CSCC Comprehensive Sickle Cell Centers

Clinical Trials Consortium

Arginine Study

Training Manual

As of January 5, 2006

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Protocol Summary

Title of the Protocol: Arginine Supplementation in Sickle Cell Anemia: Physiological and Prophylactic Effects

CSCC Protocol Number: November 28, 2005, Version 4.0

Overview: Nitric oxide is an important inflammatory mediator produced from arginine by nitric oxide synthase. Nitric oxide has a multitude of functions which could impact favorably on vaso-occlusion in sickle cell disease. Oral arginine has been shown to raise levels of nitric oxide. This study will test whether daily oral arginine results in an increase in nitric oxide and other beneficial effects in patients with sickle cell disease. The results of this study will serve as the basis for further clinical trials to determine if daily arginine is a beneficial therapy for patients with sickle cell disease.

CSCC Protocol Chair: Lori Styles, MD

Intervention: Patients will be treated with one of two doses of oral arginine (0.05 or 0.1 g/kg/day) or placebo for 12 weeks.

IND Holder: Lori Styles, MD

IND Number: 59,995

Objectives:

Primary Objective(s): To assess the physiological effects (both beneficial and deleterious) of the administration of oral arginine in patients with SCD.

Secondary Objective(s): To evaluate the effect of daily oral arginine on clinical vaso-occlusive events in SCD patients.

Hypotheses/Estimates: The hypothesis of this study is that oral arginine, given daily, will increase nitric oxide production which will, in turn, produce beneficial effects on vascular homeostasis in sickle cell disease.

Criteria for Evaluation:

Efficacy:

Primary Endpoint: Efficacy will be determined by changes in three laboratory parameters which will serve as surrogates for potential clinical benefit: nitric oxide, Gardos channel activity, and RBC density.

Secondary Endpoint: sVCAM, Nitrotyrosine, 8-iso-PGF2a, Ektacytometry, endothelin-1, fetal hemoglobin (Hb F) and echocardiogram results as well as clinical outcomes including hospitalizations, ER visits, and pain medication use.

Safety: **SAFETY VARIABLES TO BE COLLECTED IN ADDITION TO ADVERSE EVENTS**

Study Design: Double-blinded, placebo-controlled, phase II trial in which 96 patients will be randomized to receive one of two doses of arginine or placebo for 12 weeks.

Study Population: Male or female Hb SS patients age 5 or more years

Major Inclusion Criteria: History of at least one pain event in last 12 months

Major Exclusion Criteria: Major organ dysfunction, treatment with hydroxyurea or transfusion within 3 months, history of recent priapism or retinopathy, pregnancy.

Sample Size: 96 (grouped into 48 children and 48 adults)

Randomization: Two doses of arginine hydrochloride will be evaluated in this trial. Patients in each age group (children and adult) will be treated with one of two doses of arginine (0.05 g/kg/day or 0.10 g/kg/day) or placebo divided for BID dosing. Sixteen patients will be randomized to each dose level and placebo. Randomization will be stratified by center to preserve balance across treatment groups.

CSCC: Arginine Supplementation in Sickle Cell Anemia

Training, Los Angeles
April 17 – 18, 2004

Arginine and SCD

- Nitric Oxide (NO) is an important inflammatory mediator which could impact favorably on SCD.
- NO is a vasodilator which also decreases adhesion molecule expression.
- Arginine is a precursor that raises levels of NO.

Arginine and SCD

- Some promising results from inhaled NO, but difficult to administer.
- SCD patients known to be Arginine deficient and levels go lower in crisis.
- Arginine butyrate studied as a HbF moderator with few side effects.
- This is first study to look at effects on RBCs and crises.

Study Design

- Randomized, double-blind, placebo-controlled multicenter study of 96 pediatric and adults sickle cell patients (SS or Sβ-thal).
- Primary goal is to study the effects of Arginine on vascular homeostasis.
- Secondary goal is to study the effects of Arginine on decreasing clinical outcomes.

Research Centers

- Southwestern
- University of Southern California
- Cincinnati
- Bronx
- CHOP
- Boston
- Marian Anderson
- Duke-UNC
- Northern California
- St. Jude's

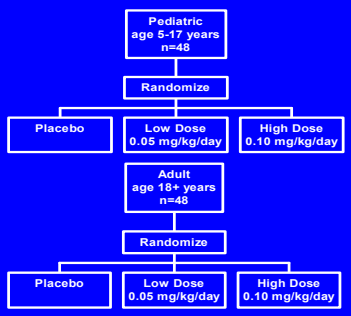
Study Population

- Male or female Hb SS patients age 5 or more years
- History of at least one pain event in last 12 months
- Cannot have:
  - Major organ dysfunction,
  - treatment with hydroxyurea or transfusion within 3 months,
  - history of recent priapism or retinopathy,
  - pregnancy.

Overview of Goals

- Understand how Arginine affects a wide range of hemostatis laboratory measurements.
- Get enough information on clinical endpoints to plan a Phase III trial to confirm efficacy.

Randomization



Laboratory Outcomes

- Primary
  - Nitric oxide,
  - Gardos channel activity, and
  - RBC density
- Secondary

--sVCAM	--Nitrotyrosine
--8-iso-PGF2a	--Ektacytometry
--endothelin-1	--Hb F

Clinical Outcomes

- Clinical Outcomes (All Secondary)
  - Echocardiogram results,
  - Hospitalizations,
  - ER visits,
  - Clinic visits for pain
  - Other SCD related health history

Safety Outcomes

- Serious Adverse Events
- Adverse Events
- Local Laboratory Measurements

Study Timeline

- Two screening visits (one month)
- Twelve weeks on study drug
  - 6 visits (weeks 1, 2, 4, 8, and 12)
- One month follow up
  - 2 visits (weeks 14 and 16)
- Total time on study: 5 months

Evaluations

- Inclusion/Exclusion
- Demographics
- Medication (History and Concomitant)
- Medical History
  - Events (ER, Hospitalizations)
  - Pain
  - General (Med Hx since last visit)

Evaluations

- Local Laboratory Measurements
- Central Laboratory Measurements
- Pregnancy Test
- Compliance (Pill Counts)

Patient Timeline and Visit Windows

Week	Day	Activity
-4	-28	Visit 1 Screening (up to day -14)
-2	-14	Visit 2 Screening (must occur at least 1 week after visit 1 and at least one week before visit 3)
0	0	Visit 3 Randomization
1	7	Visit 4 (± 1 day)
2	14	Visit 5 (± 1 day)
4	28	Visit 6 (± 3 days)
8	56	Visit 7 (± 3 days)
12	84	Visit 8 (± 3 days)
14	98	Visit 9 (± 3 days)
16	112	Visit 10 (± 3 days)

Subject Flow Diagram

Inclusion Criteria

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

1. Participant has signed the informed consent.
2. Established diagnosis of Hb SS or S-beta thalassemia
3. History of at least one vaso-occlusive pain events in last 12 months
4. Regular compliance with comprehensive care
5. History of a retinal exam in last year (for patients age 10 or more years)
6. Aged 5 years or greater
7. Patient is in his/her steady state and not in the midst of any acute complication due to sickle cell disease at enrollment

Exclusion Criteria

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

1. Inability to take or tolerate oral medications
2. Hepatic dysfunction (SGPT $\geq$ 2X normal and albumin $\leq$ 3.2)
3. Renal dysfunction (Creatinine $\geq$ 1.2 for children and $\geq$ 1.4 for adults)
4. Allergy to arginine
5. Pregnancy
6. Transfusion within the last 90 days
7. > 10 hospital admissions for pain in last 12 months **or** daily use of opiods and unstable pain (that interferes with work or daily routine) requiring > 3 Hospital Admissions **and** > 10 Emergency Department/Day Hospital visits in the last twelve months
8. Treatment with hydroxyurea within the last 90 days
9. Treatment with any investigational drug in last 90 days

Visit Activities Check List

Visit 1 – First Screening Visit

- ❑ Have informed consent signed
- ❑ Check inclusion and exclusion criteria
- ❑ Draw blood for chemistry and hematology labs to be done locally
- ❑ Draw blood to send to CHO Oakland
- ❑ Draw blood to send to BOSTON
- ❑ Obtain urine sample for urinalysis and pregnancy test (if female of child-bearing potential)
- ❑ Collect hospitalization, ER and clinic history information
- ❑ Collect demographic information
- ❑ Collect medication history information
- ❑ Collect medical history information
- ❑ Collect pain history information
- ❑ Collect concomitant medication information

Visit 2 – Second Screening Visit

- ❑ Draw blood to send to CHO Oakland
- ❑ Draw blood to send to BOSTON
- ❑ Collect hospitalization and pain information
- ❑ Collect concomitant medication information
- ❑ Check discontinuation criteria
- ❑ Collect AE information
- ❑ Obtain urine sample for pregnancy test (if female of child-bearing potential)

Visit 3 – Baseline / Study Entry Visit

- ❑ Draw blood for chemistry and hematology labs to be done locally
- ❑ Draw blood to send to CHO Oakland
- ❑ Draw blood to send to BOSTON
- ❑ Obtain urine sample for urinalysis and pregnancy test (if female of child-bearing potential)
- ❑ Perform echocardiogram
- ❑ Collect hospitalization and pain information
- ❑ Collect concomitant medication information
- ❑ Check discontinuation criteria
- ❑ Collect AE information
- ❑ Randomize patient
- ❑ Distribute study medication

Visit 4 – Week 1

- ❑ Draw blood for chemistry and hematology labs to be done locally
- ❑ Draw blood to send to CHO Oakland
- ❑ Draw blood to send to BOSTON
- ❑ Obtain urine sample for urinalysis and pregnancy test (if female of child-bearing potential)

- Collect hospitalization and pain information
- Collect concomitant medication information
- Check discontinuation criteria
- Collect AE information

Visit 5 – Week 2

- Draw blood for chemistry and hematology labs to be done locally
- Draw blood to send to CHO Oakland (NO RED TOP vacutainers)
- Draw blood to send to BOSTON
- Collect hospitalization and pain information
- Collect concomitant medication information
- Obtain urine sample for pregnancy test (if female of child-bearing potential)
- Check discontinuation criteria
- Collect AE information

Visit 6 – Week 4

- Draw blood for chemistry and hematology labs to be done locally
- Draw blood to send to CHO Oakland
- Draw blood to send to BOSTON
- Obtain urine sample for urinalysis and pregnancy test (if female of child-bearing potential)
- Collect hospitalization and pain information
- Collect concomitant medication information
- Check discontinuation criteria
- Collect AE information
- Collect unused study medication and perform pill count
- Distribute study medication

