally assessed and recorded every 6 hours until discharge from the hospital.

The secondary endpoints include the following:

- Amount and type of opioid used;
- Number and type (simple or exchange) of transfusions received;
- Duration of supplemental oxygen;
- Duration of hospitalization;
- Duration of fever;
- Duration of hypoxemia;
- Rebound hospitalizations;
- Results of pulmonary function testing (FVC, FEV_1, $FEF_{25-75\%}$, PEFR, and flow-volume loop);
- Pulmonary radiographic findings (resolved, improved, unchanged, and worse); and,
- Rating of pain (Oucher or Visual Analog Scale).

Participation Identification and Recruitment

Patients with HB SS/$S\beta^0$ with the diagnosis of ACS will be recruited by study personnel or the physicians who care for them in the emergency department or the inpatient ward. Enrollment must occur within 24 hours of the diagnosis of ACS, which is timed from the diagnostic chest radiograph. It is anticipated that a 24-month period will be required for the completion of enrollment.

Participant Visit Schedule

Eligibility screening, informed consent, completion of a medical history and physical examination, chest radiograph, laboratory evaluations, oxygen saturation and pain intensity

measurements, randomization, and first study drug administration will occur on Baseline (Day 0). The high dose of dexamethasone (0.3mg.kg) is given for a total of 2 days or 4 doses or until hospital discharge, whichever comes first. A total of six taper doses will be administered every 24 hours over the next six days. Blood samples for biomarker evaluations will be drawn on Days 0, 1, 2, and 8. A follow-up appointment in the sickle cell clinic will be made for 1 week (if the subject remains in the hospital at one week this visit will not occur) and 1 month after discharge. Adverse Events and concomitant medications will be recorded throughout the patient's participation. (see protocol Table 10.2).

Data Management

RhoFED's internet-based remote data entry system will be used to capture the data for this study. Using this system, clinical site personnel use an internet browser (Internet Explorer or similar) to key data into an electronic CRF. The system will be accessible via the CSCC website and require center-specific user ID/password privileges. Data are not stored on the site's computer. At the end of each "page," data are submitted to RhoFED's secure web server and stored in the study's "operational database." Authorized site personnel may log in to the system, review and correct previously entered data, key additional data, or lock records to prevent further inadvertent modifications at any time.

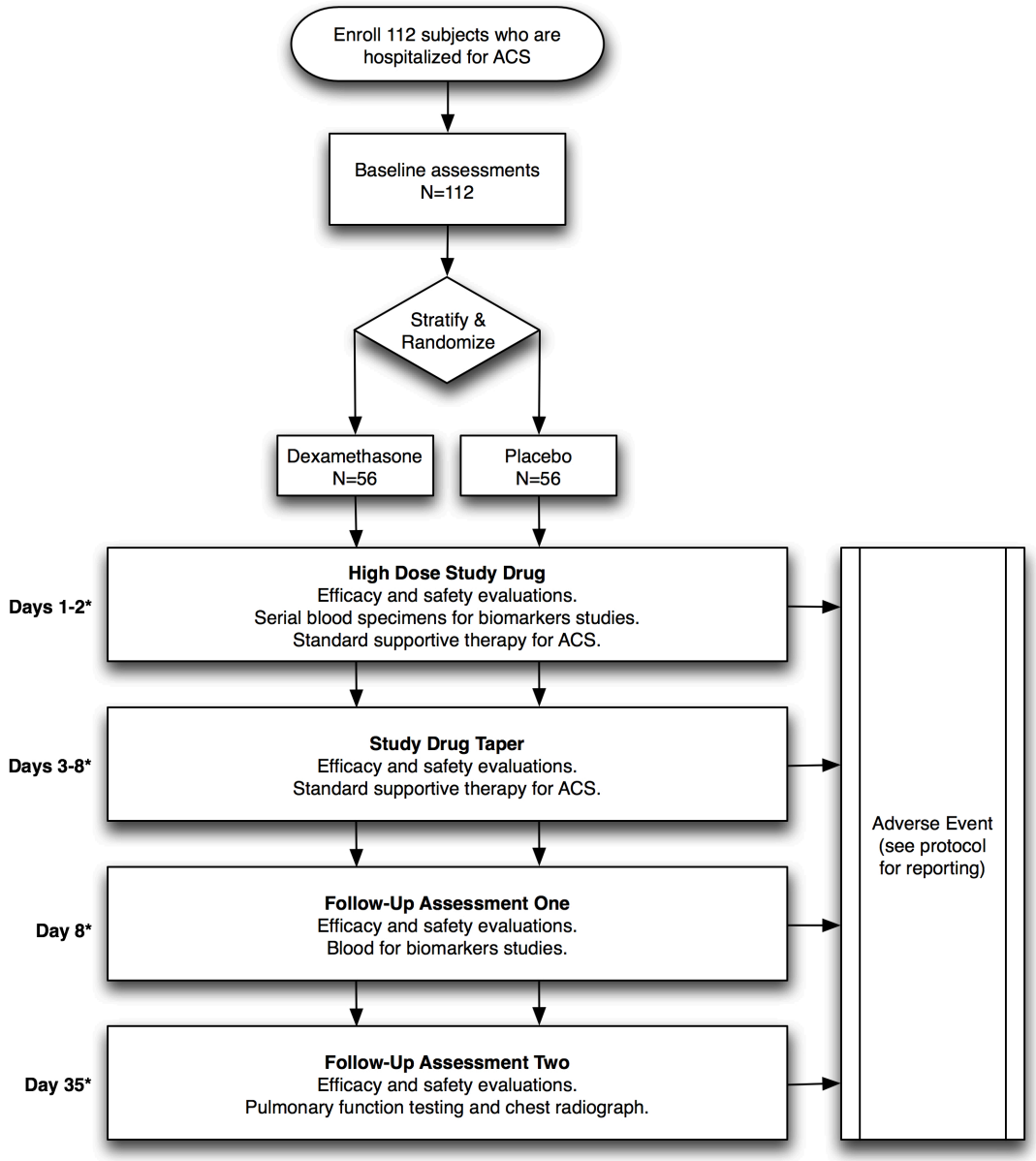
Clinical Staff Training and Data Monitoring

Prior to the onset of enrollment, clinical study coordinators and data coordinators will be centrally trained to ensure adherence to the protocol and assure the highest possible data quality. Training will be led by a combination of investigators and other staff from the clinical centers, the SDMC, and NHLBI. Training presentations will address informed consent procedures, study operations and protocol requirements, data collection procedures, maintenance of source documentation, Case Report Form (CRF) completion and review, routine reporting requirements, data entry and management, and CSCC and NHLBI policies and procedures. As needed and as time allows, face-to-face training will be provided by SDMC staff as part of periodic site visits.

Human Subjects

There are known possible risks associated with the use of dexamethasone. Potential adverse events especially when given chronically, include hypertension, hyperphagia, weight gain, hyperglycemia, striae, acne, osteopenia, personality changes, gastrointestinal ulceration and hemorrhage, and growth retardation. Dexamethasone, like other steroids, may cause avascular necrosis of bone. However, patients will be monitored daily by study personnel and may discontinue at any time for any reason during the trial, with no consequences to the quality of their treatment. Early discontinuation from this trial does not interfere with the patient receiving their routine medical care. The possible benefits of participation to patients in this trial may be earlier recovery from ACS, decreased hospital stay and elimination of rebound vaso-occlusive complications. Furthermore, the serial biomarker assays may provide a better understanding of the biologic basis of steroid administration's beneficial effects and deleterious rebound complications in order to tailor therapy for each individual patient.

D. Subject Flow Diagram



***Exact timing may vary—see protocol.**

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V. CENTER ENROLLMENT PLAN

A. Site Set-Up

Sites need to have completed the IRB and ICF approval process described in section 14.2 of the protocol. Sites will also need to have a recruitment plan, and must have study staff attend training at Rho, Inc. with regards to the EDC system, RhoLAB, and RhoRAND systems.

B. Site Initiation Visit

Site initiation visits will be required for each site. Site initiation visits will take place after the site has IRB approval and has submitted all of their regulatory documents to Rho. The Rho monitor assigned to the Dexamethasone protocol will conduct the initiation visit.

C. Subject Screening

Subject's eligibility to enroll in the study will be assessed by study personnel or the physicians who care for them in the emergency department or the inpatient ward. Subjects who meet all of the Inclusion Criteria and have none of the Exclusion Criteria will be enrolled in the study after providing informed consent.

D. Inclusion Criteria

Subjects who meet all of the following criteria are eligible for enrollment into the study:

1. Age ≥ 5 years;
2. Diagnosis of sickle cell anemia (Hgb SS) or sickle-β^0-thalassemia (Hgb Sβ^0);
3. Current episode of ACS defined as a new lobar or segmental pulmonary infiltrate seen on a chest radiograph and <u>two</u> or more of the following findings in the 24 hours preceding enrollment (signing consent):

   temperature ≥ 38.5°C,

   tachypnea,

   dyspnea or increased work of breathing,

chest wall pain, and

oxygen saturation of < 90% in room air by pulse oximetry;

4. Subjects must have <u>one</u> or more of the following findings at the time of enrollment:

   tachypnea,

   dyspnea or increased work of breathing,

   chest wall pain, and

   oxygen saturation of < 90% in room air by pulse oximetry;

5. Current episode of ACS diagnosed within the preceding 24 hours;
6. Ability to take medication in capsule form;
7. Written, informed consent provided by the subject and/or parent(s) or guardian(s) before study entry.

E. Exclusion Criteria

Subjects who meet any of the following criteria are disqualified from enrollment in the study:

1. Prior participation in this study;
2. A condition that will likely be exacerbated by corticosteroid therapy, including:

   diabetes mellitus,

   hypertension,

   esophageal or gastrointestinal ulceration or bleeding, or

   known avascular necrosis;

3. Diagnosis of ACS in the 6 months preceding enrollment;
4. Treatment with oral or parenteral corticosteroid therapy for any reason within the preceding 14 days;
5. Use for respiratory illness in the preceding 3 months of:

   oral corticosteroids, or

   parenteral corticosteroids;

6. A chronic pulmonary condition that requires treatment with corticosteroids;

7. Current participation in a program of chronic transfusions.

   "Current participation" denotes that the subject's last transfusion was given in the 4 months preceding study entry

   "Program of chronic transfusions" is defined as a regimen of serial simple or exchange transfusions given at least every 6 weeks for at least 3 consecutive transfusions for the prevention of SCD-related complications.

8. Pregnancy;
9. Treatment with any investigational drug in preceding 90 days.
10. A history of either tuberculosis or a positive skin test for tuberculosis;
11. Known infection with HIV or a current systemic fungal infection.

F. Privacy, Confidentiality, Security of Data

Electronic resources used by the CSCC SDMC at Rho, Inc. are protected through numerous physical security measures and user access controls. It is impossible, however, to completely eliminate the risk of damage to network files from various threats, including physical catastrophes, virus attacks, user errors, or other unusual circumstances. Rho's back-up and security procedures ensure that Rho can recover quickly from such an event with minimal data loss.

Web-based Network Communication System

Security for the CSCC secure website has been set up through a table of authorities, which controls the level of access. Access rights are automatically applied to the user as a function of the login process. All users affiliated with the CSCC sites or NHLBI are required to arrange a login name and password prior to accessing the site. Access restrictions will be automatic, and features for which the user does not have access will not appear on the menu.

Back-up and Recovery and Virus Protection

All CSCC files and data are stored on the SDMC network; these network files are backed-up routinely to tape on a semi-daily basis.

Virus Protection

The need to exchange files with CSCC Investigators and study site personnel can expose the CSCC SDMC network and workstations to the possibility of attack by computer viruses and related entities. Each computer on the Rho network has anti-virus software running at all times. The software is configured to automatically scan all floppy disks and executable files introduced to the system.

G. Reimbursement/Compensation

Subjects will be paid $25 dollars at the time of the first follow-up visit to reimburse them for their time and parking fees. Subjects will be paid $50 dollars at the time of the second follow-up visit to reimburse them for the additional time required to complete all of the study procedures, as well as their parking fees.

H. Assessing Literacy

Literacy of eligible, as well as, enrolled study subjects is an important issue that warrants consideration for all CSCC related research. Subjects' reading comprehension is dependent upon numerous factors including vocabulary, knowledge of sentence structure and understanding of the content of the material presented. Obtaining informed consent in accordance with ICH and policies for clinical research requires that the subject has the ability to fully understand benefits, risks and the rationale behind the study in which he or she is being asked to participate. Study coordinators should also provide assistance if participants are unable to read the Informed Consent Forms.

There are two approaches that may be employed by clinical researchers to assess literacy. One approach is to administer a standardized measure to subjects. There are a number of standardized literacy assessments used in clinical research including the WRAT-3, The Rapid Estimate of Adult Literacy in Medicine (REALM), The Test of Functional Health Literacy (TOFHLA), as well as a graph format called the Fry Readability Scale. Another approach is to

ask the subject to fill out a very brief general survey about topics such as neighborhood information, and have the study coordinator or interviewer subjectively decide whether or not the subject seems to have a literacy deficit.