Visit 7 – Week 8

- Draw blood for chemistry and hematology labs to be done locally
- Draw blood to send to CHO Oakland
- Draw blood to send to BOSTON
- Collect hospitalization and pain information
- Collect concomitant medication information
- Obtain urine sample for pregnancy test (if female of child-bearing potential)
- Check discontinuation criteria
- Collect AE information
- Collect unused study medication and perform pill count
- Distribute study medication

Visit 8 – Week 12

- ❑ Draw blood for chemistry and hematology labs to be done locally
- ❑ Draw blood to send to CHO Oakland
- ❑ Draw blood to send to BOSTON
- ❑ Obtain urine sample for urinalysis and pregnancy test (if female of child-bearing potential)
- ❑ Collect hospitalization and pain information
- ❑ Collect concomitant medication information
- ❑ Check discontinuation criteria
- ❑ Collect AE information
- ❑ Collect unused study medication and perform pill count
- ❑ Perform Echocardiogram ONLY IF Visit 3 Echo was ABNORMAL

Visit 9 – Week 14

- ❑ Draw blood for hematology labs to be done locally
- ❑ Draw blood to send to CHO Oakland (ONLY YELLOW TOP VACUTAINERS)
- ❑ Draw blood to send to BOSTON
- ❑ Obtain urine sample for pregnancy test (if female of child-bearing potential)
- ❑ Collect hospitalization and pain information
- ❑ Collect concomitant medication information
- ❑ Check discontinuation criteria
- ❑ Collect AE information

Visit 10 – Week 16

- ❑ Draw blood for chemistry and hematology labs to be done locally
- ❑ Draw blood to send to CHO Oakland
- ❑ Draw blood to send to BOSTON
- ❑ Obtain urine sample for urinalysis and pregnancy test (if female of child-bearing potential)
- ❑ Collect hospitalization and pain information
- ❑ Collect concomitant medication information
- ❑ Check discontinuation criteria
- ❑ Collect AE information

Visit Activities Table

Test	Week –4	Week –2	Study Entry	Week 1	Week 2	Week 4	Week 8	Week 12	Week 14	Week 16
Have Informed Consent Signed	X									
Check Inclusion and Exclusion Criteria	X									
Collect demographic information	X									
Collect medical history information	X									
Collect pain history information	X									
Collect concomitant medication information	X	X	X	X	X	X	X	X	X	X
Perform pregnancy test	X	X	X	X	X	X	X	X	X	X
Collect hospitalization and pain information		X	X	X	X	X	X	X	X	X
Check discontinuation criteria		X	X	X	X	X	X	X	X	X
Collect AE information		X	X	X	X	X	X	X	X	X
Randomize patient			X							
Distribute study medication			X	X	X	X	X			
Collect unused study medication and perform pill count				X	X	X	X	X		
CBC/retic	X		X	X	X	X	X	X	X	X
Chem panel	X		X	X	X	X	X	X		X
Urinalysis	X		X	X		X		X		X
Met Hb	X		X	X		X	X	X		
βHCG	X	X	X	X	X	X	X	X	X	
Echocardiogram			X					X		
Research Labs										
NO—serum	X	X	X	X	X	X	X	X	X	X
Arginine	X	X	X	X	X	X	X	X	X	X
Arginase	X	X	X	X	X	X	X	X	X	X
Free Radical Biology										
Nitrotyrosine	X	X	X	X	X	X	X	X		X
8-iso-$PGF_{2\alpha}$	X	X	X	X	X	X	X	X		X
Endothelial Function										
ET-1	X	X	X	X		X	X	X		X
SVCAM-1	X	X	X	X		X	X	X		X
Erythrocyte Characterization										
Advia	X	X	X	X	X	X	X	X	X	X
Ektacytometry	X	X	X	X	X	X	X	X	X	X
Gardos Channel	X	X	X	X	X	X	X	X	X	X
Fetal Hemoglobin	X	X	X			X	X	X		X

Treatment Assignment and Blinding

Patients will be randomized at baseline (Visit 3). Subjects will be randomized to one of three treatment groups: 0.05 g/kg/day oral arginine, 0.1 g/kg/day oral arginine, or placebo. Randomized blocks within each site will be used to maintain similar enrollment into the three treatment groups. Each site will receive two lists of randomization numbers: one for children and one for adults.

The pharmacy at each site will not be blinded and will have a list of all randomization numbers with their corresponding treatments. The Study Coordinator will give the pharmacist the subject's CSCC subject identification number, visit, age, and weight. The pharmacists will note the subject's ID and prepare the patient's study medication. The pharmacist will return the subject's randomization code with the study drug. The study coordinator will then record the randomization number on the Study Drug Record page of the CRF.

Randomization data are kept strictly confidential, accessible only to the person(s) responsible for preparing the drug, until the time of unblinding at the end of the study. The investigator site personnel as well as the personnel involved in the monitoring or conducting of the trial are blinded to the randomization code, except in the case of an emergency.

One complete set of emergency code break envelopes will be provided to the site by the SDMC. The investigator will receive a blinded code envelope for each patient, with the details of drug treatment inside. In an emergency the seal on the envelope can be broken to determine the treatment given.

The envelopes are not to be opened for any reason, other than an emergency where the treatment needs to be known. When the investigator opens the envelope he/she must note the date, time and reason for opening it and retain this information on the protocol deviation form. He/she must also enter this information into the study termination page of the CRF and alert Lori Styles (510-428-3553) and the SDMC Safety Specialist (919-408-8000 x229) immediately.

Only when the study has been completed, the data file verified, and the protocol violations determined will the drug codes be broken and made available for data analysis.

SUPPLEMENTAL ARGININE: ADULT DOSING TABLE 500mg CAPSULES			
WEIGHT (KG)	**PLACEBO**	**LOW DOSE * (.05G/KG/D)**	**HIGH DOSE (.10G/KG/D)**
40-44	4 BID	4 BID	4 BID
45-54	5 BID	5 BID	5 BID
55-64	6 BID	6 BID	6 BID
65-74	7 BID	7 BID	7 BID
75-84	8 BID	8 BID	8 BID
85-94	9 BID	9 BID	9 BID
95+	10 BID	10 BID	10 BID

***Subjects randomized to the "low dose" of arginine will take 500 mg-sized capsules that contain 250 mg arginine and the rest placebo.**

SUPPLEMENTAL ARGININE: PEDIATRIC DOSING TABLE 250mg CAPSULES			
WEIGHT (KG)	**PLACEBO**	**LOW DOSE * (.05G/KG/D)**	**HIGH DOSE (.10G/KG/D)**
15-19	4 BID	4 BID	4 BID
20-24	5 BID	5 BID	5 BID
25-29	6 BID	6 BID	6 BID
30-34	7 BID	7 BID	7 BID
35-40	8 BID	8 BID	8 BID
>40: use adult dosing table			

*** Children randomized to the "low dose" of arginine will take 250 mg-sized capsules that contain 125 mg of arginine and the rest placebo.**

CTM Reorder

Study drug will not be distributed to the site until a patient has been enrolled and has completed Visit 2, the second screening visit. Once the patient has finished this visit and the discontinuation criteria has been checked, the study coordinator must contact the pharmacist with the patient's CSCC ID#, age, and weight. The pharmacist will calculate how many bottles of the study drug that the patient is randomized to (based on weight and age), and will contact Jamie Spencer either by phone (919-408-8000 ext. 450) or by email (jspencer@rhoworld.com) with the exact number of bottles needed. Upon request, Jamie Spencer will order your study drug. This should be done within ONE WEEK of visit 3. You should also copy Karen Kesler on this e-mail (kkesler@rhoworld.com). This is the procedure that will be followed for every new patient.

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

ARGININE SUPPLEMENTATION STUDY

Pharmacy Log

Rand Code	CSCC ID	Weight	Visit 3 Date DD MMM YYYY	Visit 4 Date DD MMM YYYY	Visit 5 Date DD MMM YYYY	Visit 6 Date DD MMM YYYY	Visit 7 Date DD MMM YYYY
xxxx			/ / **Number of Pills Dispensed:**	/ / **Number of Pills Dispensed:**	/ / **Number of Pills Dispensed:**	/ / **Number of Pills Dispensed:**	/ / **Number of Pills Dispensed:**
xxxx			/ / **Number of Pills Dispensed:**	/ / **Number of Pills Dispensed:**	/ / **Number of Pills Dispensed:**	/ / **Number of Pills Dispensed:**	/ / **Number of Pills Dispensed:**
xxxx			/ / **Number of Pills Dispensed:**	/ / **Number of Pills Dispensed:**	/ / **Number of Pills Dispensed:**	/ / **Number of Pills Dispensed:**	/ / **Number of Pills Dispensed:**
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xxxx			/ / Number of Pills Dispensed:	/ / Number of Pills Dispensed:	/ / Number of Pills Dispensed:	/ / Number of Pills Dispensed:	/ / Number of Pills Dispensed:

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

RGININE SUPPLEMENTATION STUDY

RANDOMIZATION NUMBER _____ AGE _____

IDENTIFICATION NUMBER _____ DATE _____

R WEIGHT _____

VISIT _____

_____

(SIGNATURE)

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

ARGININE SUPPLEMENTATION STUDY

RANDOMIZATION NUMBER _____ AGE _____

IDENTIFICATION NUMBER _____ DATE _____

R WEIGHT _____

VISIT _____

_____

(SIGNATURE)

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R WEIGHT _____

VISIT _____

_____

(SIGNATURE)

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ARGININE SUPPLEMENTATION STUDY

RANDOMIZATION NUMBER _____ AGE _____

IDENTIFICATION NUMBER _____ DATE _____

R WEIGHT _____

VISIT _____

_____

(SIGNATURE)

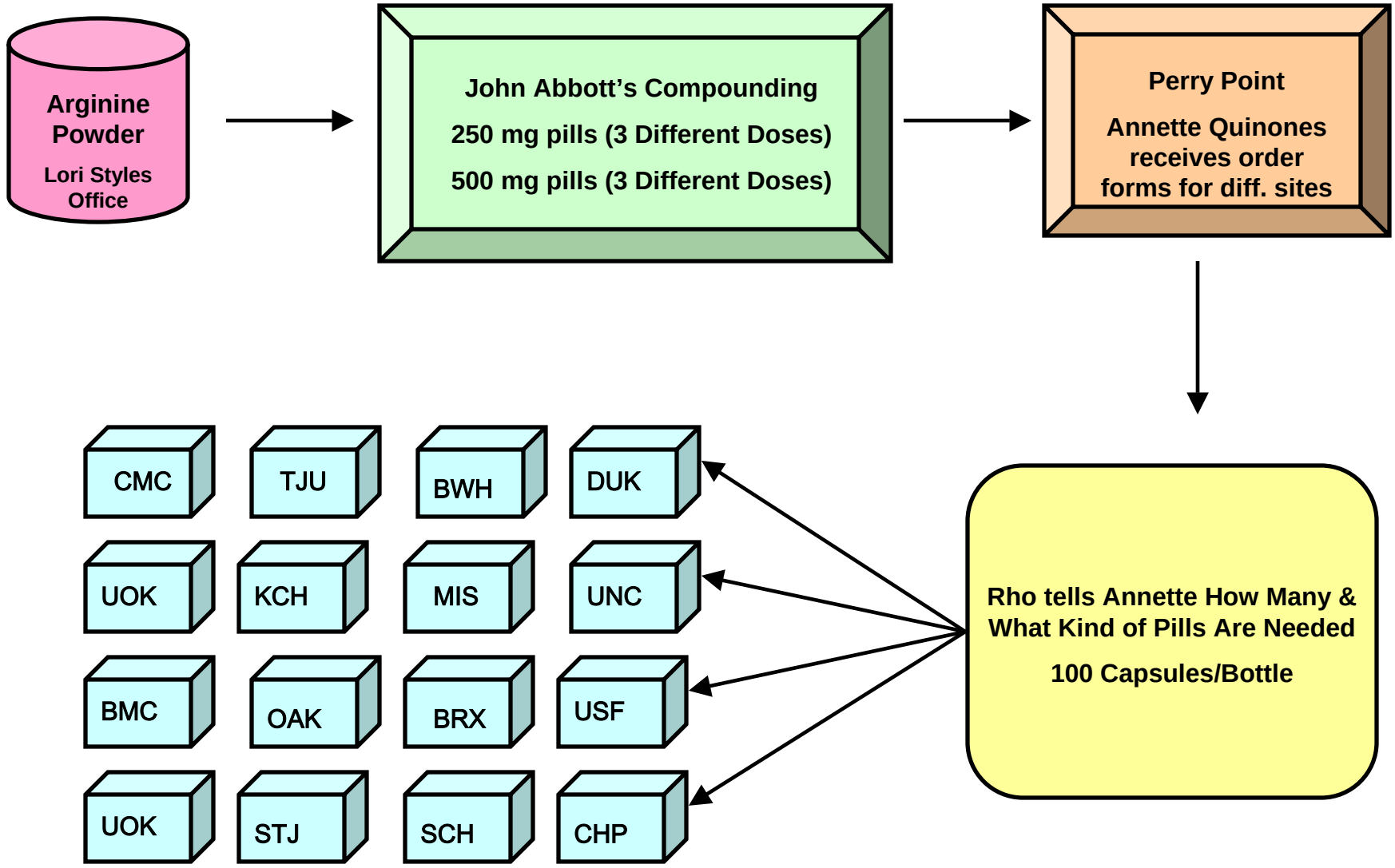
Pregnancy Testing

The effect of arginine of pregnant females and their unborn offspring is not known. Therefore, all female arginine patients ages 8 years and older will be required to have a urine pregnancy screening at all visits. If a patient becomes 8 years old during the study, pregnancy testing will begin at that time and continue for the duration of the study.

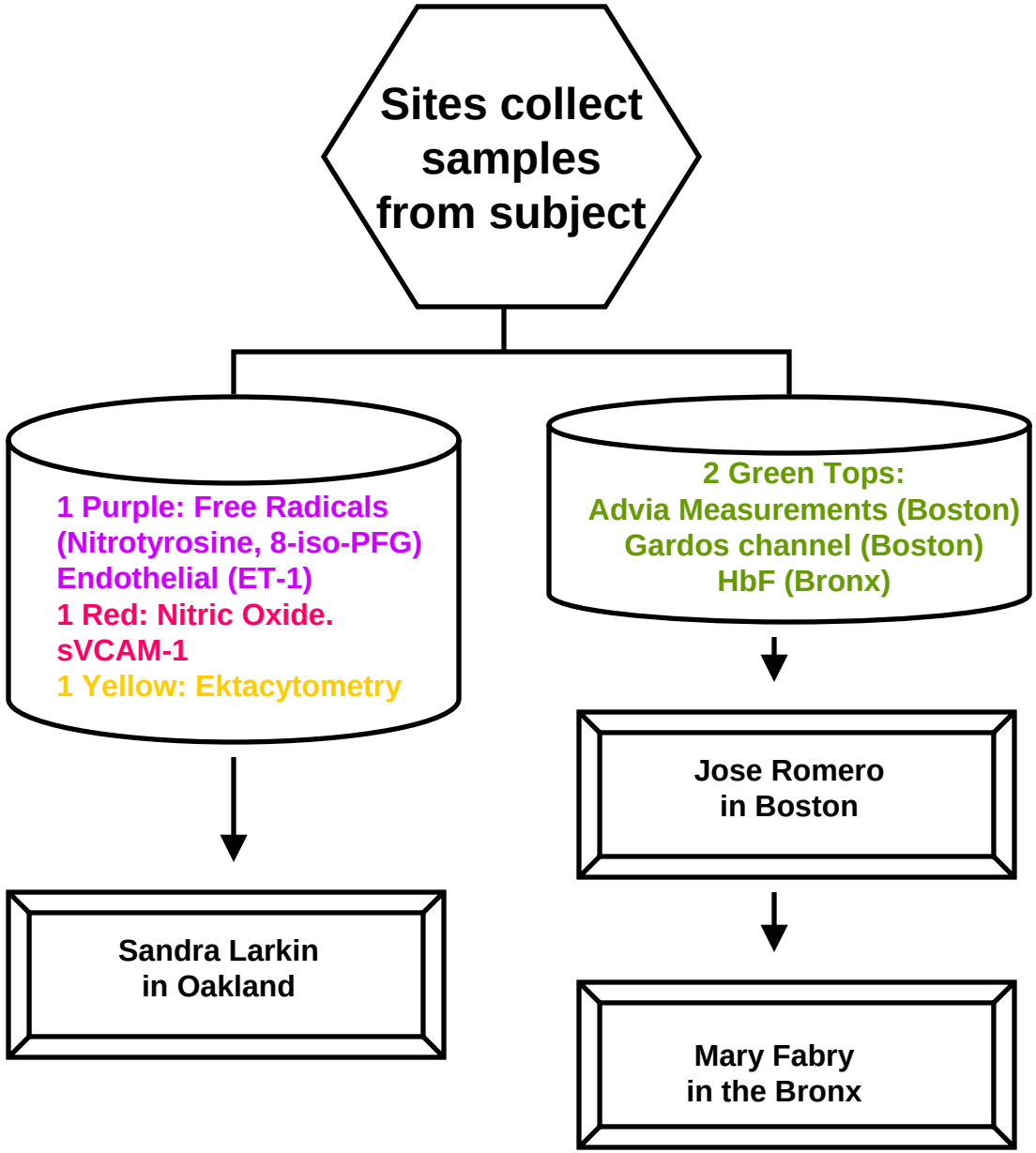
No specific test brand is required. The directions accompanying the test should be followed. Information about the test and the results should be recorded on the Pregnancy Test Results portion of the case report form.

If the result of the pregnancy test is positive, the study drug will not be administered and the participant will be discontinued from the study. Although pregnancy itself is not a serious adverse event, it should be reported as such for purposes of the Arginine Study. If a participant becomes pregnant, it should be reported on the Serious Adverse Events case report form and should also be followed to determine the outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

Arginine Study Drug Flow



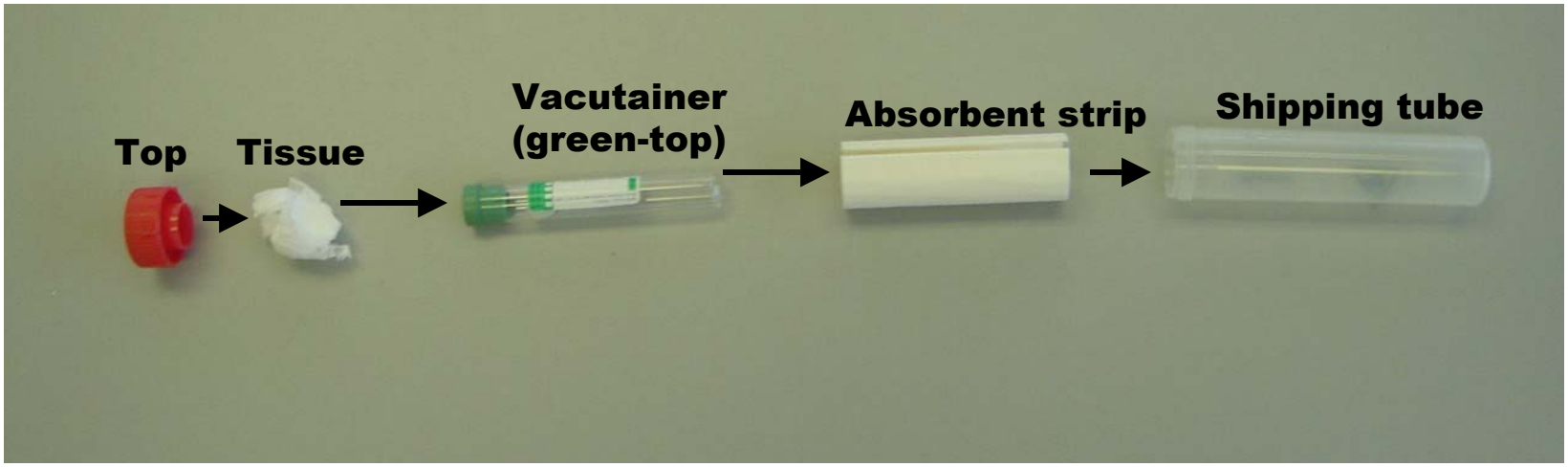
Arginine From Sites to Labs

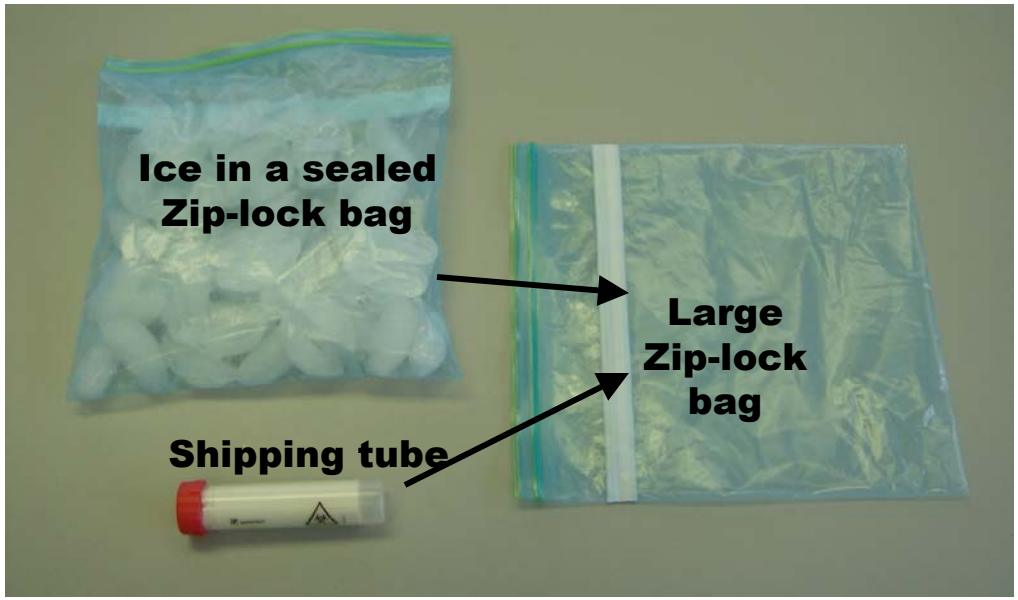


Arginine Study
Shipping to Central Lab at Boston
Instructions Revised February 23, 2005