I. Subject Study Withdrawal or Discontinuation

Subjects may choose to discontinue from the study at any time. The site Principal Investigator or the sponsor may choose to discontinue the subject from the study for the following conditions:

1. Subject's chest syndrome gets worse.
2. Investigator determines that participation in study is no longer safe for the subject.
3. Investigator determines other treatment may be more helpful.
4. The sponsor or FDA stops the research for the safety of the participants.
5. The sponsor cancels the research.
6. Investigator determines the subject is unable to adhere to study directions.

Upon study discontinuation for any reason, the Study Completion form in the EDC system must be completed. Subjects who discontinue prematurely from the study for any reason, including those subjects determined to be ineligible after signing informed consent, will be encouraged to complete the last follow-up visit.

J. Training

Slides from the July 19-20, 2006 training session at Rho, Inc. are found on the secure CSCC website on the Dexamethasone study page under Training and Help documents.

VI. STUDY ACTIVITIES

A. Patient Recruitment and Eligibility

All sickle cell anemia (Hgb SS) or sickle-β^0 –thalassemia (hgb S $\beta^{0)}$patients greater than five years of age seen in the emergency department or inpatient ward at a CSCC site with a diagnosis of Acute Chest Syndrome, should be screened by study personnel for eligibility. A current diagnosis of Acute Chest Syndrome (ACS) is defined as a new lobar or segmental pulmonary infiltrate seen on a chest radiograph **and** two or more of the following findings:

- Temperature $\geq 38.5^0$ C,
- Tachypnea,
- Dyspnea or increased work of breathing,
- Chest wall pain, and
- Oxygen saturation of <90% in room air by pulse oximetry.

Enrollment must occur within 24 hours of the diagnosis of ACS, which is timed from the diagnostic chest radiograph. Qualifying patients will be enrolled after providing informed consent. In total, 112 subjects (56 children and 56 adults) will be randomized either to dexamethasone or placebo.

B. Obtaining Informed Consent

Sites are obligated to obtain informed consent from each subject and to ensure that all of the information gathered remains confidential. "Informed Consent" means that study staff have explained the purpose of the study, what their participation entails, and whether it will cause any harm or provide any benefit to the participant. Only after this explanation can the potential study subject be expected to make an 'informed' decision about whether he/she wants to participate. Study staff must assure the participant that all of the information collected is completely confidential and will never be linked to the participant. "Confidentiality" means that every effort is made to protect the identity of the participant. Study staff must read the informed consent statement to the potential participant and make sure they understand what it means.

When obtaining informed consent, attention should be focused on the following elements of the informed consent statement:

- Purpose of the study
- Sponsorship of the study
- Study procedures
- Risks and discomforts associated with the study
- Benefits of the study
- Confidentiality of information
- Payment for participation in the study

C. Daily Activity Visit Checklist

Day 0 (Baseline/Study Enrollment Visit)

- ❑ Have informed consent signed
- ❑ Check inclusion and exclusion criteria
- ❑ Chest radiograph
- ❑ ACS Assessments (every 4 hrs by nurse or study personnel)
- ❑ Physical Exam
- ❑ Weight
- ❑ Vital signs (every 4 hrs while in-patient recorded in medical record)
- ❑ Draw blood for CBC and reticulocyte count labs to be done locally
- ❑ Draw blood culture if temperature $\geq$ 38.5º C
- ❑ Draw blood for Biomarkers to process (will batch and ship to TJU every 2 weeks)
- ❑ Obtain blood sample for pregnancy test (if female of child-bearing potential)
- ❑ Pain Intensity rating (every 4 hours while in-patient)
- ❑ Peripheral oxygen saturation (by pulse oximetry and every 4 hours while in-patient)
- ❑ Fluid Balance (ins and outs recorded in the medical record)
- ❑ **Randomization[1]**
- ❑ **Study Drug Administration[2]**
- ❑ Collect medical history
- ❑ Collect demographic information
- ❑ Collect concomitant medication information
- ❑ Collect Occurrence of AEs and SAEs

Day 1

- ❑ ACS Assessments (every 4 hrs by nurse or study personnel)
- ❑ Physical Exam
- ❑ Vital Signs (every 4 hrs while in-patient recorded in medical record)
- ❑ Draw blood for CBC and reticulocyte count labs to be done locally
- ❑ Draw blood culture if temperature $\geq$ 38.5º C
- ❑ Draw blood for Biomarkers to process and store
- ❑ Pain Intensity rating (every 4 hours while in-patient)
- ❑ Peripheral oxygen saturation (by pulse oximetry and every 4 hours while in-patient)
- ❑ Fluid Balance (ins and outs recorded in the medical record)
- ❑ **Study Drug Administration[2]**
- ❑ Collect concomitant medication information
- ❑ Collect Daily amount and type of Opioid use
- ❑ Collect number and type of transfusions
- ❑ Collect AE and SAE information

Day 2

- ❑ ACS Assessments (every 4 hrs by nurse or study personnel)
- ❑ Physical Exam
- ❑ Vital Signs (every 4 hrs while in-patient recorded in medical record)
- ❑ Draw blood for CBC and reticulocyte count labs to be done locally
- ❑ Draw blood culture if temperature ≥ 38.5º C
- ❑ Draw blood for Biomarkers to process and store
- ❑ Pain Intensity rating (every 4 hours while in-patient)
- ❑ Peripheral oxygen saturation (by pulse oximetry and every 4 hours while in-patient).
- ❑ Fluid Balance (ins and outs recorded in the medical record)
- ❑ **Study Drug Administration[2]**
- ❑ Collect concomitant medication information
- ❑ Collect Daily amount and type of Opioid use
- ❑ Collect number and type of transfusions
- ❑ Collect AE and SAE information

Day 3[3]

- ❑ ACS Assessments (every 4 hrs by nurse or study personnel)
- ❑ Physical Exam
- ❑ Vital Signs (every 4 hrs while in-patient recorded in medical record)
- ❑ Draw blood for CBC and reticulocyte count labs to be done locally
- ❑ Draw blood culture if temperature ≥ 38.5º C
- ❑ Pain Intensity rating (every 4 hours while in-patient)
- ❑ Peripheral oxygen saturation (by pulse oximetry and every 4 hours while in-patient)
- ❑ Fluid Balance (ins and outs recorded in the medical records)
- ❑ **Study Drug Administration[2]**
- ❑ Collect concomitant medication information
- ❑ Collect Daily amount and type of Opioid use
- ❑ Collect number and type of transfusions
- ❑ Collect AE and SAE information

Day 4[3]

- ❑ ACS Assessments (every 4 hrs by nurse or study personnel)
- ❑ Physical Exam
- ❑ Vital Signs (every 4 hrs while in-patient recorded in medical record)
- ❑ Draw blood for CBC and reticulocyte count labs to be done locally
- ❑ Draw blood culture if temperature ≥ 38.5º C
- ❑ Pain Intensity rating (every 4 hours while in-patient)
- ❑ Peripheral oxygen saturation (by pulse oximetry and every 4 hours while in-patient)
- ❑ Fluid Balance (ins and outs recorded in medical records)
- ❑ **Study Drug Administration[2]**
- ❑ Collect concomitant medication information
- ❑ Collect Daily amount and type of Opioid use
- ❑ Collect number and type of transfusions
- ❑ Collect AE and SAE information

Day 5[3]

- ACS Assessments (every 4 hrs by nurse or study personnel)
- Physical Exam
- Vital Signs (every 4 hrs while in-patient recorded in medical record)
- Draw blood for CBC and reticulocyte count labs to be done locally
- Draw blood culture if temperature $\geq$ 38.5º C
- Pain Intensity rating (every 4 hours while in-patient)
- Peripheral oxygen saturation (by pulse oximetry and every 4 hours while in-patient)
- Fluid Balance (ins and outs recorded in medical records)
- **Study Drug Administration[2]**
- Collect concomitant medication information
- Collect Daily amount and type of Opioid use
- Collect number and type of transfusions
- Collect AE and SAE information

Day 6[3]

- ACS Assessments (every 4 hrs by nurse or study personnel)
- Physical Exam
- Vital Signs (every 4 hrs while in-patient recorded in medical record)
- Draw blood for CBC and reticulocyte count labs to be done locally
- Draw blood culture if temperature $\geq$ 38.5º C
- Pain Intensity rating (every 4 hours while in-patient)
- Peripheral oxygen saturation (by pulse oximetry and every 4 hours while in-patient)
- Fluid Balance (ins and outs recorded in medical records)
- **Study Drug Administration[2]**
- Collect concomitant medication information
- Collect Daily amount and type of Opioid use
- Collect number and type of transfusions
- Collect AE and SAE information

Day 7[3]

- ACS Assessments (every 4 hrs by nurse or study personnel)
- Physical Exam
- Vital Signs (every 4 hrs while in-patient recorded in medical record)
- Draw blood for CBC and reticulocyte count labs to be done locally
- Draw blood culture if temperature $\geq$ 38.5º C
- Pain Intensity rating (every 4 hours while in-patient)
- Peripheral oxygen saturation (by pulse oximetry and every 4 hours while in-patient)
- Fluid Balance (ins and outs recorded in medical records)
- **Study Drug Administration[2]**
- Collect concomitant medication information
- Collect Daily amount and type of Opioid use
- Collect number and type of transfusions
- Collect AE and SAE information

Day 8[3]

- ACS Assessments (every 4hrs by nurse or study personnel)
- Physical Exam
- Vital Signs (every 4 hrs while in-patient recorded in medical record)
- Draw blood for CBC and reticulocyte count labs to be done locally
- Draw blood culture if temperature $\geq$ 38.5º C
- Draw blood for Biomarkers to process and store **(after the last dose of study drug)**
- Pain Intensity rating (every 4 hours while in-patient)
- Peripheral oxygen saturation (by pulse oximetry and every 4 hours while in-patient)
- Fluid Balance (ins and outs recorded in medical records)
- **Study Drug Administration[2]**
- Collect concomitant medication information
- Collect Daily amount and type of Opioid use
- Collect number and type of transfusions
- Collect AE and SAE information

Day 1 – 8 if patient has been discharged from the hospital

- Reminder phone call to encourage to take study drug until complete taper
- Schedule 1 Week Follow-up visit which occurs between days 7-10 after study enrollment and after the last dose of study drug (if patient has been discharged from the hospital)
- Dispense Study Drug Diary and give instructions for use and return of unused study drug

Follow-up Visit #1 After Hospital Discharge (Day 7 – 10)

- Interim History
- Vital Signs
- ACS Assessment
- Draw blood for CBC and reticulocyte count labs to be done locally
- Draw blood for Biomarkers to process and store (if patient was discharged prior to Day 8)
- Pain Intensity rating
- Peripheral oxygen saturation (by pulse oximetry)
- Compliance with home administration of study drug
- Collection of study drug diary and any un-used study drug
- Collect concomitant medication information
- Collect Daily amount and type of Opioid use
- Collect AE and SAE information
- Schedule Follow-up visit #2 which occurs 30 days +/- 3 days after hospital discharge

Follow-up Visit #2

- ❑ Interim History
- ❑ Physical Exam
- ❑ ACS Assessment
- ❑ Weight
- ❑ Vital Signs
- ❑ Draw blood for CBC and reticulocyte count labs to be done locally
- ❑ Chest radiograph
- ❑ Pulmonary Function Testing
- ❑ Pain Intensity rating
- ❑ Peripheral oxygen saturation (by pulse oximetry)
- ❑ Compliance
- ❑ Collect concomitant medication information
- ❑ Collect Daily amount and type of Opioid use
- ❑ Collect AE and SAE information

[1]Refer to SIM section VI Study Activities - F. Randomization
[2]Refer to Drug dosing Chart
[3]Use Day 3- 8 check list when the patient is an in-patient

D. Table of Clinical Evaluations and Procedures

	Inpatient				Inpatient or Outpatient	
	Baseline	Daily	Inter-mittent	Contin-uous	Follow-up #1(7-10 d) [6]	Follow-up #2 [6]
Assessment of structured discharge criteria[1]	X		Every 4h		X	X
History	X				Interval[2]	Interval[2]
Physical exam	X	X				X
Weight	X					X
Vital signs	X		Every 4h[5]		X	X
CBC, reticulocyte count	X	X			X	X
Blood culture	X	X[3]				
Chest radiograph	X					X
Pain scale[4]	X		Every 4h		X	X
Concomitant Medications	X	X	X	X	X	X
Opioids used (quantified)		X				
Pulse oximetry (record every 4 hrs)	X			X (q4h)	spot	spot
Fluid balance (ins and outs)			Every 8h			
Pregnancy test (if applicalble)	X					
Study drug administration			Every 12-24h			
Occurrence of AEs or SAEs				X	X	X
Number of transfusions		X				
Pulmonary function testing						X
Compliance					X	X

[1]Appendix3.
[2]Includes pain history, pain treatment, respiratory symptoms, inpatient or outpatient evaluations and management of SCD-related complications (rebound VOC).
[3]Only if temperature ≥38.5ºC or at discretion of attending physician
[4]Oucher Scale (age <10 years) or numeric rating scale (age ≥10 years)
[5] Vital signs recorded every 4 h and I/Os every 8 h on subject's medical record. Study personnel will collect the maximum values of the subject's vital signs every 24h.
[6]Follow-up #1 is after completion of study drug between days 7-10. Follow-up #2 is thirty days (+/- 3 days) after discharge from hospital and no more than 60 days after study enrollment

E. Dexamethasone Dosing Chart

Dose (mg/kg)	Max single Dose (mg)	Frequency	24hr dose (mg/kg)	Duration (days)	
0.3	12	Every 12H	0.6	2 (or hospital discharge)	"High Dose"
0.3	12	Every 24H	0.3	2	"Taper"
0.2	8	Every 24H	0.2	2	
0.1	4	Every 24H	0.1	2	

A template for physician's orders can be found on the secure CSCC website on the Dexamethasone study page under Training and Help documents. A Dosing Taper Chart, Drug Dosing Regimen Tool and Subject Diary can be found on the Dexamethasone study page under Source Documents.

F. Randomization and Masking

After enrollment, subjects will be randomized to one of two treatment arms. Subjects in Arm 1 will receive oral dexamethasone. Subjects in Arm 2 will receive oral placebo. A computer-generated, adaptive randomization schema will be used to allocate subjects 1:1 between the two treatment arms. Randomization will be stratified by site, age and the severity of ACS (see Section 8.3). In order to increase the likelihood of balance in treatment allocations, subjects will be randomized using the standardized range variation (79) of the sequential allocation algorithm of Pocock and Simon (80), a minimization method. This method attempts to achieve treatment balance on several subject characteristics (i.e. age group, site, and severity of ACS in this study) simultaneously – not within separate strata. Minimization consists of biasing the treatment allocation so as to minimize the total imbalance between the treatment groups on some scale (81). The order of entry of the subjects to the various centers and in the various prognostic groups is assumed to be random. As minimization is a dynamic method that uses information on subjects already entered to allocate treatment to the next subject, a continuous updating of the information related to previous treatment allocations is required, thus a centralized randomization system will be used.

Pharmacists at each center will be unblinded and will utilize information from the interactive voice/web randomization system (IVRS) at the SDMC to obtain a new treatment assignment

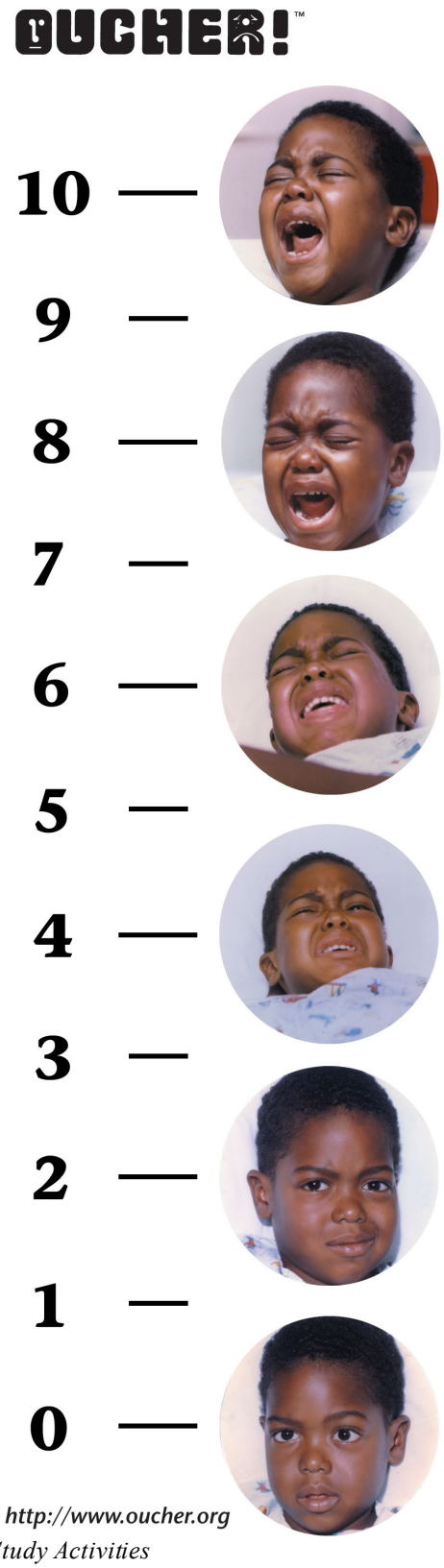
for a subject and provide each subject with appropriate dosing of both therapies. The IVRS system has the capability of providing unblinding information in case of a medical emergency where the exact study drug is needed in order to appropriately treat a subject.

The time interval between Randomization and the first dose of study drug administration will be no longer than 2 hours. In the event a subject's first dose occurs outside the 2-hour time limit, the subject will still be included in the study and the analysis. This is in the spirit of the intention-to-treat analysis. The amount of time in excess of the 2-hour limit until the first dose of study drug will also be recorded. This event will be documented as a protocol deviation.

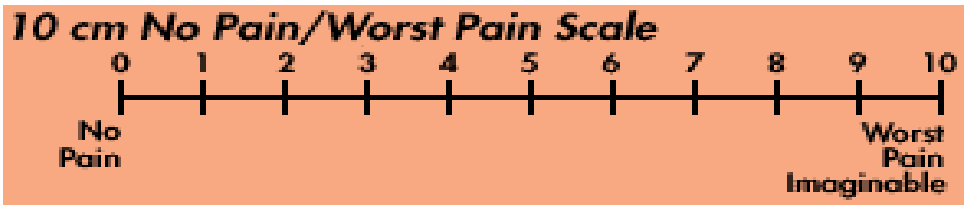
The subject's physicians, nurses, and ancillary support staff will not be aware of the treatment assignment. The placebo formulations will be identical in appearance and taste to the active compounds (see protocol Section 9.1.3).

G. Pain Intensity Rating

Oucher Pain Rating Poster
Reprinted with permission from Judith Beyer



10-point Numeric Rating Scale for subjects ≥ 10 yrs and older



H. Subject Compensation

Subjects will be paid $25 dollars at the time of the first follow-up visit to reimburse them for their time and for parking fees. Subjects will be paid $50 dollars at the time of the second follow-up visit to reimburse them for the additional time this visit requires to complete all of the study procedures as well as their parking fees.

I. Principal Investigator Quality Control and Documentation

The principal investigator at each local site will review all entry chest radiographs and perform each physical exam and indicate he or she has done so by initialing the corresponding source document form.

Additionally, the principal investigator at each local site will also review all Medical History, discharge criteria, study drug orders, adverse and serious adverse event case report forms for each study subject.

Sites may elect to establish an additional process for review to ensure that data have been accurately collected.

VII. WEBSITE OVERVIEW

A. Website Content

The "Dexamethasone" study webpage is accessed via a link located on the right-hand side of the CSCC Website Homepage. You must be an authorized user for the study to see the Dexamethasone link on the website. Access to various documents will depend on your user level.

User Levels:

1) **Basic User –** Basic access allows the individual to view the staff directory, the calendar, the committees, and CSCC templates.
2) **Second Level User** – Study-specific access that allows the user to view all documents associated with a particular protocol.
3) **EDC/RhoLAB User –** For users who will perform data entry into the applications developed by Rho (the SDMC) as sources of data capture and specimen tracking from site to central lab. EDC is used for all CSCC studies and users must obtain permission from their site PI. RhoLAB is used only for studies that involve central labs and also requires PI permission.

Categories:

1) **General Protocol Documents** – Contains the most recent protocol and PI Signature Page, the current budget, and the Dexamethasone Protocol Committee Roster.

2) **EDC Links** – Provides a direct link to the EDC system and the list of patients registered at each Center. This list can be viewed in a table that is sorted by hospital or by CSCC Subject Identification Numbers.

3) **Case Report Forms** – Provides access to the paper version of the most recent Case Report Forms (CRFs), as well as annotated CRFs that include Completion Guidelines.

4) **Training and Help Documents** – Contains Frequently Asked Questions (FAQs) related to this study and the most recent version of the Study Information Manual. When revisions are

made to either of these documents, an e-mail will be sent to the Dexamethasone listserv directing members to the website and to the specific documents or sections that were updated.

5) **Informed Consent Documents** – Contains the Informed Consent Process Summary, the Consent Form Checklist, and the most recent Informed Consent Templates.

6) **Teleconference Minutes** – Contains detailed minutes from each Dexamethasone study teleconference call.

7) **Study Progress** – Contains enrollment reports and an IRB status report.

8) **Educational Documents and Materials** – Contains a PDF version of the staff brochure. Contains a slide presentation that may be used by in-service nursing staff. Contains a template for in-patient door sign, in-patient study stickers, and in-patient physician orders. Contains a letter template that may be used to thank nursing staff assisting in the collection of the study assessments.

9) **Source Documents and Bedside Nursing Staff Binder -** Contains Source Document templates that may be used to collect study data. These documents are provided to serve as tools that will ensure that all data required for the CRF is collected and all evaluations and procedures required by the protocol are completed. Additionally, these tools can be easily given to another coordinator to perform a study visit or procedure in the event that the study coordinator specifically trained on the protocol is unable to be there. The source documents are intended to increase overall organization of the study at each site and to increase efficiency during the site monitoring visits.

   The Dexamethasone Study Drug Dosing Regimen Tool is available to help investigators and coordinators verify correct study drug dosing. The Subject Diary is to be administered at hospital discharge in the event that the Taper Regimen has not been completed. Coordinators

will collect the Diary at Follow-up Visit One and file in the subject's Source Document binder.

The Oucher and Numeric Rating Scale Posters are located here as well as the documents required for the ACS Assessments performed by the bedside staff nurse.

B. CSCC Website Instructions

I. Accessing the secure website

A. The CSCC secure website is a password-protected website resource for staff who are working on CSCC trials, including Investigators and Study Coordinators. This site provides a staff directory and study specific documents and information (displayed in your browser in PDF format). Adobe Reader is required to read the PDFs.

B. Select a username (the first letter of your first name followed by up to seven letters of you last name) and password (six or more characters, with a numeric digit somewhere in the middle) by completing a "Website Access Form." An access form is provided in this Study Information Manual. The completed form should be returned to Allison Overington at the SDMC. For security purposes, please **DO NOT** use email to notify the SDMC of your username and password. Your username and password will be activated no later than one week after returning the access form.

C. Once you have been granted access to the secure website, go to www.rhoworld.com. To access the RhoNET™ login page, select the LOGIN button in the upper-right corner of the page.

II. RhoNET™ Login Page

A. Type your username and password, then click "Login" to access RhoNET™, your access point to the CSCC website.

B. On the next page you will see the following categories: "User Preferences" and "Comprehensive Sickle Cell Centers."

C. To change your password, click on "Change Password" under User Preferences.

D. Otherwise, click on "Comprehensive Sickle Cell Centers."

III. The Secure Website Home Page

A. The "Comprehensive Sickle Cell Centers" banner with blue letters will appear at the top of any page on the site, except when you are viewing a document such as the Protocol or consent forms.

B. Announcements will be displayed in the gray box in the center of the Home Page. These announcements will include upcoming meetings or conference calls, as well as a link to relevant documents for each of the specific events.

IV. The Calendar

A. The calendar lists all scheduled events related to CSCC studies such as conference calls, annual meetings, and certain deadlines.

B. When you click on the calendar link, the current month will be displayed. To view following months, click on the pull-down menu on the upper-left side of the calendar and choose the month you wish to view.

C. To view details for a scheduled event, click on the name of the event in the calendar. A small pop-up window will provide additional information about the event.

V. Enrolled Patient Lists

A. These lists have been generated from the Electronic Data Capture System that study coordinators use to input data about each of their patients involved in a CSCC Study. These lists are center-specific in visibility and are sorted in one of two ways, by site ID or by patient ID. Study coordinators can use these tables to view IDs and the demographic information that correlates to them to prevent patients from getting assigned multiple CSCC IDs when they are involved in more than one study.

B. These lists are also located under the EDC Links Category on the Dexamethasone webpage where they are referred to as Patient Registration ID Numbers.

VI. Staff Directory

A. The staff directory contains information for everyone involved with CSCC studies.

B. After clicking on the Staff Directory link, you will see a pull-down menu on the top left. This menu allows you to filter by a group of contacts (e.g., Center Directors, Peripheral Data Coordinators, SDMC members). Simply choose the group you are interested in and click the "Go" button. The list you asked for will be displayed below in alphabetical order.

VII. Dexamethasone Study Webpage

A. To view study documents and forms, click on the Dexamethasone link listed on the right side of the home page.

B. After clicking on the Dexamethasone link, you will be brought to the Dexamethasone webpage. This page will have several different categories with several different types of documents as described above. Choose the study document that you are interested in reviewing and click directly on it.