1. Insert the needle into the rubber top of the green-top, sodium heparin vacutainer and deposit blood half way into the green-top vacutainer. **Do <u>NOT</u>** remove the rubber top of the vacutainer. Either send TWO half-filled 5 ml vacutainers or ONE half-full 10 ml vacutainer.
2. Affix one of the preprinted labels on the outside of the green-top vacutainer. If you are using two vacutainers, make sure they have IDENTICAL ID Specimen#s. Put the labels on the vacutainer(s) as well as on the pre-made Data Collection Sheet. When you are ready to log into RhoLAB, it will prompt you to enter the Specimen ID# before you are able to enter data for that specimen. The Data Collection Sheet allows you to collect the specimen and record it into RhoLAB at a separate time and/or location. It is okay if you make a mistake or mess up one of the labels; just use the next one.
3. **Be sure to MIX WELL before placing in shipping tube.**
4. Place the green-top vacutainer in the shipping tube with rubber top down. The glass bottom should be at the top where the shipping tube will be sealed.
5. Make sure that the absorbent strip that came with the shipping tube is in place around the vacutainer inside the shipping tube.
6. Place tissue in the top of the shipping tube to cushion the glass and keep the green-top vacutainer from moving around and breaking.
7. Tightly secure the red screw cap of the shipping tube. You **DO NOT NEED TO** tape the red screw cap onto the shipping tube after securing the lid.
8. Place ice into two separate zip-lock bags and seal. "Double-bag" each zip-lock bag containing ice. It is very important that the ice be "double bagged" and that the seal is completely closed to avoid leakage.
9. **Place both the zip-lock bags of ice and the shipping tubes into another zip-lock bag and seal. Note that the shipping tube should not be inside one of the zip-loc bags with ice, since the ice may cause moisture in the vacutainer.**
10. Place the zip-lock bag (which contains 2 bags of ice and either 1 shipping tube for 1-10ml vacutainer or 2 shipping tubes for 2-5ml vacutainers) into the Styrofoam mailer inside the outer cardboard box.
11. Add a **third doubled-bag of ice** into the Styrofoam mailer.
12. Log into RhoLABS, enter the predetermined Specimen ID# in order to enroll the subject, add the specimen and create a shipping batch for the green-top vacutainer to go to Boston. Remember that there are three sheets of identical labels for the 2-5mL green vacutainers.
13. Print the packing slip and tape it onto the top of the lid of the styrofoam mailer (using **only one piece** of tape). You **DO NOT NEED TO** tape the styrofoam lid onto the styrofoam mailer. Use a **minimal** amount of packing tape to seal the cardboard box.
14. Affix **two of the preprinted labels** (one on each of two opposite vertical sides of the box) sent to you by Rho that says "DIAGNOSTIC SPECIMENS—PACKED IN COMPLIANCE WITH IATA PACKING INSTRUCTIONS 650" on the outside of the cardboard box with the two "up" arrows showing the orientation of the top of the box.
15. Affix one of the preprinted labels sent to you by Rho that says "LAB OPEN IMMEDIATELY—ARGININE STUDY" on the outside of the cardboard box.
16. Affix two of the preprinted labels sent to you by Rho that has the Diagnostic Specimen and the black diamond with UN3373 inside in the same manner as the label in direction #14 (see above).
17. Write "Wet Ice" with your Sharpie pen on the outside of the cardboard box.
18. Using the preprinted FedEx labels provided, write your address in the sender area and ship to the address below. The person who packed the boxes MUST be the person on the shipping label.

Dr. Jose R. Romero
Endocrine, Diabetes & Hypertension Division, EBRC-201
Brigham and Women's Hospital
221 Longwood Avenue
Boston, MA 02115
Telephone: 617 732-5978
jromero@rics.bwh.harvard.edu


Top
Tissue
Vacutainer
(green-top)
Absorbent strip
Shipping tube


Ice in a sealed
Zip-lock bag
Large
Zip-lock
bag
Shipping tube

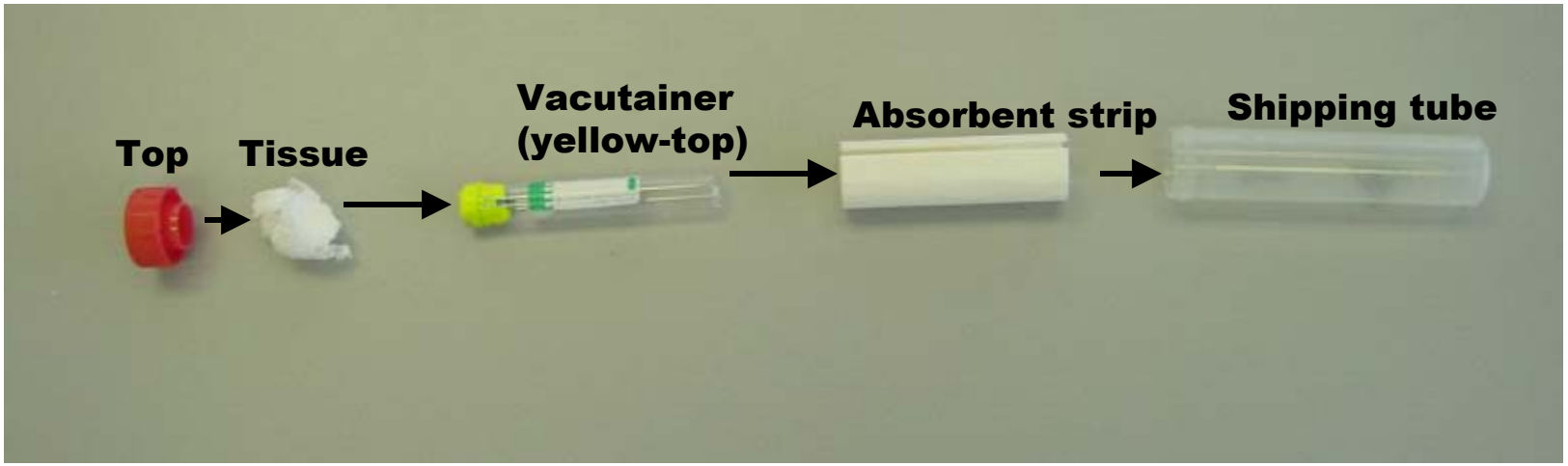
Bag of ice and shipping tube sealed in a large Zip-lock bag

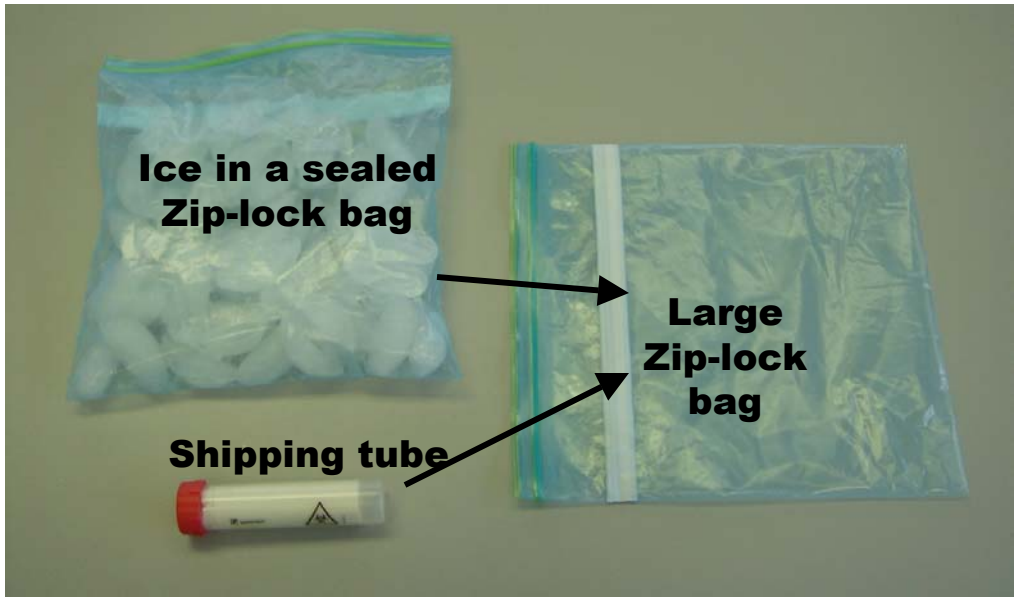
Bag with ice and shipping tube inside of shipping box

Arginine Study
Shipping to Central Lab at Oakland
Instructions Revised February 23, 2005

1. Insert the needle into the rubber tops of the red-top and yellow-top vacutainers and deposit blood approximately half way into the vacutainers. Do NOT remove the rubber tops of the vacutainers.
2. Insert the needle into the rubber top of the purple-top deposit blood into the vacutainer *until it is full*. Do NOT remove the rubber top of the vacutainer. The blue-top vacutainer **IS NOT** being used anymore.
3. Affix one of the preprinted labels on the outside of each vacutainer. Place the duplicate Specimen label on the pre-made Data Collection Sheet. When you are ready to log into RhoLAB, it will prompt you to enter the Specimen ID# before you are able to enter data for each specimen. The Data Collection Sheet allows you to collect the specimen and record it into RhoLAB at a separate time and/or location. It is okay if you make a mistake or mess up one of the labels; just use the next one.
4. **Be sure to MIX WELL before placing in shipping tube.**
5. Place each vacutainer in a shipping tube with rubber top down. The glass bottom should be at the top where the shipping tube will be sealed.
6. Make sure that the absorbent strip that came with the shipping tube is in place around the each vacutainer inside each shipping tube.
7. Place tissue in the top of each shipping tube to cushion the glass and keep each vacutainer from moving and breaking around.
8. Tightly secure the red screw cap of each shipping tube. You **DO NOT NEED** to tape the red screw cap onto the shipping tube after securing the lid.
9. Place ice into two separate zip-lock bags and seal. "Double-bag" each zip-lock bag containing ice. It is very important that the ice be "double bagged" and that the seal is completely closed to avoid leakage.
10. **Place both the zip-lock bags of ice and the shipping tubes into another zip-lock bag and seal**. **Note that the shipping tube should not be inside one of the zip-loc bags with ice, since the ice may cause moisture in the vacutainer.**
11. Place the zip-lock bag (which contains 2 bags of ice and the 4 shipping tubes) into the styrofoam mailer inside the cardboard box. Log into RhoLABS, enter the predetermined Specimen ID# to enroll the subject, add the specimen, and create a shipping batch for the red-top, yellow-top, purple-top and blue-top vacutainers to go to Oakland.
12. Add a **third doubled-bag of ice** to the styrofoam shipper.
13. Print the packing slip and securely place the sytrofoam lid onto the styrofoam mailer. Using a minimal amount of tape, tape the packing slip on the outside of the sytrofoam lid. Use the packing tape to seal the cardboard box. **DO NOT USE EXCESS TAPE.**
14. Affix two of the preprinted labels (one on each of two opposite vertical sides of the box) sent to you by Rho that says "DIAGNOSTIC SPECIMENS—PACKED IN COMPLIANCE WITH IATA PACKING INSTRUCTIONS 650" on the outside of the cardboard box with the two "up" arrows showing the orientation of the top of the box.
15. Affix one of the preprinted labels sent to you by Rho that says, "LAB OPEN IMMEDIATELY—ARGININE STUDY" on the outside of the cardboard box.
16. Affix two of the preprinted labels sent to you by Rho that has the Diagnostic Specimen and has the black diamond with UN3373 on it in the same manner as direction #14 (see above).
17. Write "Wet Ice" with your Sharpie pen on the outside of the cardboard box.
18. Using the preprinted Fedex labels provided, write your address in the sender area and ship to the address below. The person who packed the boxes MUST be the person on the shipping label.

Annabeth Miller
Children's Hospital Oakland Research Institute
5700 Martin Luther King Jr. Way
Oakland, CA 94609
Phone: 510-450-7621
Fax: 510-450-7910
amiller@chori.org


Top
Tissue
Vacutainer
(yellow-top)
Absorbent strip
Shipping tube


Ice in a sealed
Zip-lock bag
Large
Zip-lock
bag
Shipping tube

Bag of ice and shipping tube sealed in a large Zip-lock bag

Bag with ice and shipping tube inside of shipping box

CSCC Collaborative Data Project "Electronic" Case Report Form

What will you need?

- **A computer with access to the internet**
- **A CSCC website login and password, which has been set up with "EDC" rights**

CSCC Collaborative Data Project "Electronic" Case Report Form

How do you get a CSCC login and password?

Email Jamie Spencer at jspencer@RhoWorld.com or call at (919) 408-8000 ext. 450 in order to get a Website Access Form.

CSCC SECURE WEBSITE ACCESS FORM and CHANGE FORM

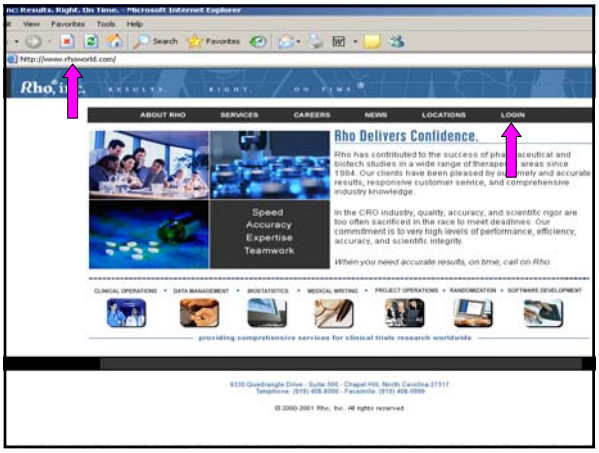
CSCC Collaborative Data Project "Electronic" Case Report Form

Data Security:

- **Each user will be assigned access to a project by the Rho website administrator**
- **Projects to which a user does not have access will *not appear* at all on the user's web pages**
- **No user will be able to view or access data from any other center**

CSCC Collaborative Data Project "Electronic" Case Report Form

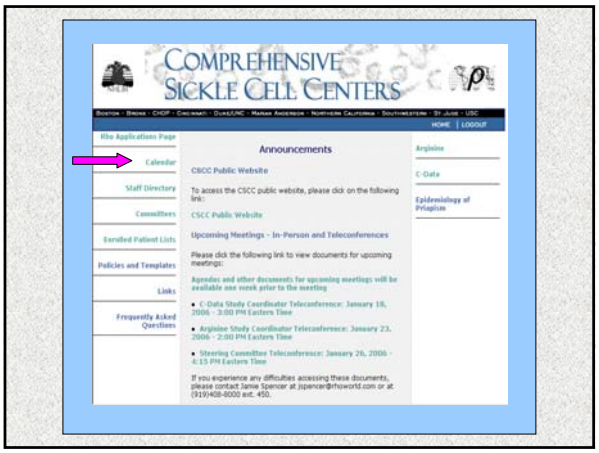
How do you get to the CSCC "EDC"?

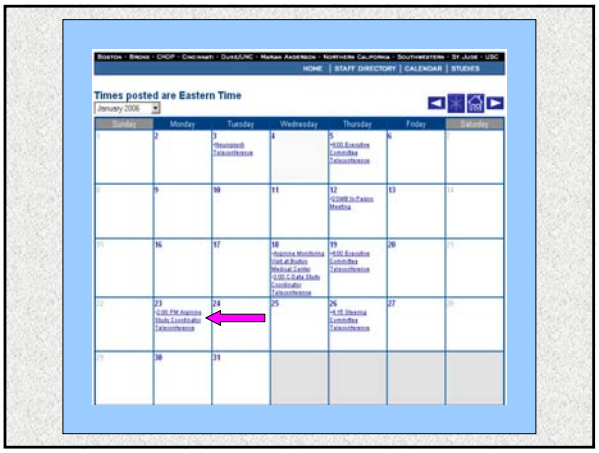


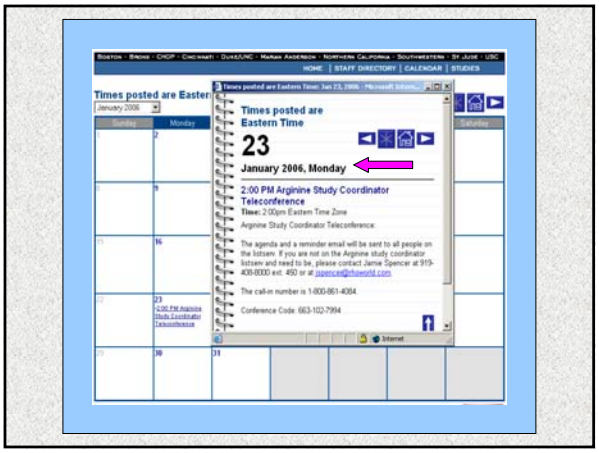

RhoNET
RhoCMS Sites and Applications
Rho, inc.


COMPREHENSIVE SICKLE CELL CENTERS
HOME | LOGOUT
Announcements
CSCC Public Website
Upcoming Meetings - In-Person and Teleconferences
Arginine
C-Data
Epidemiology of Priapism


COMPREHENSIVE SICKLE CELL CENTERS
HOME | LOGOUT
CSCC Upcoming Events
C-Data Study Coordinators
Neuropsych
Arginine Study Coordinators
Steering Committee Meeting Materials


COMPREHENSIVE SICKLE CELL CENTERS
HOME | LOGOUT
Rho Applications Page
Calendar
Staff Directory
Committees
Enrolled Patient Lists
Policies and Templates
Links
Frequently Asked Questions
Announcements
CSCC Public Website
To access the CSCC public website, please click on the following link:
CSCC Public Website
Upcoming Meetings - In-Person and Teleconferences
Please click the following link to view documents for upcoming meetings:
Agendas and other documents for upcoming meetings will be available one week prior to the meeting
C-Data Study Coordinator Teleconference: January 18, 2006 - 3:00 PM Eastern Time
Arginine Study Coordinator Teleconference: January 23, 2006 - 2:00 PM Eastern Time
Steering Committee Teleconference: January 26, 2006 - 4:15 PM Eastern Time
If you experience any difficulties accessing these documents, please contact Jamie Spencer at jspencer@rhoworld.com or at (919)408-8000 ext. 450.
Arginine
C-Data
Epidemiology of Priapism


HOME | STAFF DIRECTORY | CALENDAR | STUDIES
Times posted are Eastern Time
January 2006
Sunday
Monday
Tuesday
Wednesday
Thursday
Friday
Saturday


HOME | STAFF DIRECTORY | CALENDAR | STUDIES
Times posted are Eastern Time
23
January 2006, Monday
2:00 PM Arginine Study Coordinator Teleconference
Time: 2:00pm Eastern Time Zone
Arginine Study Coordinator Teleconference
The agenda and a reminder email will be sent to all people on the listserv. If you are not on the Arginine study coordinator listserv and need to be, please contact Jamie Spencer at 919-408-8000 ext. 450 or at jspencer@rhoworld.com
The call-in number is 1-800-861-4084
Conference Code: 663-102-7994