C. Protocols and all consent form templates will be displayed in your browser in PDF format. You may then print the desired document(s) from your computer if you wish. You must have Adobe Reader installed on your computer to view any document in PDF format. You can download this software for free from http://www.adobe.com.

D. Many other forms will be saved as Microsoft Word documents. You may then print or save the form to your computer. After saving, you may edit the document as needed.

VIII. Logging Off and Support

A. To log out, click the "Log Out" hyperlink on the upper-right side of the home page. Simply closing your browser or going to another URL will not log you off.

B. If you have question regarding content, updates, or technical issues contact Allison Overington (919-408-8000, ext. 581) at Rho or by email at aoverington@rhoworld.com.

C. If you have forgotten your username or password, call the SDMC Help Desk at Rho at 1-800-905-0460.

C. CSCC Website Access Form

The website access form can be downloaded from the CSCC secure website under the **Forms** section. Print the form, fill it out, and fax it to Allison Overington (Fax: 919-287-0126) in order to gain access to the secure CSCC website.

D. Electronic Data Capture Instructions

The following pages provide instructions for using Rho's electronic data capture (EDC) system. These instructions are also available electronically within the EDC system.

VIII. DATA COLLECTION

A. Assignment of ID Numbers

Each patient enrolled in any CSCC study (both multi-center and within-center) will be registered as a CSCC patient through Rho's electronic data capture (EDC) system, and assigned a 7-digit CSCC ID number. This CSCC ID number will be used to identify subjects in the Dexamethasone study, and all CSCC studies (both multi-center and within center) thereafter. As such, the CSCC ID# is not study specific and can be used to track a patient's progress in multiple CSCC studies. The first two digits of the CSCC ID# will identify the Center at which the patient is enrolled, and the next five digits will uniquely identify the patient.

If a study coordinator is enrolling a subject in their second (or third, etc) study they will go to the EDC Link for the study in which they want to enroll the subject; in this case, Dexamethasone. On the subject page of the EDC system, the study coordinator will click on "Import." Select the subject's CSCC ID# and click on "Import" again. The subject is automatically enrolled into the new study and the EDC system will advance to the study Case Report Forms.

If you are unsure as to whether or not a subject is already enrolled in a CSCC study, ask the subject first. If you are still unsure, or if you don't know their CSCC ID#, go to the "List of Patient Registration ID Numbers"; this document is located under EDC Links on the webpages for each of the individual studies. These documents are created directly from data entered into the EDC system and will give the study coordinator basic demographic information that will allow the patient's CSCC ID# to be located.

B. CSCC ID Number Assignment Log

CENTER NAME: _____ HOSPITAL: _____

CSCC ID Number	Subject Name	Subject Birthdate	Medical Record #	Date ID Assigned

C. Electronic Data Capture (EDC)

EDC, Rho's internet-based remote data entry system, will be used to capture the data for the Dexamethasone study. Using this system, the clinic's study coordinator or data coordinator uses an internet browser (Internet Explorer or similar) to key data into electronic case report forms. Univariate and multivariate data validation tests are performed as the data are keyed and/or submitted and most implausible data values are resolved immediately. Data are not stored on the site's computer. At the end of each "page," data are submitted to Rho's secure web server using SSL (128 byte public key encryption methodology) and stored in the study's "operational database." (The database used for capturing, validating, updating, and storing the data is called an "operational database.") The database is backed up nightly; backup tapes are saved in a secure, off-site location. At any time site personnel may log in to the system, review and correct previously entered data, key additional data, or lock records to prevent further inadvertent modifications.

The pages will be accessible via the CSCC website and require Center-specific user ID/password privileges. The data will be converted to intermediate datasets prior to incorporation into the Dexamethasone study format (SAS datasets).

D. Source Documentation

Any of the documents addressed in this manual may be subject to and available for audit and inspection by federal regulatory authorities. For this reason, it is absolutely necessary to obtain quality data from individuals' medical records and interviews.

To substantiate that each subject meets the subject inclusion criteria, the investigator should maintain records of the subject's medical history before enrollment in the Dexamethasone study (if these records exist in the investigator's own research files or hospital files).

E. Monitoring Visits

Representatives from the SDMC will visit each site at least twice annually for data and regulatory monitoring. Additional visits may be necessary if there are problems with data quality, subject accrual, etc.

The main purpose of these visits is to assist the site personnel in accurate data collection and use of the EDC system. At this visit, the representatives will:

- Review study documentation
- Review and discuss recruitment and enrollment
- Observe data abstraction and data entry process to ensure adherence to the protocol
- Review compliance with Informed Consent procedures
- Review participants' records and case report forms for completeness
- Review and discuss data management issues
- Discuss any site-specific issues, problems, or suggestions

The length of the visit will vary based on the amount of data to be reviewed.

No special preparation is required for these visits except to have the research and medical records available and the appropriate CRF pages completed via the EDC system. The visitors will need a private space or room in which to review participants' research and medical records and other study documentation. A written report will be sent to the site following the visit.

IX. RHORAND

A. RhoRAND Links:

RhoRAND is the Centralized Interactive Randomization system for the Dexamethasone protocol. Sites will access this system by logging into the CSCC secure website with a RhoNET User ID, just as they do for EDC and other study documents. Select "RhoRAND > Dexamethasone" on the Dexamethasone study page to access RhoRAND. Users must have a RhoRAND user ID and PIN to gain access to the system. Each user will need to submit the RhoRAND user access form found on the Dexamethasone study page to the Rho Study Administrator.

- Sites will have access to both web and phone RhoRAND applications. Users must execute the randomization practice function on the web interface at least one full business day prior to randomizing a subject.
- Users interested in using the phone interface must also practice via the phone one full business day prior to randomizing a subject. The Phone number to randomize a subject is: 1-888-RAND-DEX or 1-888-726-3339.
- Users must keep their email addresses or fax numbers current in Rho*RAND*™ so notifications are sent to the correct location.
- Help Desk hours are 7 days a week 8:00 am to 12:00 am, excluding company designated holidays. The Help Desk number is: 1-888-DEX-9110 or 1-800-905-0460.
- Subject IDs are 7 digits. The first 2 digits represent the center number at which the subject is enrolled. The 3rd through 6th digits are a sequential count of subjects at the center, beginning with 0001 within each center. The 7th digit is a check-digit.

B. RhoRAND Reference Guides:

The Study Coordinator Dexamethasone Reference Guide, Site Pharmacist reference Guide, and Blind Break Guide are located under the RhoRAND section of the Dexamethasone study page. These guides provide users with information regarding

randomizing a subject, shipment of drug, and breaking the blind. **Note: If possible, the Medical Monitor or Protocol Chair must be contacted prior to accessing RhoRAND to perform the Blind Break function.** Their contact information is located under Dexamethasone Contact Information, SDMC study team and below. The practice Blind Break function must be performed (as all other RhoRAND functions) at least one business day prior to a user having live access.

Protocol Chair: **Charles T. Quinn, M.D.**
The University of Texas Southwestern
Medical Center at Dallas (CMC)
Non-Emergency: (214) 648-3896, office
Emergency Only: (214) 707-2027, cell
(972) 206-9157, pager
Charles.quinn@utsouthwestern.edu

Medical Monitor: **Rupa Redding-Lallinger, MD**
UNC Hospital at Chapel Hill, NC
Non-Emergency: (919) 966-8080 – Office
Emergency Only: (919) 216-3522
rredding@med.unc.edu

C. RhoRAND Training Slides:

The RhoRAND training slide pdf documents for site pharmacists and coordinators are located under the RhoRAND section on the Dexamethasone study page. Please review these slides PRIOR to screening for subjects.

D. RhoRAND Worksheet:

The RhoRAND worksheet is located under the RhoRAND section on the Dexamethasone study page. This worksheet has the information required when sites access either the web or phone applications to randomize a subject. There is both a simple and detailed version of the worksheet.

X. RHOLAB

A. RhoLAB Links:

RhoLAB is the Central Laboratory Tracking system for the Biomarker specimens. Sites will access this system by logging into the CSCC secure website with a RhoNET User ID, just as they do for EDC and other study documents. Select "RhoLAB > Dexamethasone" on the Dexamethasone study page to access RhoLAB directly.

Sites will use barcode scanners and labels to enter specimen information into the system. Sites will create and track shipments of samples (batched every 2 weeks) to the Central Lab of Dr. Marie Stuart. The system will also track shipments from Dr. Stuart's Lab to Dr. Frans Kuypers lab (Central Lab #2).

B. RhoLAB User Guide:

Dexamethasone User Guide: click on this link to access the User Guide directly. You may also print out a paper copy to use in your lab manual.

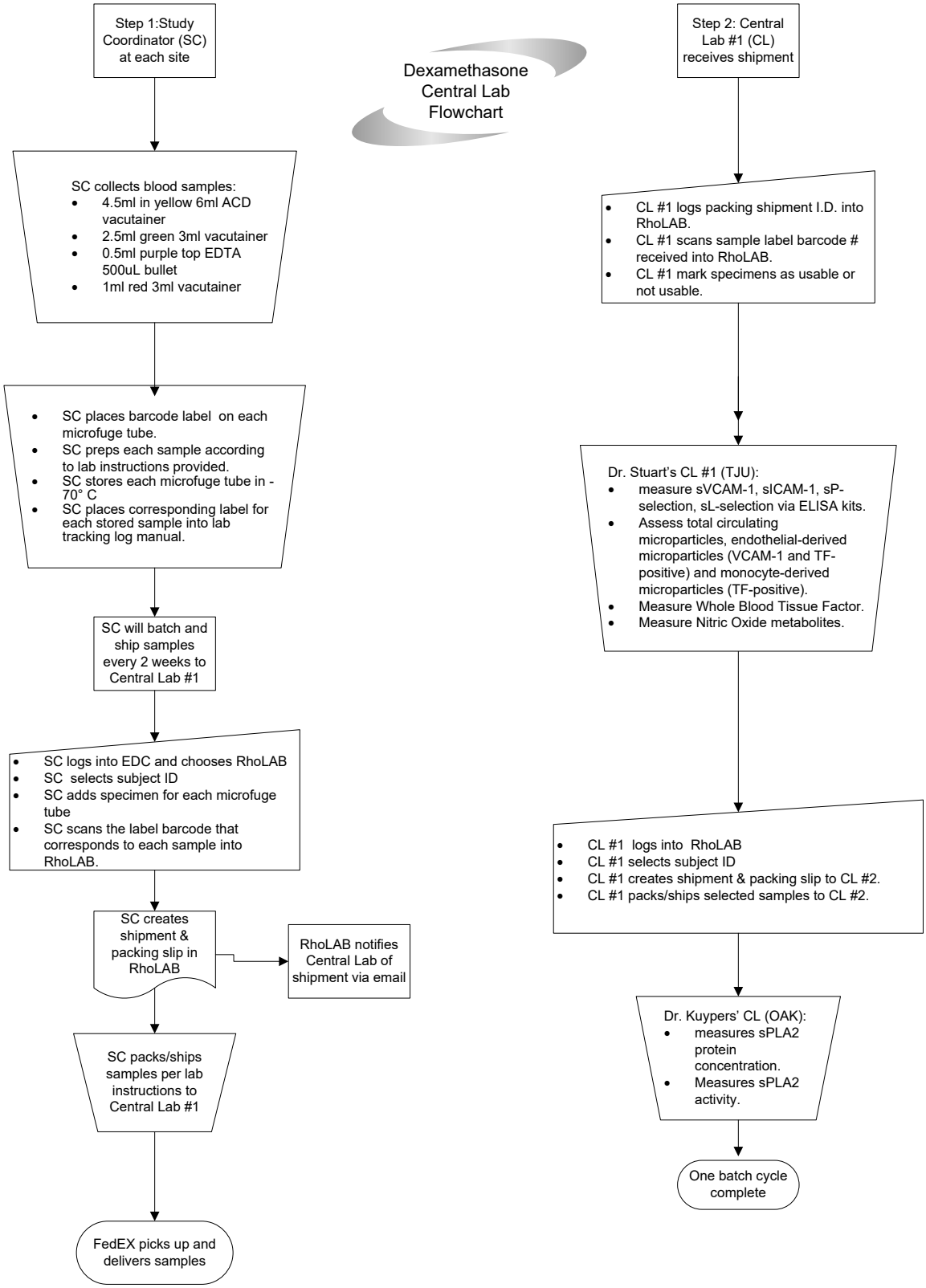
C. RhoLAB Training Slides:

The RhoLAB training slides pdf document is located under the RhoLAB section on the Dexamethasone study page. Please review the slide presentation PRIOR to your SIV and screening for subjects.

D. RhoLAB Processing and Guidelines for Obtaining Samples Documents:

The RhoLAB Processing Chart and Guidelines for Obtaining Samples are located under the RhoLAB section on the Dexamethasone study page. These are instructional guides to use while drawing and processing the Biomarker specimens. They also describe the comments and information about the specimens that are needed in the RhoLAB and EDC systems.

E. **RhoLAB Visio Flow Chart:**



F. RhoLAB Tracking Log:

The RhoLAB Tracking log is located under the RhoLAB section on the Dexamethasone study page. This log **MUST** be used as a source document for the biomarker bar code numbers. Rho will send each site pre-printed specimen labels with the bar code number on them. The labels come in rolls with 3 labels per row. Coordinators will use one row per specimen, placing one label on the cryovial, one in the Tracking Log, and one left over in the event of an error (i.e. label tears while placing in log or on cryovial). Discard or line through the 3rd label on a row if it is not used.

G. RhoLAB Lab Kit Supply Order Form:

The RhoLAB lab kit supply order form is located under the RhoLAB section on the Dexamethasone study page. Therapak will be shipping lab supply kits and dry ice shippers to each site. Rho will place each site's initial order after IRB approval. Sites will use the Therapak re-order form to replenish their supplies after this. Please note that Therapak will ship supplies via FedEx ground service, therefore plan for sufficient time for shipment of supplies while ordering.

XI. GENERAL STUDY POLICIES

A. Site Approval Process

Study sites for the Dexamethasone study must meet the Human Rights Issues requirements in order to conduct the study. All study staff must be trained in all aspects of the study conduct and procedures, which is covered in the Training section.

Human Rights

1. IRB/Informed Consent Approval

The IRB approval process as established by the NHLBI and adopted by the CSCC is described in great detail in this Study Information Manual under section **V. IRB Process.** In summary, sites must obtain approval of their individual site-customized informed consent materials from the Dexamethasone study informed consent review committee **before** submission to site IRBs. Any IRB-requested changes in the informed consents must be resubmitted to the informed consent review committee and approved before resubmission to site IRBs. Once site IRB approval is obtained, sites must forward **any communications** from site IRBs, including requests for revisions, as well as the actual approval letter to the SDMC at Rho, Inc. who will in turn, forward these to NHLBI to indicate approval for release of study funds to the site.

2. NIH Human Subjects Training Certificate

The NIH requires that all investigators and research staff who apply or receive NIH funds for research involving human subjects or research data related to human subject research must have completed the mandatory NIH Human Participant Protections: Education for Research Teams training. The NIH has developed a web-based course and it may be accessed at: http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp

Certificates of completion of the training are provided for printout by the NIH website and should be kept in hard copy on file at each study site for each member of the research staff. An example of this certification is attached.

Completion Certificate

This is to certify that

Joe Research Coordinator

has completed the **Human Participants Protection Education for Research Teams** online course, sponsored by the National Institutes of Health (NIH), on 10/08/2003.

This course included the following:

- key historical events and current issues that impact guidelines and legislation on human participant protection in research.
- ethical principles and guidelines that should assist in resolving the ethical issues inherent in the conduct of research with human participants.
- the use of key ethical principles and federal regulations to protect human participants at various stages in the research process.
- a description of guidelines for the protection of special populations in research.
- a definition of informed consent and components necessary for a valid consent.
- a description of the role of the IRB in the research process.
- the roles, responsibilities, and interactions of federal agencies, institutions, and researchers in conducting research with human participants.

National Institutes of Health
http://www.nih.gov

http://cme.cancer.gov/cgi-bin/cms/cts-cert5.pl 10/8/03

B. Confidentiality and Security of Data

1. Patient Confidentiality

As in all medical research projects, personnel involved in the Randomized Trial of Oral Dexamethasone for Acute Chest Syndrome should keep the confidentiality of the study participants foremost in their minds. The following list includes just the basic issues that must be attended to at all research sites and the Statistics and Data Coordinating Center (SDCC).

- All study forms should be kept in secure, locked file cabinets when not being used for research purposes such as interviewing, editing, data entry, etc.

- Dexamethasone study participants provide us with very personal and sensitive medical information. This information should be treated with respect and should not be discussed.

- Study computers should not be left on and unprotected with study information on the screen or accessible to non-study personnel. Those who use the dexamethasone data management system should log out when they will be away from the computer for more than a few minutes.

- Participant information should be provided to other study personnel on a need-to-know basis only.

- Participant information should not be provided to anyone other than study personnel without discussing the request with the study site Principal Investigator.

2. Data Security

An electronic data capture (EDC) system, Rho's internet-based remote data entry system, will be used to capture the data for the Dexamethasone Study. Using this system, the clinic's study coordinator or data coordinator uses an internet browser (Internet Explorer or similar) to key data into electronic case report forms. Data are not stored on the site's computer. At the end of each "page," data are submitted to Rho's secure web server using SSL (128 byte public key encryption methodology) and stored in the study's "operational database." (The database used for capturing, validating, updating, and storing the data is called an "operational database.") The

database is backed up nightly; backup tapes are saved in a secure, off-site location. At any time site personnel may log in to the system, review and correct previously entered data, key additional data, or lock records to prevent further inadvertent modifications.

The pages will be accessible via the CSCC website and require Center-specific user ID/password privileges. The data will be converted to intermediate datasets prior to incorporation into the Dexamethasone Study analysis datasets format (SAS datasets). Displays of their data will be sent to the study sites to confirm the data have been incorporated.

3. List of Rho, Inc. SOPs

Administrative	
Physical Security	AD 105
Data Management	
Study Setup	DM 202
Handling Controlled Documents	DM 218
Data Management Disaster Recovery Plan	DM 219
Handling of Completed CRFs	DM 220
Statistical Analysis/Computing	
Database Transfers	ST 314
Information Technologies	
Access Control	IT 401
Virus Protection	IT 403
Software Development	
Commercial Off the Shelf Software Validation	IT 426/SD 1012
Clinical Operations	
Investigator Study Files	CL 504/CO 504
Medical Writing	
Production, Review, and Approval of Protocols for Study Reports	MW 602
Regulatory Affairs	
Document Control Room Procedures	RA 702
Essential Documents File Structure – Document Control Room	RA 706
Informed Consent	RA 714
Document Control Management Procedure	RA 716
Standard Operating Procedure Deviations	RA 723
Quality Assurance	
Sponsor Audit	RA 709/QA 901
Internal Audit	RA 710/QA 902
Regulatory Agency Audit	RA 711/QA 903
Vendor Audit	RA 712/QA 904
Site Audit	RA 713/QA 905

4. Information Technology

Electronic resources at Rho are protected through numerous physical security measures and user access controls. It is impossible, however, to eliminate completely the risk of damage to network files from various threats, including physical catastrophes, virus attacks, user errors, or other unusual circumstances. Rho's back-up and security procedures ensure that Rho can recover quickly from such an event with minimal data loss.

Web-based Network Communication System

Security for the Web site will be implemented through a table of authorities developed in agreement with Rho and NHLBI. Access rights will be automatically applied to the user as a function of the login process. Each user will be required to access the site through a login screen, with the login screen having a mechanism by which the public can log into the system as a "Guest." Users affiliated with Rho and NHLBI or their sites or laboratories affiliated with the study will be required to arrange a login name and password with Rho prior to accessing features of the site not available to the public. Level of access for those individuals will be controlled through the table of authorities. Access restrictions will be automatic, and features for which the user does not have access will not appear on the menu.

Back-up and Recovery

The network administrator is responsible for all back-ups and restorations. Network files are backed-up to tape on a routine schedule established by the director of Information Technology, with back-up typically scheduled daily. The schedule has a combination of incremental and full back-ups with a full back-up obtained at least once weekly. To perform the back-up, the IT Director loads the appropriate tape into the tape drive on the designated back-up servers prior to the end of business hours each day. The back-up is performed automatically by the system at regularly scheduled times between 11:30 p.m. and 5:00 a.m. The next business day, the IT Director retrieves the tape, checks the back-up server's activity log to ensure that the back-up was executed successfully, enters the date/time of the back-up completion and tape identification, and reviews/initials/dates the back-up log. The back-up tape is removed to a secure remote location and maintained in a fire safe box.

Daily back-up tapes are rotated through a cycle of at least four weeks. A full back-up tape is taken out of rotation at the end of every month, and these designated tapes are retained for two years as archival material. In the event of network data loss, the network administrator retrieves the appropriate back-up tape. The tape is write-protected and used to restore data to the network.

Virus Protection

The need to exchange files with clients and other business associates exposes Rho's network and workstations to the possibility of attack by computer viruses and related entities. Each computer on the Rho network has anti-virus software running at all times. The software is configured to automatically scan all floppy disks and executable files introduced to the system, as well as all documents that may contain executable macros. The network administrator ensures that all computers are using up-to-date versions of the anti-virus software.

Workstations are configured to update their virus definitions automatically on a weekly basis. Virus definitions are also updated when special virus alerts are received from software vendors or other sources. Workstations are configured to update their virus definitions from the file server automatically on a weekly basis. When a new alert is received, the network administrator alerts all users to manually update their virus definitions immediately.

An additional layer of virus protection is installed on Rho's corporate mail server. The mail server scans all incoming and outgoing emails and attachments for viruses before they are delivered. The software checks for updated virus definitions every night. If a virus is detected in an email, the message is deleted and the sender gets an automated alert that they have transmitted an infected email.

Disaster Recovery

Preparing and testing disaster recovery procedures, and performing a recovery after a disaster, are the responsibilities of the network administrator at Rho, Inc. These plans fall into two general categories: overall preparation and recovery, and preparation for a potential disaster for which advance warning is available.

Electric current to all Rho computer and telephone equipment is supplied via Uninterruptible Power Supplies (UPS) for protection from power interruptions, power surges (e.g., from lightning strikes), and other power abnormalities. An information technology professional is on call during all business hours and most non-business hours to deal with an information technology emergency.

As described above, a network administrator oversees routine back-ups of all network files, including all project and system files. Each business day the back-up media from the previous night or weekend are stored in a fire safe box at a secure off site location. For long-term storage, a network administrator retains the last full back-up of each calendar month in a bank safety deposit box. Media (such as magnetic tapes) from other dates are retained for three months and then re-used. All Rho, Inc. data are stored on Redundant Disk Arrays (RAID) at the file servers and are backed up routinely; no project files are stored on individual computers.

The LAN file servers are kept in network equipment rooms that also contain other dedicated servers and equipment. These interior rooms are protected from the elements and are equipped with a fire extinguisher, smoke detector, and environmental monitor. All equipment in these rooms is located well off the floor in order to avoid or minimize water damage, e.g., in the event of a fire. A network administrator's office is located in close proximity to each network equipment room. The room is locked at all times. Access is limited to network administrators, their back-up personnel, and senior management.

Rho maintains four gas powered electrical generators that will be used to produce electricity for critical electronic equipment in the event of prolonged power outage.
All paper documents relating to computer software and equipment are stored either in the network equipment room or in the controlled documents room that is protected from the elements and from unauthorized access.

Preparation for Potential Disaster with Advance Warning
Rho personnel will prepare for any possible disaster for which advance warning is available. The most probable of these in the Chapel Hill area are power outages from an ice storm or a

hurricane. Preparations will include protecting the equipment and electronic data. In such an event, all users are required to log out of the system, to turn off their IT equipment, and unplug all of the equipment from the wall outlets. The network administrator makes a complete back-up of the network drives; the back-up media are stored in a secure off site location.

The file servers will be shut down according to equipment requirements, and all electrical equipment will be turned off and unplugged from electric outlets. All equipment will be temporarily moved to the tops of desks or on shelves, well off the floor. No equipment will be stored on the floor, with the exception of equipment that is too large and heavy to be supported any other way. All critical equipment will be covered with plastic, and, if the event is deemed likely to involve wind and water (e.g. a hurricane), all equipment will be covered with plastic. Large equipment will be moved to interior rooms if possible.

The procedure is tested at least annually for network servers and a representative selection of other equipment. If the procedures are tested by preparation for an actual event, further testing is required within the year following the event. The network administrator documents the test and signs off on having conducted the test, whether as part of an actual event or a test.

Testing

Testing the ability to recover from an IT emergency is performed at least annually if no actual IT emergency has occurred from which recovery was successfully performed. If such an emergency has occurred, then the next scheduled test would be conducted within a year of such recovery or immediately after a significant procedure change. The network administrator is responsible for testing. The ability of the network to recover from an emergency is tested by intentionally bringing the network down. To minimize disruption of productive work, the test is conducted after usual business hours. Immediately prior to the test the network administrator produces a complete back-up of all network drives. All users are required to log out of the system prior to the disruption of network service. After all users have logged off, several workstations are logged in so that the test can be conducted with some workstations on the network.

The network administrator turns off the power to the file server and all logged in workstations, literally by pulling the electric plugs from wall sockets. The testers observe the responses of the UPS to the loss of electrical power. The UPS should continue to power the network file server for at least 30 minutes and the workstations for at least 15 minutes. After a specified period and before loss of UPS power, each network file server should shut itself down automatically and gracefully. Test personnel manually shut down workstations before loss of UPS power.