COMPREHENSIVE SICKLE CELL CENTERS
HOME | LOGOUT
Rho Applications Page
Calendar
Staff Directory
Committees
Enrolled Patient Lists
Policies and Templates
Links
Frequently Asked Questions
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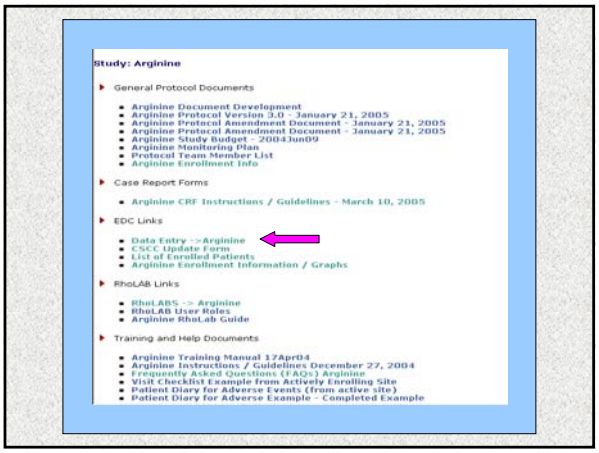
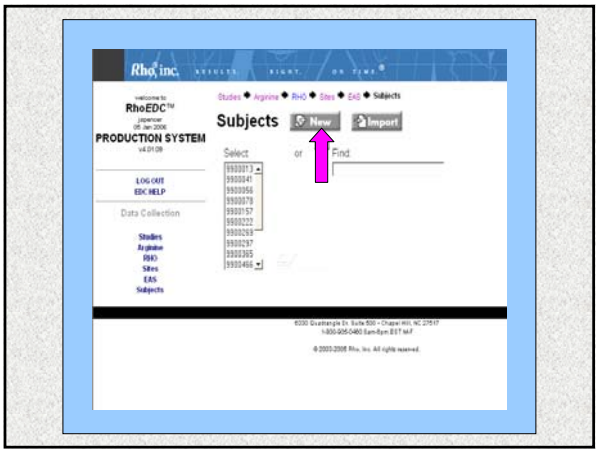
If you experience any difficulties accessing these documents, please contact Jamie Spencer at jspencer@rhoworld.com or at (919)408-8000 ext. 450.
Arginine
C-Data
Epidemiology of Priapism

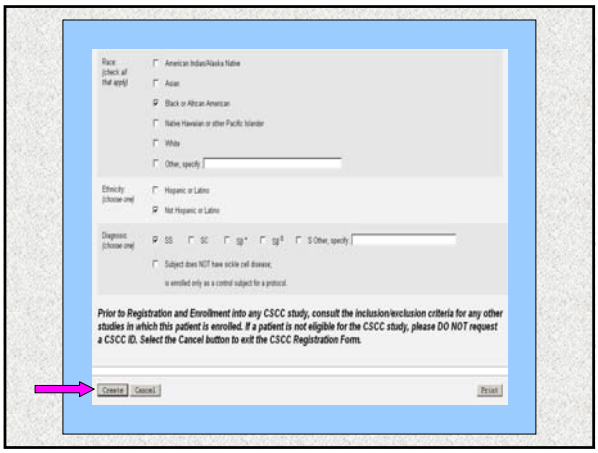

Study: Arginine
General Protocol Documents
Arginine Document Development
Arginine Protocol Version 3.0 - January 21, 2005
Arginine Protocol Amendment Document - January 21, 2005
Arginine Protocol Amendment Document - January 21, 2005
Arginine Study Budget - 2004Jun09
Arginine Monitoring Plan
Protocol Team Member List
Arginine Enrollment Info
Case Report Forms
Arginine CRF Instructions / Guidelines - March 10, 2005
EDC Links
Data Entry -> Arginine
CSCC Update Form
List of Enrolled Patients
Arginine Enrollment Information / Graphs
RhoLAB Links
RhoLABS -> Arginine
RhoLAB User Roles
Arginine RhoLab Guide
Training and Help Documents
Arginine Training Manual 17Apr04
Arginine Instructions / Guidelines December 27, 2004
Frequently Asked Questions (FAQs) Arginine
Visit Checklist Example from Actively Enrolling Site
Patient Diary for Adverse Events (from active site)
Patient Diary for Adverse Example - Completed Example

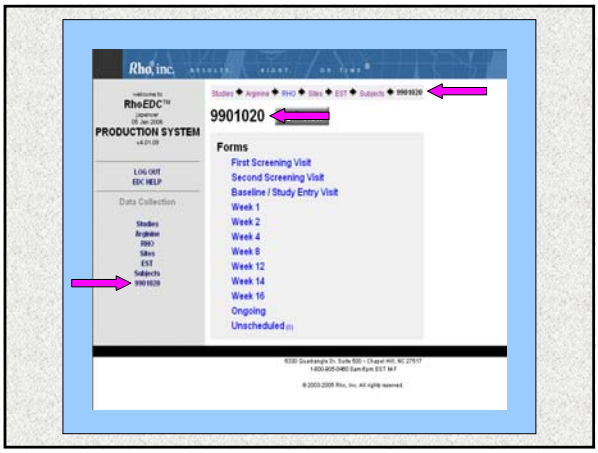

Rho, inc.
RhoEDC
PRODUCTION SYSTEM
RHO
Edit
Forms
Sites
LOG OUT
EDC HELP
Data Collection

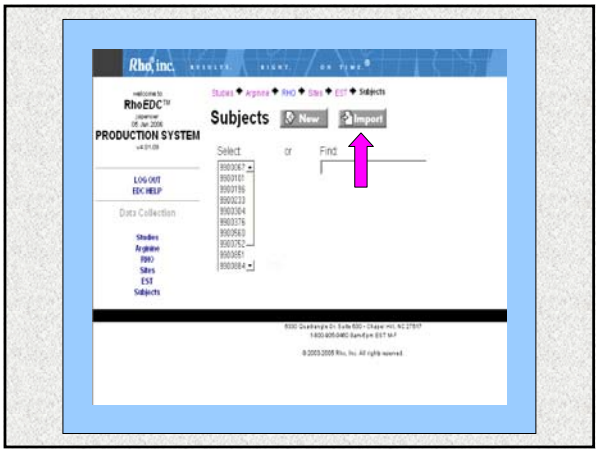

PRODUCTION SYSTEM
RHO
Forms
User's Guide


RhoEDC™
PRODUCTION SYSTEM
LOG OUT
EDC HELP
Data Collection
Studies
Arginine
RHO
Sites
EAS
Subjects
Subjects
New
Import
Select
or
Find:


Comprehensive Sickle Cell Centers
CSCC Registration
Prior to Registration and Enrollment into any CSCC study, consult the inclusion/exclusion criteria for any other studies in which this patient is enrolled. If a patient is not eligible for the CSCC study, please DO NOT request a CSCC ID. Select the Cancel button to exit the CSCC Registration Form.
Gender:
Male
Female
Black or African American
White


Race (check all that apply)
American Indian/Alaska Native
Asian
Black or African American
Native Hawaiian or other Pacific Islander
White
Other, specify
Ethnicity (choose one)
Hispanic or Latino
Not Hispanic or Latino
Diagnosis (choose one)
SS
SC
S Other, specify
Subject does NOT have sickle cell disease;
is enrolled only as a control subject for a protocol.
Prior to Registration and Enrollment into any CSCC study, consult the inclusion/exclusion criteria for any other studies in which this patient is enrolled. If a patient is not eligible for the CSCC study, please DO NOT request a CSCC ID. Select the Cancel button to exit the CSCC Registration Form.
Create
Cancel
Print


RhoEDC™
PRODUCTION SYSTEM
LOG OUT
EDC HELP
Data Collection
Studies
Arginine
RHO
Sites
EST
Subjects
9901020
Forms
First Screening Visit
Second Screening Visit
Baseline / Study Entry Visit
Week 1
Week 2
Week 4
Week 8
Week 12
Week 14
Week 16
Ongoing
Unscheduled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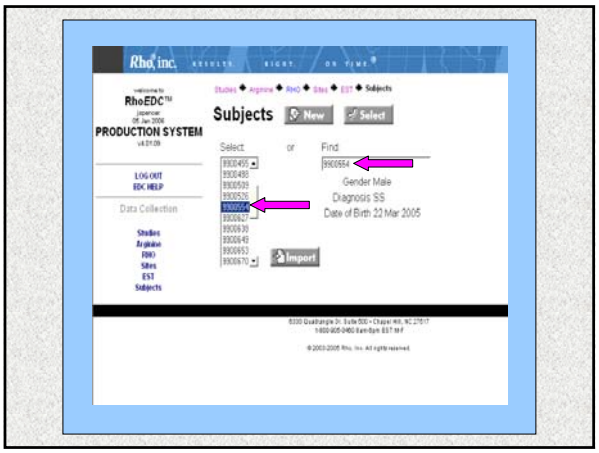
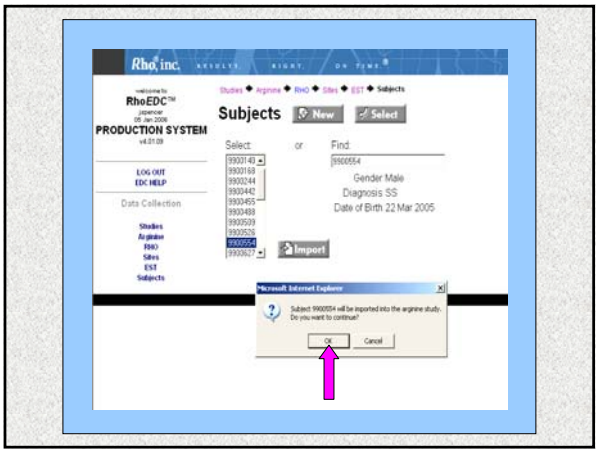
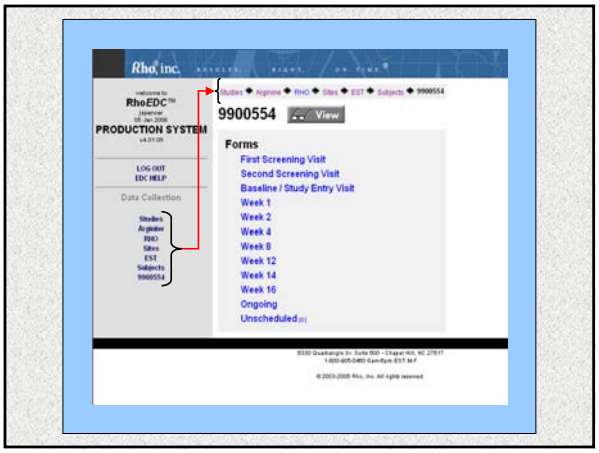
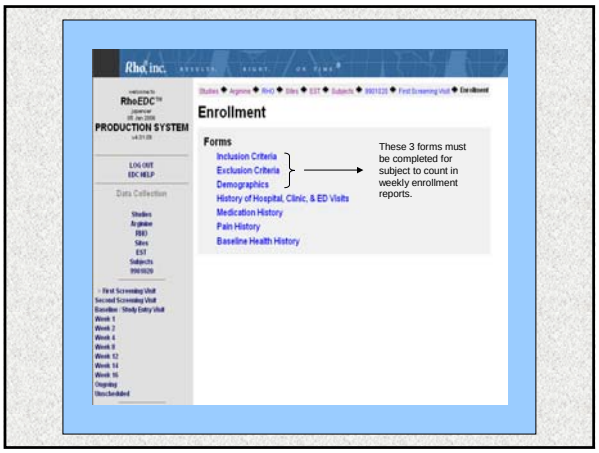
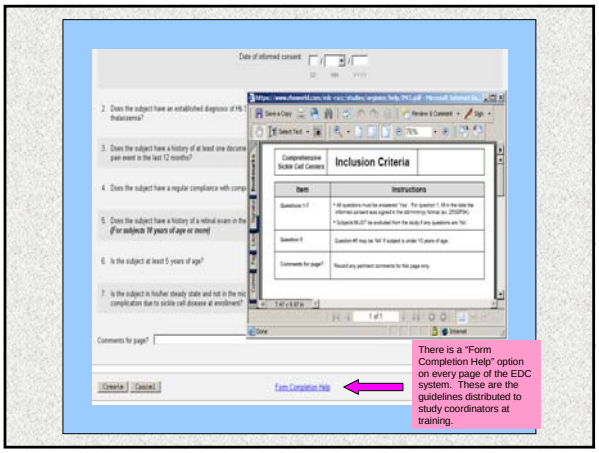
Arginine
RHO
Sites
EST
Subjects
Subjects
New
Import
Select
or
Find