Power is restored to the system to test the restoration process. A representative set of files is restored from the back-ups that were made immediately prior to the test. The files are restored to a logical drive different from the original drives. The network administrator compares the restored files to the original files and IT personnel investigate any discrepancies. If problems are discovered, corrective actions are taken, and the process is repeated. The network administrator documents the test and initials and dates the form indicating that the test has been completed.

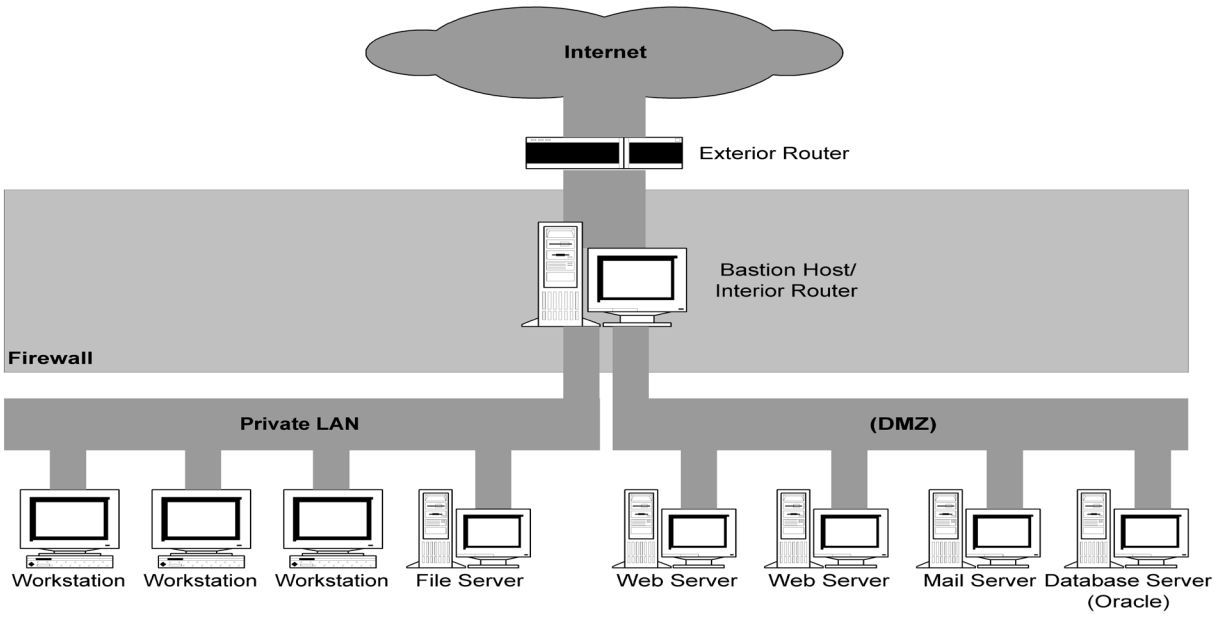
Recovery

In the event of an actual disaster, it is the responsibility of the IT personnel and senior management to assess the extent of the damage and make decisions about recovery. A recovery team will be comprised of the following positions: President, Vice President in charge of Information Technology, Controller, IT personnel, and a representative from Data Management, Software Development, and Statistical Programming. The recovery team will meet at the facility of Rho, Inc. as soon as the danger to safety has passed to assess the damage and determine an optimal course of action. Should the company facility not be available, an alternate facility will be chosen at this point.

The recovery strategy will, of course, depend on the nature and extent of the disaster, but the major decision makers for the company will be involved in the recovery team. The goal will be to restore productivity, and the responsibility of the recovery team is to restore productivity as soon as possible.

Website Security

Over the past five years, Rho has developed and implemented extensive procedures to safeguard information on Rho's networks, including websites maintained by RhoFED for NIH studies. The figure below shows the network architecture employed at Rho.



As shown in the figure, Rho uses a packet filtering firewall to control, monitor, and restrict communications to and from internal networks. Two networks exist within the firewall. The first is sealed off from communications initiated from outside. This private internal network is used for all production work, such as clinical trial data management or creation of analysis datasets. No communications with this network can be initiated from outside the firewall or from the second network, called "the DMZ."

The DMZ contains web servers, email servers and other servers that are involved in responding to communications initiated from outside the firewall. To safeguard information located on the DMZ, Rho uses network security features that restrict access to system files and scripts so that only IT support staff can access them.

The network administrator ensures that no software daemons are running on servers located in the DMZ except those necessary for the operation of the server.
The web development team uses SSH Secure Shell protocol to handle remote management of web servers. This capability is provided only for management within Rho's firewall. No remote management from outside the firewall is permitted.

The system console is kept in a locked room, to which only a few individuals have key access. In addition, the system console has machine-specific login restrictions – only IT support staff can login to it.

The firewall is configured to restrict the types of communications allowed to servers located in the DMZ. Additional safeguards implemented through web server software include encryption of secure web pages by using 128-bit server certificate and restriction of access to web server logs to IT support personnel.

All data are transmitted over the Internet securely using SSL (Secure Socket Layer). This is the same mechanism used by financial institutions for secure transmission of financial data and transactions.

Web pages are implemented using a proprietary framework called RhoNET™, which provides additional security features:

- Access to secure pages requires a RhoNET™ user ID/password login.
- Users are presented only with pages to which they have been granted access privileges.
- User access privileges are managed by a central administrator, and can be specified down to the level of individual files.

With regard to protection against spyware, the primary point of risk is a clinic's workstation. In most cases spyware is downloaded from the internet along with legitimate material when an unwary user clicks an "OK" button to download the legitimate material. This particular form of attack is not directly relevant to Rho's internet servers, which do not download such material. In addition, Rho's servers are protected by antiviral and anti-spyware software that is updated frequently (multiple times per day in the recent past). Rho cannot protect clinic workstations from spyware.

It is very unlikely that the central database would be the target of a spyware attack. The worst possible case would seem to be the use of spyware to capture an authorized user's central database userid and password, granting the attacker access to the data in the central database (but

not the structure or operating system). The attacker could view data, but without personal identifiers. In the worst case the attacker could also modify or delete data. Rho's systems would very likely detect the attack after the fact, and original data could be reconstructed from back-up data, but the cost would be high. Fortunately, such attackers are generally more interested in gaining access to people's bank accounts or charge card accounts and we note that this is a problem the financial industry–with its huge resources–is still attempting to solve.

C. Subject Study Withdrawal or Discontinuation

The following criteria will be used to determine whether or not subjects exhibit toxicities of the study drug(s) sufficient to require discontinuation from the study.

Study personnel will closely monitor signs, symptoms, and laboratory findings to assess for unexpected toxicities. Oral dexamethasone will be discontinued in any subject who experiences the following:

1. New hypertension (not pre-existing) that requires treatment with antihypertensive medications;
2. Stroke;
3. Gastrointestinal hemorrhage; or
4. Pregnancy

In addition, subjects will also have dexamethasone discontinued if they become unable to orally ingest dexamethasone or, at the request of the subject, for any reason. Investigators may discontinue any subject at their discretion, if in their professional opinion, the subject's health, safety, and/or well-being is threatened by continued participation in the study. In the event that dexamethasone is stopped, subjects will continue to be followed by study personnel to assess for potential side effects of dexamethasone administration.

Adverse events caused by participation in the study may necessitate modifications to a subject's level of participation or discontinuation from the study. Subjects who discontinue early from the study will be replaced.

Subjects who discontinue prematurely from the study for any reason will be encouraged to maintain the follow-up clinic visits that are scheduled after discharge. Study personnel will contact subjects by phone to encourage attendance.

Upon study discontinuation, the study completion page of the case report form must be completed (see CRF on the Dexamethasone study page found on the secure CSCC website).

D. Adverse Event and Serious Adverse Event Reporting

1. Adverse Events

An Adverse Event (AE) for the dexamethasone study is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. AE data are recorded on the Adverse Event Case Report Form (CRF).

An unexpected AE is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (i.e., Investigator's Brochure for an unapproved investigational medicinal product). Cases in which the AE is more severe than currently described in the Investigator's Brochure are also considered "unexpected".

2. Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death;

- Is life-threatening (i.e., an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- In the opinion of the investigator, important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require an intervention to prevent one of the other outcomes listed in the definition above, may be serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

For the purpose of this study, an **expected SAE** is an AE that is serious, expected, and likely related to the subject's underlying disease process. SAE data are recorded on the Serious Adverse Event Case Report Form (CRF). For this study AEs listed in the following table are expected SAEs.

Table A. List of Expected Adverse Events in this Study

Expected AE	Expected AE	Expected AE
Acne	Fluid Retention	Pain, long bone
Acute chest syndrome	Gastric Ulceration	Pain, severe abdominal
Anemia	Gastritis	Priapism
Aplastic crisis	Glucosuria	Pulmonary thromboembolism (age ≥18 yr only)
Aplastic crisis/anemia	Hand-foot syndrome	Pulmonary hypertension
Arthralgia	Hematuria	Pulmonary parenchymal infiltrates on chest x-ray
Avascular Necrosis	Hemiplegia	Pyelonephritis
Avascular necrosis of hip/shoulder	Hemolysis	Renal failure
Avascular necrosis of the femoral head	Hepatosplenomegaly	Renal insufficiency/albuminuria
Bone infarction	Hyperglycemia	Renal papillary necrosis
Cardiomegaly	Hyperplastic bone marrow	Reticulocytosis (∃10%–20%)
Cerebrovascular accident	Hypertension	Retinal disease
Cholecystitis, hepatic sequestration	Hyposthenuria	Retinal hemorrhage
Cranial nerve palsy	Hypoxemia (PO2 < 65mm Hg)	Rash
Decreased kidney function	Infection, pneumococcal	Rhabdomyolysis
Decreased lung function	Jaundice	Sepsis
Delayed growth/puberty	Leukocytosis	Skin ulcers
Delayed wound healing	Meningitis	Splenic sequestration
Depressed ESR	Mood Changes	Vaso-occlusive crisis
Dyspepsia	Nausea and vomiting	Weight Gain
Elevated urinary urobilinogen	Pain, joint	Pulmonary parenchymal infiltrates on chest x-ray
Fever		

3. Assessment of Adverse Event and Serious Adverse Event Severity

The following scale will be used to grade the severity of all AEs and SAEs:

1	Mild. Awareness of sign, symptom, or event, but easily tolerated; does not interfere with usual daily activities or tasks.
2	Moderate. Discomfort enough to cause interference with usual daily activity; may warrant therapeutic intervention.
3	Severe. Incapacitating; inability to perform usual activities and daily tasks; significantly affects clinical status; requires therapeutic intervention.
4	Life-threatening. Adverse event is life-threatening.
5	Death. Adverse event causes death.

4. Assessment of AE/SAE Relationship to Study Drug

The standard nomenclature for defining the causal relationship between an AE/SAE and the study drug used by CSCC is listed in the table below. The category that overall best "fits" the relationship between the AE/SAE and the study drug should be chosen and recorded on the AE or SAE case report form.

Table B. Relationship Between Study Product (Drug) and AE

Unrelated	• No temporal association to study product. • An alternate etiology has been established. • The event does not follow the known pattern of response to study product. • The event does not reappear or worsen with re-challenge.
Probably not related / remote	• No temporal association to study product. • Event could readily be produced by clinical state, environmental, or other interventions. • The event does not follow the known pattern of response to study product. • The event does not reappear or worsen with re-challenge.
Possibly related	• Reasonable temporal relationship to study product. • The event is not readily produced by clinical state, environmental, or other interventions. • The event follows a known pattern of response to the study product or as yet unknown pattern of response.
Probably related	• There is a reasonable temporal association with the study product. • The event is not readily produced by clinical state, environmental, or other interventions. • The event follows a known pattern of response to the study product. • The event decreases with de-challenge.
Definitely related	• There is a reasonable temporal relationship to the study product. • The event is not readily produced by clinical state, environmental, or other interventions. • The event follows a known pattern of response to the study product. • The event decreases with de-challenge and recurs with re-challenge.

5. SAE Reporting Time Period

- SAE reporting will begin with events that occur after the informed consent is signed until **30 days** after the last dose of study drug.
- An unexpected SAE must be reported within **8 hours** of discovering the event has occurred to the Lead PI and the CSCC SDMC Product Safety Associate.

- An expected SAE must be reported within **3 business days** of discovery to the Lead PI and the CSCC SDMC Product Safety Associate.
- All site PIs are responsible for reporting SAEs to the appropriate IRB in accordance with their local laws and regulations.
- Forward an SAE Announcement Email to the SDMC Product Safety Associate and the CSCC SAE Team, alerting them a SAE has occurred. The email address is: DexamethasoneSAE@RhoWorld.com
- Fax the completed SAE Report form and supporting documentation to the attention of the CSCC Clinical Safety Specialist, Rho Clinical Trials Safety Center at: **(919) 287-3998.**
- The **SAE Form** is found on the secure CSCC website on the Dexamethasone study page under **Regulatory Documents.**

CSCC SAE Team:

1. Lead Principal Investigator: **Charles Quinn, MD**
2. Medical Monitor: **Rupa Redding-Lallinger, MD**
3. Rho, Inc. SDMC Lead: **Karen Kesler, PhD**
4. Rho, Inc. Study Coordinator: **Melanie Chelednik**
5. Rho, Inc. SDMC Product Safety Associate: **Victoria C. Williams, PharmD**

6. General Instructions for SAE Reporting and Documentation

1. Complete all fields/boxes on the AE and SAE forms. The persons processing the form will not know if you left something blank intentionally (because the information is not available) or if you forgot to fill it in.
2. It is important to provide as much information as possible on the initial SAE report.
3. **If some information is not available at the time the initial SAE report is completed, provide at minimum the following:**
    - CSCC Id
    - Center code

- Hospital code
- Site name
- Report date
- SAE category
- Study Product Data
- Event Name
- Onset Date
- Relationship of the event to the study drug.

4. Write legibly staying within the boxes provided. If additional space is needed please use additional pages.
5. To delete or change an entry, please use a black pen and draw a single line through the original entry. Initial and date the change.
6. Write "UNK" in the fields where information is not yet available. Please provide the missing information in the follow-up.
7. The date format is DD/MMM/YYYY (e.g.. 10/Feb/2006)
8. **Note:** The Protocol Chair, Charles Quinn, must be consulted prior to permanent premature discontinuation of the study medication.

7. Instructions for Initial SAE Report

1. Check the Initial Report box, located in the upper left corner, on all three pages of the SAE form.
2. Write the **CSCC ID, Center Code, Hospital Code, Site Name** and the **Report Date** on all pages of the SAE form.
3. Write the **subject's age in years.**
4. Write the **subject's weight.** Circle the appropriate unit—**lbs**. **or kgs**.
5. Check the check box corresponding to the **subject's gender**.
6. **SAE category:** check all that apply.
7. **Study Product Data:**

A. If the study product has not been started, write "not applicable" in the dose and date fields and indicate that study product has not been started in the "Other, specify" area of the **Study Product Status** field at the bottom left of page 1.

B. If the study product administration was complete before the SAE, write "not applicable" in the dose and date fields and check the "Study Product Administration Complete" check box in the **Study Product Status** field.

C. If the subject is on study product, indicate the time of the SAE, include the entire dosing schedule the subject had received in the Event Summary section of the SAE report form (including the taper given, if applicable).

D. **Dose, Route, Schedule of Study Product(s) at SAE Onset:** (e.g. 12mg po q 12 hours).

E. **Study Product Start Date**: the date the subject began the dose indicated in the ***Dose, Route, Schedule of Study Product(s) at SAE Onset*** field.

F. **Study Product Stop Date**: the date the subject stopped the dose indicated in the ***Dose, Route, Schedule of Study Product(s) at SAE Onset*** field.

8. **Event:** provide the diagnosis. Symptoms may be provided initially, but a diagnosis should be provided in follow-up. (e.g. Influenza instead of runny nose and fever)
9. **Date of Onset:** date the event or symptom(s) began.
10. **Severity:** check one box only.
11. **Relationship to Study Product: Check one box only.**
12. **If NOT RELATED, what is the event related to**: check the box(es) corresponding to the investigator's opinion of what the event is related to if "unrelated" was checked in the ***Relationship to Study Product*** field. Additionally, specify what the event is related to.
13. **Study Product Status:** indicate if the administration of the treatment regimen was completed, continuing, deferred, adjusted, or whether a study product was discontinued permanently as a result of the SAE. If another course of action was utilized, please specify what that was. If the study product had not yet been started indicate in the "Other" check box that study product has not been started prior to SAE.

14. **Subject Status/Outcome:** if "Ongoing" is checked, the event must be followed until it is resolved or stable to a point that is acceptable to both the Investigator and the Medical Monitor. If the event outcome is "Resolved with sequelae," please list the sequelae (e.g. if a subject were to experience a CVA with resulting left-sided weakness, the sequelae would be listed as left-sided weakness.)
15. **Event Summary:** please provide a complete description of the event, including any diagnostic or laboratory tests that were performed for diagnosis of the event. Also include intervention(s) provided for the event, course of the event, and outcome. Include any medical history that is relevant to the event. **Be sure to include the site number and the CSCC ID number on all supporting documentation. Delete or completely obscure all personal information (name, subject initials, medical record number, etc.)** Write the entire dosing schedule the subject has received (including the taper given if applicable) in the **Event Summary**.
16. **Laboratory tests:** include relevant abnormal lab results that contribute to an understanding of the event. Provide normal ranges and previous lab results, which may be relevant to the event. **Please attach the lab reports to the SAE report form and indicate relevant results. Be sure to include the site number and the CSCC ID number on all lab reports. Delete or completely obscure all personal information (name, subject initials, medical record number, etc.)**

    Note: the following laboratory ranges may be used as **guidelines** for determining if lab results are abnormal for the patient population in this protocol. These are guidelines only and ultimately the decision as to whether any abnormal lab values are an AE/SAE for the subject is up to the site investigator:

	Low	High
WBC	2,500	49,999
RBC	1.5 million	4 million
HgB	5 g/dL	12 g/dL
HCT	15 %	36 %
MCV	50 fL	125 fL
Platelets	50,000	750,000
Reticulocytes %	1%	50%
Absolute Reticulocytes	15,000	750,000

17. **Diagnostic Tests:** list relevant tests and test results for the event. **Please attach the diagnostic report to the SAE report form and indicate relevant results. Be sure to include the site number and the CSCC ID number on all diagnostic reports. Delete or completely obscure all personal information (name, subject initials, medical record number, etc.)**
18. **Concomitant medications:** list all relevant medications the subject was taking, starting from one month prior to SAE onset up to the time of SAE onset. Include the standard supportive care given to the patient (Analgesia, GI prophylaxis, and antimicrobial therapy). Enter the start date, stop date, dose, route, frequency, indication, and whether the medication was suspected in the causality of the SAE. If the medication was suspected in the causality of SAE, provide further detail in the event summary. If dose is unknown, check the unknown check box. If the subject was taking no relevant concomitant mediations, check the "No relevant concomitant medications" check box.
19. **Completed by/Investigator's signature:** the study staff member who completed the SAE form and the Investigator must sign and date the form.

8. Instructions for follow-up SAE Reports

1. Please complete a new CSCC SAE Report form promptly when new significant information is obtained regarding the SAE.
2. Complete the **CSCC ID**, **Center Code**, **Hospital Code**, **Site Name** and the **Report Date** on all pages of the SAE report form
3. Check the **Follow-up Report** box located in the upper left corner, on all pages of the SAE report form.
4. With the exception of the event and onset date, enter only information that is new or changed from the information on the previously submitted report. Include the event and onset date for reference.
5. The study staff member who completed the SAE form and the Investigator must sign and date form.
6. Follow the SAE Reporting Guidelines listed under instructions for initial SAE report for directions on specific fields.

For questions about completing this form, please contact the CSCC Clinical Safety Specialist at (919)408-8000 extension 237. Hours of availability are Monday-Friday, 8:30am-5:30pm, United States Eastern Standard Time.

Contact Information:
CSCC SDMC Product Safety Specialist
Rho Clinical Trials Safety Center
633 Quadrangle Drive, Suite 500
Chapel Hill, NC 27517
Phone: (919) 408-8000 x 237
Fax: (919) 287-3998

9. Assessment of Adverse Events and Serious Adverse Events Outcome

Every AE/SAE must be followed to a satisfactory outcome or stabilization of the event, even when this requires a time period beyond the scope of the study. Outcome includes information on recovery and any sequelae, as well as specific tests and/or treatment that may have been required and their results. For a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction should be provided.

The terms used to define outcome areas follow:

- Ongoing,
- Resolved without sequelae,
- Resolved with sequelae, and
- Death.

Actions taken in response to an AE/SAE and follow-up results must be recorded in the subject's medical record (this includes follow-up laboratory results). Any treatment administered for the AE must be recorded in the subject's CRF. When subjects are discontinued from the study due to an AE/SAE, relevant clinical assessments and laboratory tests will be repeated as necessary until final resolutions or stabilization occurs.

E. Study Suspension Guidelines

Serious safety issues that arise in this study will be brought to the attention of the CSCC Data and Safety Monitoring Board (DSMB), which will make recommendations to the National Heart, Lung, and Blood Institute (NHLBI) regarding possible suspension of the study. The NHLBI will consider the DSMB's recommendations, determine an appropriate action and notify the Principal Investigator (PI) and the CSCC Statistics and Data Management Center (SDMC) on the pending status of the study. The Principal Investigator will notify all participating investigators, who will implement the actions directed by NHLBI. This section defines "serious safety issues" and describes procedures for bringing them to the attention of the DSMB.

The SDMC or PI will make the following types of reports that can alert the DSMB to a potential safety issue:

- Ad hoc reports of unexpected SAEs that are made within 7 or 15 calendar days, as specified in subsequent paragraphs.
- Reports of quarterly statistical analyses of all SAEs. The SDMC makes such analyses quarterly, but files a report to the DSMB only when analyses indicate that a safety issue has arisen, as defined by the "alert" criteria in Table 11.3.
- Semi-annual DSMB reports of analyses of adverse events and of clinical laboratory results. These reports will highlight any safety issues revealed by the analyses that meet the "alert" criteria in Table 11.3

Definitions for Suspension Guidelines

Table C contains definitions of words and phrases that have special meanings in Suspension Guidelines. The definitions are identical to, or as close as practical to definitions in Food and Drug Administration (FDA) regulations or "Guidance" documents.

Some of the definitions refer to "expected" or "unexpected" adverse events. Table A contains the list of "expected" adverse events in this study.

TABLE C. Definitions of Words and Phrases with Special Meanings in the Suspension Guidelines

Word or Phrase and (Abbreviation)	Definition
Adverse event (AE)	Any untoward clinical or medical occurrence.
Serious adverse event (SAE)	Any adverse event that results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
Expected Serious Adverse Event (Expected SAE)	An *expected SAE* for subjects in this study is an adverse event that is listed in Table 11.2 and is a serious adverse event, as defined above.
Unexpected Serious Adverse Event (Unexpected SAE)	An *unexpected SAE* for subjects in this study is any AE that is **not** listed in Table 11.2 and is a serious adverse event, as defined above.
Fisher's Exact Test (FET) statistic	Fisher's exact test is a statistic computed from an $r \times 2$ frequency table to test the null hypothesis of independence of the rows and columns vs. the alternative hypothesis that the rows and columns are not independent, both conditioned on the marginal total frequencies. The FET statistic is a p-value. The algorithm for computing the FET statistic is given in numerous statistics textbooks.
Adverse Clinical Laboratory Results	Each 6 months the SDMC will analyze the available clinical laboratory data for treatment related trends in change from baseline. Any "statistically significant" (defined in Table 11.3) trends will be reported to the DSMB.

PROCEDURES

This section specifies procedures for alerting the DSMB to serious safety issues that arise in this study. The procedures are summarized in Table D.

Reports to the DSMB, Study Investigators, IRBs, and Other Authorities

The site investigator, the Principal Investigator, and the SDMC SAE Regulatory Specialist will collaborate to prepare a report of the unexpected SAE using the current version of FDA's SAE reporting forms. A fatal or life-threatening unexpected SAE will be reported to the DSMB within 7 calendar days of the receipt of the initial report by the SDMC SAE Regulatory Specialist. A non-fatal, non-life-threatening unexpected SAE will be reported to the DSMB within 15 calendar days of the receipt of the initial report by the SDMC SAE Regulatory Specialist.

The Principal Investigator will submit the DSMB report to the Chair of the DSMB Subcommittee appointed to monitor this study and to the NHLBI Project Officer.

The Principal Investigator will submit the unexpected SAE report to all study investigators. Each study investigator will submit the unexpected SAE report to the local IRB and other local authorities in accordance with the institution's regulations.

Serious adverse events are also recorded in the Adverse Events section of the study's case report form.

The site investigator will follow the progress of a subject who experiences an unexpected SAE until the SAE is resolved. When the unexpected SAE has not resolved by the report deadline, the site investigator will make follow-up reports in accordance with directions from the DSMB and/or the site's IRB.

Expected Serious Adverse Events Reports

Three months after the first subject is enrolled in the study, and at the end of each 3 months thereafter, if any SAEs (expected or unexpected) have been reported in the study during the preceding 3 months, the SDMC will:

- Use the current version of the MedDRA dictionary to code all AEs (serious or not) that have been recorded on study AE forms.
- Make a "snapshot" copy of the adverse events data, including MedDRA codes.
- Create frequency tables of treatment x occurrence (yes or no, since inception of the study) of all patients. One table will be created for each highest level MedDRA term for which SAEs have been reported. The counting units are patients, not events.
- Compute Fisher's Exact Test (FET) statistic to test the alternative hypothesis that occurrence of SAEs is not independent of treatment group. The FET p-value is not adjusted for multiplicity.