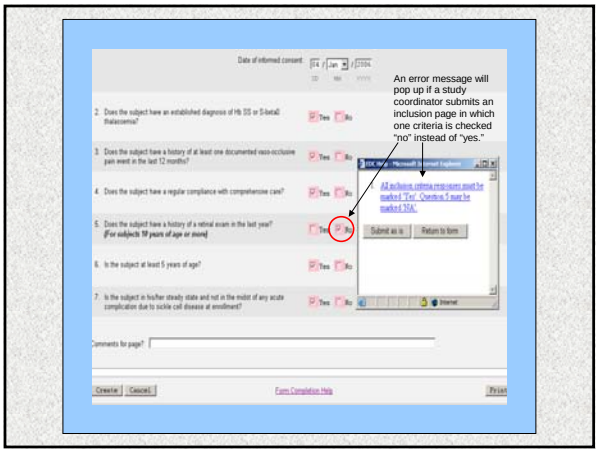

Rho, inc.
RhoEDC™
PRODUCTION SYSTEM
LOG OUT
EDC HELP
Data Collection
Studies
Arginine
RHO
Sites
EST
Subjects
Subjects
New
Select
Select
or
Find
Gender Male
Diagnosis SS
Date of Birth 22 Mar 2005
Import

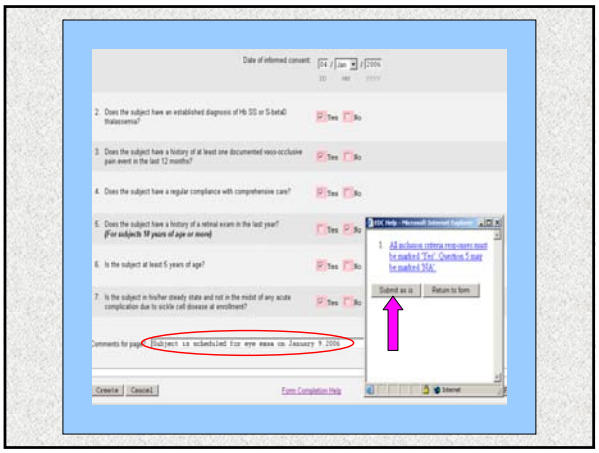

Rho, inc.
RhoEDC™
PRODUCTION SYSTEM
LOG OUT
EDC HELP
Data Collection
Studies
Arginine
RHO
Sites
EST
Subjects
Subjects
New
Select
Select
or
Find
Gender Male
Diagnosis SS
Date of Birth 22 Mar 2005
Import
Microsoft Internet Explorer
OK
Cancel

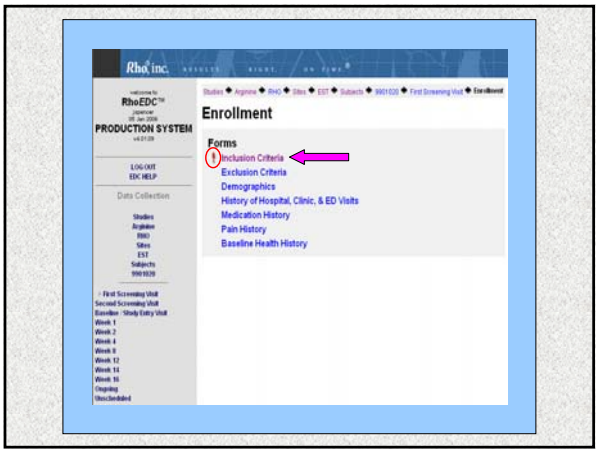

Rho, inc.
RhoEDC™
PRODUCTION SYSTEM
LOG OUT
EDC HELP
Data Collection
Studies
Arginine
RHO
Sites
EST
Subjects
9900554
9900554
View
Forms
First Screening Visit
Second Screening Visit
Baseline / Study Entry Visit
Week 1
Week 2
Week 4
Week 8
Week 12
Week 14
Week 16
Ongoing
Unscheduled


RhoEDC™
PRODUCTION SYSTEM
Enrollment
Forms
Inclusion Criteria
Exclusion Criteria
Demographics
History of Hospital, Clinic, & ED Visits
Medication History
Pain History
Baseline Health History
These 3 forms must be completed for subject to count in weekly enrollment reports.

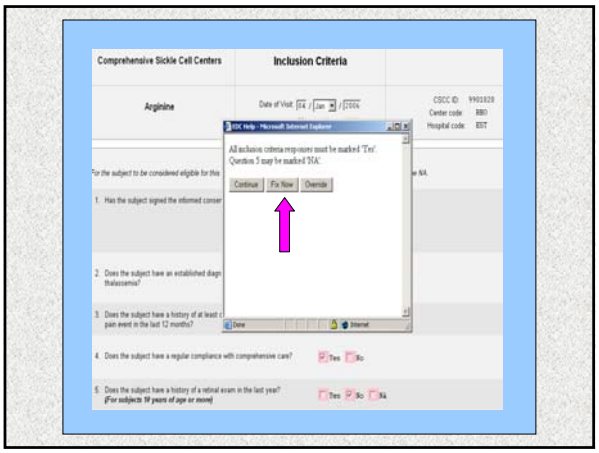

Inclusion Criteria
Form Completion Help
There is a "Form Completion Help" option on every page of the EDC system. These are the guidelines distributed to study coordinators at training.

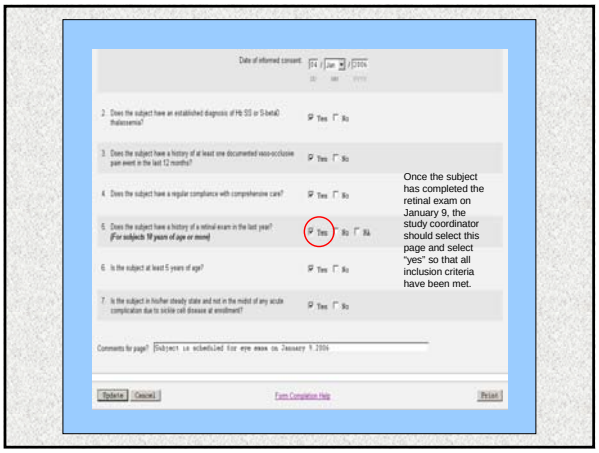

An error message will pop up if a study coordinator submits an inclusion page in which one criteria is checked "no" instead of "yes."
Submit as is
Return to form


Date of informed consent:
2. Does the subject have an established diagnosis of Hb SS or S-beta0 thalassemia?
3. Does the subject have a history of at least one documented vaso-occlusive pain event in the last 12 months?
4. Does the subject have a regular compliance with comprehensive care?
5. Does the subject have a history of a retinal exam in the last year? (For subjects 10 years of age or more)
6. Is the subject at least 5 years of age?
7. Is the subject in his/her steady state and not in the midst of any acute complication due to sickle cell disease at enrollment?
Comments for page: Subject is scheduled for eye exam on January 9 2006
Create
Cancel
Form Completion Help
1. All inclusion criteria responses must be marked 'Yes'. Question 5 may be marked 'N/A'.
Submit as is
Return to form

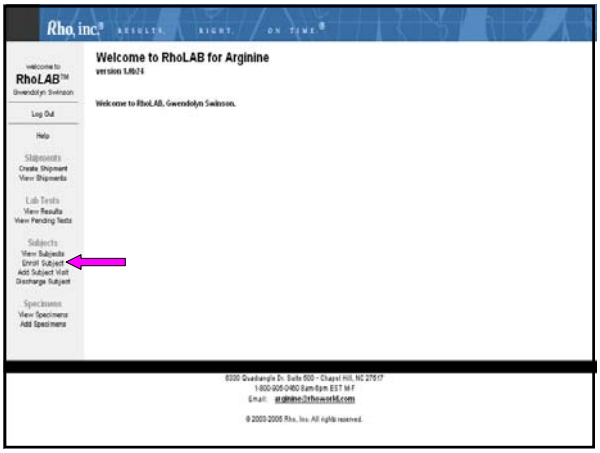

Rho inc.
RhoEDC™
PRODUCTION SYSTEM
LOG OUT
EDC HELP
Data Collection
Enrollment
Forms
Inclusion Criteria
Exclusion Criteria
Demographics
History of Hospital, Clinic, & ED Visits
Medication History
Pain History
Baseline Health History

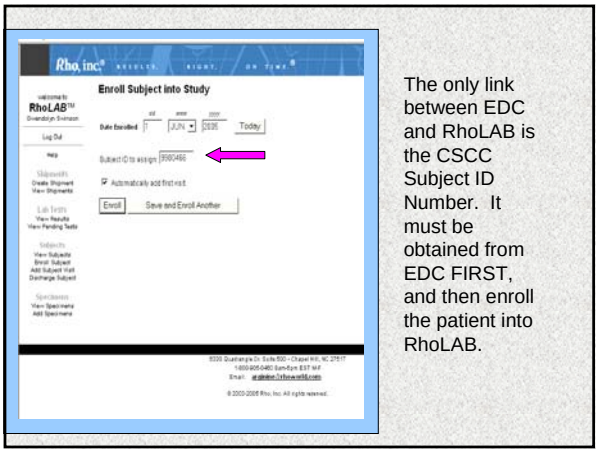

Rho inc.
RhoEDC™
PRODUCTION SYSTEM
LOG OUT
EDC HELP
Data Collection
Inclusion Criteria
Edit
CRF Queries
All inclusion criteria responses must be marked 'Yes'. Question 5 may be marked 'N/A'.