- If the FET p-value is less than the critical value shown in Table 11.3 and the active treatment group has a higher AE rate, the SDMC will conduct further statistical analyses as indicated by the circumstances and report the results to the Chair of the DSMB subcommittee monitoring this study, the Principal Investigator, and the NHLBI Project Officer.
- The SDMC will not file a report of expected SAEs if none of the FET p-values is less than the critical value shown in Table D or if the relative risk is less than 1.

Adverse Event Reports

Six months after the first subject is enrolled in the study, and at the end of each 6 months thereafter, the SDMC will:

- Use the current version of the MedDRA dictionary to code all AEs that have been recorded on study AE forms.
- Make a "snapshot" copy of the adverse events data, including MedDRA codes.
- Create frequency tables of treatment x occurrence (yes or no, since inception of the study) of all patients. One table will be created for each highest level MedDRA term for which AEs have been reported. The counting units are patients, not events.
- Compute Fisher's Exact Test (FET) statistic to test the alternative hypothesis that occurrence of AEs is not independent of treatment group. The FET p-value is not adjusted for multiplicity.
- If the FET p-value is less than the critical value shown in Table 11.3 and the active treatment group has a higher AE rate, the SDMC will conduct further statistical analyses as indicated by the circumstances and alert the DSMB to this finding in the semi-annual DSMB report.
- Collaborate with the Principal Investigator to incorporate the results into the study's semi-annual report to the DSMB and the NHLBI Project Officer.

Clinical Laboratory Results

Six months after the first subject is enrolled in the study, and at the end of each 6 months thereafter, the SDMC will:

- Make a "snapshot" copy of the study's clinical laboratory data.
- Perform an appropriate statistical analysis of clinical laboratory change-from-baseline data for each clinical laboratory evaluation obtained in this study.
- Perform an appropriate statistical test of
    - H_o: (The mean [or median, or proportion, as appropriate] change-from-baseline of the clinical laboratory values for the active treatment group is the same as for the control group), vs.
    - H_a: (The mean [or median, or proportion] change-from-baseline in the active treatment group is "worse" than for the control group). The meaning of "worse" depends upon the specific clinical lab measurement. The test statistic p-value is not adjusted for multiplicity.
    - If the hypothesis test p-value is less than the critical value shown in Table 11.3, the SDMC will conduct further statistical analyses as indicated by the circumstances and highlight this finding in the semi-annual DSMB report.
- Collaborate with the Principal Investigator to incorporate the results into the study's semi-annual report to the DSMB and the NHLBI Project Officer.

Reporting of Vaso-Occlusive Crisis Rebounds

Three months after the first subject is enrolled in the study, and at the end of each 3-month period thereafter, the SDMC will:

- Make a "snapshot" copy of the rebound data.
- Create frequency tables of treatment x occurrence of rebound (yes or no, since inception of the study) of all subjects. The counting units are subjects, not rebound events.

- Compute Fisher's Exact Test (FET) statistic to test the alternative hypothesis that occurrence of rebound is not independent of treatment group. The FET p-value is not adjusted for multiplicity.
- If the FET p-value is less than 0.025 and the active treatment group has a higher AE rate, the SDMC will conduct further statistical analyses as indicated by the circumstances and report the results to the Chair of the DSMB subcommittee monitoring this study, the PI, and the NHLBI Project Officer.
- The SDMC will not file a report of rebounds if the FET p-value is less than 0.025 or if the relative risk is less than 1.

TABLE D. Summary of Procedures and Timing for Alerting the DSMB and NHLBI Project Officer of Possible Serious Safety Issues

Situation or Event	Summary of Procedure (See text for details.)	Critical Value for DSMB "Alert"
Unexpected SAE	1. Site investigator notifies SDMC SAE Regulatory Specialist and Principal Investigator within 8 hours.	Alert all cases.
	2. Site investigator, SDMC SAE Regulatory Specialist and Principal Investigator prepare report using FDA forms and submit report to DSMB, NHLBI Project Officer, IRBs, study investigators. Report: 1. Fatal or life-threatening: within 7 calendar days. 2. Otherwise: within 14 calendar days.	Alert all cases.
Expected SAE	1. SDMC performs quarterly analyses of MedDRA-coded SAEs, tabulates patients with SAEs classified by highest level MedDRA term. Report only when p < critical value and active treatment group has higher AE rate. 2. The SDMC will report the following SAEs quarterly to the DSMB, regardless of incidence rates: • Development of clinically significant alloantibodies • Development of autoantibodies associated with hemolysis that result in inability to transfuse safely. • Development of clinically significant hemolytic transfusion reactions.	$p < 0.01$ p not adjusted for multiplicity Report all cases
Adverse Events (all)	SDMC performs semi-annual analyses of MedDRA-coded AEs, tabulates patients with AEs classified by highest level MedDRA term. Report every 6 months. Alert only when FET p < critical value and active treatment group has higher AE rate.	$p < 0.01$ p not adjusted for multiplicity

F. Protocol Deviations

Definition of a Protocol Deviation

Protocol deviations occur when there is non-adherence to the protocol, including failure to follow informed consent, safety surveillance and enrollment procedures or to adhere to good clinical practices. Deviations may occur when there is non-adherence to study procedures or schedules by either the subject or investigator, as specified by the protocol.

Source Documentation for Protocol Deviations

All deviations from the protocol must be addressed in study subject source documentation, and should include the reasons for the deviation and all attempts to prevent or correct it. For example, documentation of a missed visit would properly consist of a note explaining the missed visit and the site's attempt to locate the study subject to request that he/she come in to make up that visit.

Sites need to document all protocol deviations on a Protocol Deviation Form. Deviations should be documented as they occur, and the documented information should include:

- Date of the deviation,
- Description of the deviation,
- Reason for the deviation, and
- A corrective action plan to assure future protocol compliance

A separate protocol deviation form should be completed for each occurrence, and the site PI must sign the form. All protocol deviations must be reported promptly to the SDMC Study Coordinator and to the study site's Institutional Review Boards (IRB) per the IRB's Standard Operating Procedures.

Reporting Timeframes

Deviations that affect subject safety or integrity of the data should be reported to the SDMC within three days. Other deviations should be reported to the SDMC within thirty days of occurrence.

Types of typical protocol deviations include, but are not limited to:

- Randomization errors
- Missed visits or mistimed visits
- Missed procedures or assessments
- Inclusion/Exclusion errors
- Patient Safety

CSCC PROTOCOL DEVIATION FORM

Randomized Trial of Oral Dexamethasone for Acute Chest Syndrome

Complete a new form for each deviation from the protocol

SITE NAME: ___ABC University___ SUBJECT CSCC ID NUMBER: 1234567_____ SUBJECT RANDOMIZED? ☒ **No** ☐ **Yes** ☐ **NA** STUDY DAY NUMBER: __3__

Complete a new form for each deviation from the protocol.

Date of protocol deviation: _11_ / __15_ / _04__ (MM/DD/YY)

Description of deviation from protocol: Visit 2 falls outside of the window for the visit____

Reason for deviation from protocol: Subject was unable to come in for visit during the window due to a death in the family_____

Did this deviation result in an adverse experience? ☒ **No** ☐ **Yes** (*If yes, complete AE form*)
Will the subject continue with the study? ☐ **No** ☒ **Yes**
Does this deviation meet IRB reporting requirements? ☒ **No** ☐ **Yes**

Based on your IRB reporting guidelines, when does this protocol deviation need to be reported to your IRB? Does not need IRB reporting_____

What steps were taken to resolve this deviation and prevent recurrence? __checked with study PI, Dr. Vichinsky, and he approved the deviation for the subject to continue the study

COMPLETED BY (print and sign):

Print Name: ___Site Study Coordinator Name_ Signature: _____

DATE: _____ / _____ / ____ (MM/DD/YY)

Investigator's Signature: __Site Investigator_____ _____ / _____ / ____ (MM/DD/YY)

Date Submitted/Faxed To: (MM/DD/YY)

☐ **Site IRB** _____ / _____ / ____

☐ **SDMC 919-408-0999** _____ / _____ / ____

☐ **Other, specify: _____** _____ / _____ / ___

G. Source Documentation

Source documents are the original records, or source, from which data recorded on the Case Report Forms, was obtained. When source documents exist, they must be maintained in the subject's file, so that information on the Case Report Forms can be traced to, and verified from, the source.

The table below defines the source document and Case Report Form page for each study activity.

Activity	Source Document	Case Report Form
Informed consent	Signed consent form	N/A
Inclusion/exclusion criteria	Worksheet and Medical Records	Inclusion criteria and Exclusion criteria pages
Randomization	Worksheet & RhoRAND	Randomization page
Height, weight, gender, date of birth, physical exam and sickle cell diagnosis	Medical Records	Demographics Page
Medical History	Medical Records	Medical History Page
Emergency Room, hospitalization , clinic visits, hospital discharge dates	Medical Records & worksheets with subject/parent report if Med Rec not available	History of Hospital, Clinics , ED; Hospital Discharge; Interim Health History pages
Study Drug	Medical records for in-patient dosing & Subject Drug Diary for out-patient dosing	Study drug page
Concomitant Medications	Medical Records	Medication History page
Opioids use	Medical Records	Opioids quantified page
Fluid Balance	Medical Records	Fluid Balance page
Pulse Oximetry	Medical Records & worksheets	Pulse oximetry page
Oxygen saturation	Medical records & worksheets	Oxygen saturation page
Pain Intensity Ratings	NRS and Oucher worksheets	Pain Intensity Rating Page
Vital Signs	Medical Records	Vital Signs Page
Blood culture	Medical Records	Blood culture page
Hematology, reticulocyte Labs	Lab results report from Medical Records	Hematology and reticulocyte Labs page
Biomarker Labs	Central Lab Tracking Log	RhoLAB
Pregnancy test	Medical records	Pregnancy Test page
Chest radiograph	Medical Records	Chest radiograph page
Check ACS Assessments	worksheets	ACS CRF pages
transfusions	Medical Records	Transfusion Record page
Pulmonary function testing	medical & clinic records	PFT page
Study completion	Medical records & worksheets	Study Completion CRF page

XII. Regulatory Documents

The following documents are provided as part of the Regulatory Packet:

- Regulatory Packet Instructions
- FDA Form 1572
- Financial Disclosure Forms for both American Regent Laboratories, Inc. and Roxane Laboratories, Inc.
- Dexamethasone Signature and Responsibility Log

All of these documents can be found on the secure CSCC website on the Dexamethasone Study page. These documents must be completed by all sites for all investigators and study coordinators that are listed on the 1572 form before study initiation. Please return the completed documents to the SDMC Clinical Trials Associate, Holly Forde (holly_forde@rhoworld.com) and retain a copy of each in your site Regulatory Binder.

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

Dexamethasone Regulatory Packet Instructions

October 5, 2006

➢ Section A: FDA form 1572

- Item # 1: site Principal Investigator name and address
- Item #2: Include copy of current professional license. Check CV is no more than 2 years old. Sign/date front page.
- Item #3: mailing address of P.I's hospital
- Item #4: name and mailing address of local clinical lab
- Item #5: site's IRB mailing address
- Item #6: names of subinvestigators at this site.
- Item #6: CVs (no more than 2 yrs old) and current professional license for all subinvestigators listed. Sign/date front page.
- Item #7: enter "Randomized Trial of Oral Dexamethasone for Acute Chest Syndrome".
- Item #8: check box for Phase 2 or 3
- Item #9: review. Print out completed document
- Item #10: signature
- Item #11: enter date completed. Make a copy for your study records.
- Financial Disclosure Forms for each PI and Sub I. Make a copy for your study records.
- Laboratory certification(s) (CLIA preferred).
- Laboratory normal ranges for CBC with reticulocyte counts, containing lab name (or other identifier linking the ranges to the laboratory) and version date.
- Mail original signed/dated 1572 and P.I.'s CV and copy of medical license via FedEx **prior to study initiation**.

➢ Section B: Required Documents for Study Initiation

- Training documentation for PI and each Sub-Investigator on the Protection of Human Subjects in Research. Examples of acceptable documentation include rosters from training sessions, copy of a completion certificate or a note from the training group. The NIH offers free online training at http://cme.nci.nih.gov/ that provides documentation via certificate.

- Investigator Protocol/Protocol Amendment Agreement Page(s): signed and dated original(s). This is page 2 of the protocol, and is not available until you receive the final version of the protocol.

- IRB Compliance Documentation: FWA # and IRB roster if available. If a roster is not available, a statement from the IRB of CFR compliance will suffice.
- IRB Approval Documentation: The IRB approval letter must identify the principal investigator or sub-investigator by name, reference all approved documents (protocol, informed consent, advertisements if applicable) including version numbers and version dates.
- IRB Approved ICF's and advertisements if applicable.
- Please submit the following regulatory documents **prior to study initiation at your site.**