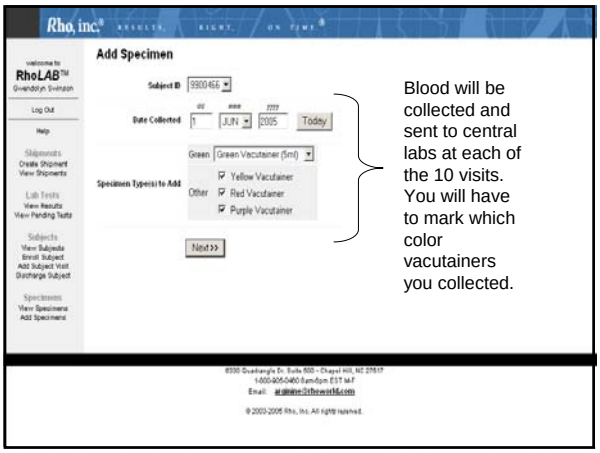


Once the subject has completed the retinal exam on January 9, the study coordinator should select this page and select "yes" so that all inclusion criteria have been met.

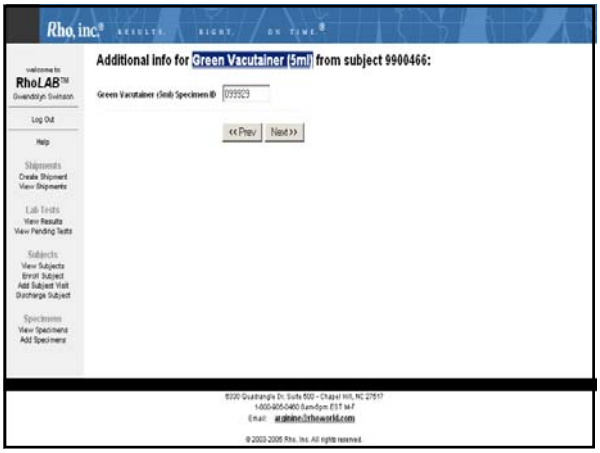


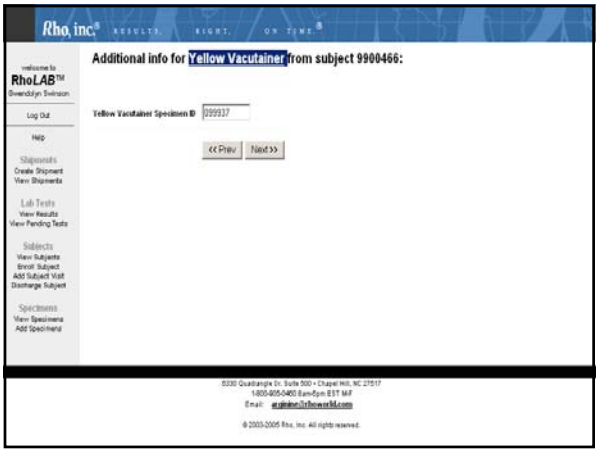


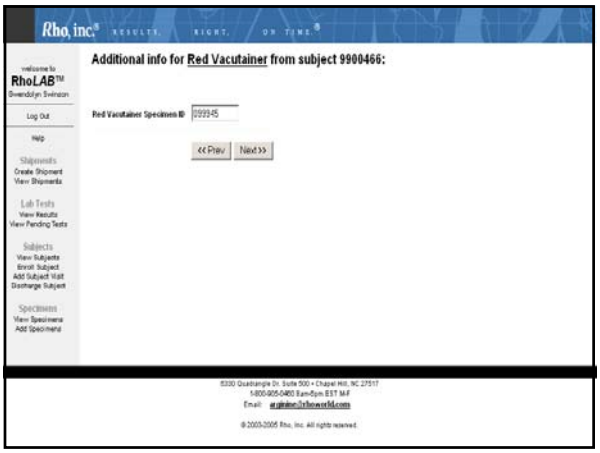
The only link between EDC and RhoLAB is the CSCC Subject ID Number. It must be obtained from EDC FIRST, and then enroll the patient into RhoLAB.

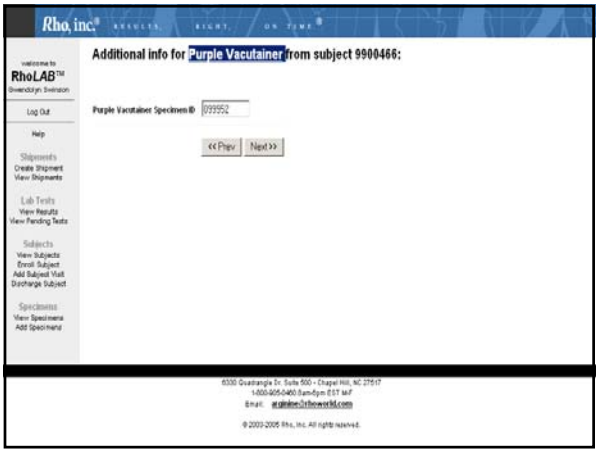


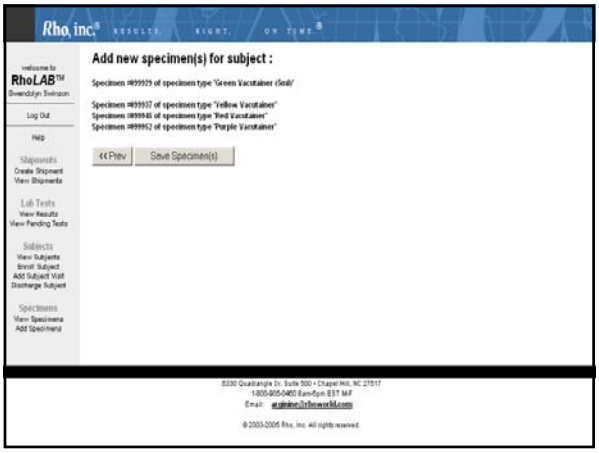
Blood will be collected and sent to central labs at each of the 10 visits. You will have to mark which color vacutainers you collected.

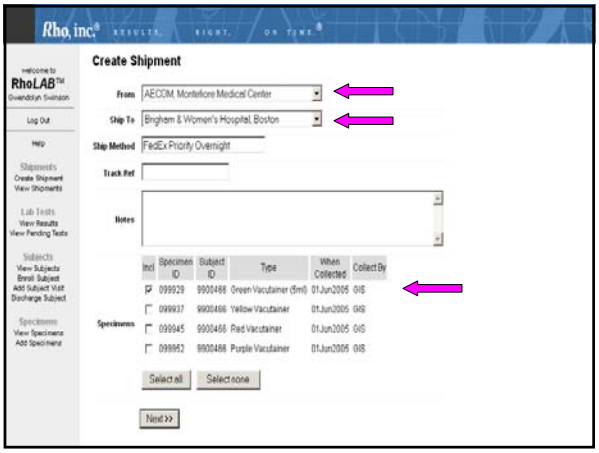


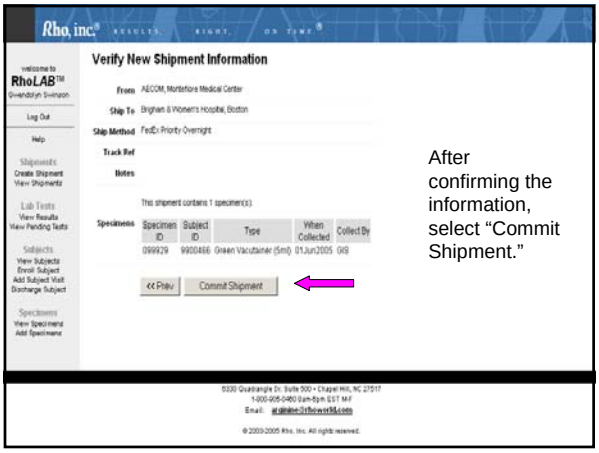



Rho, inc.
RESULTS. RIGHT. ON TIME.
Additional info for Red Vacutainer from subject 9900466:
Red Vacutainer Specimen ID
099945
<< Prev
Next >>

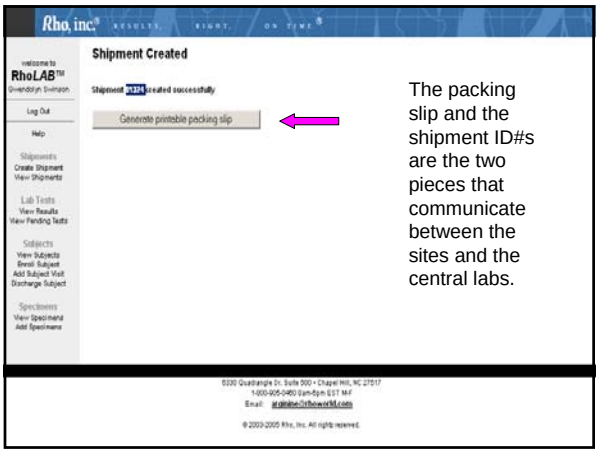

Rho, inc.
RESULTS. RIGHT. ON TIME.
Additional info for Purple Vacutainer from subject 9900466:
Purple Vacutainer Specimen ID
099952
<< Prev
Next >>


Rho, inc.
RESULTS. RIGHT. ON TIME.
Add new specimen(s) for subject :
Specimen #099929 of specimen type 'Green Vacutainer (5ml)'
Specimen #099937 of specimen type 'Yellow Vacutainer'
Specimen #099945 of specimen type 'Red Vacutainer'
Specimen #099952 of specimen type 'Purple Vacutainer'
<< Prev
Save Specimen(s)

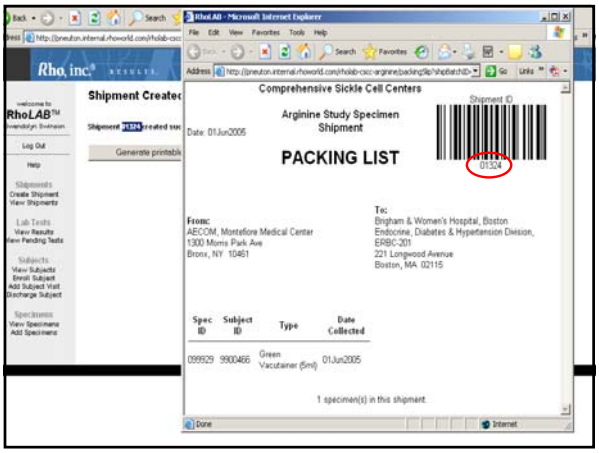


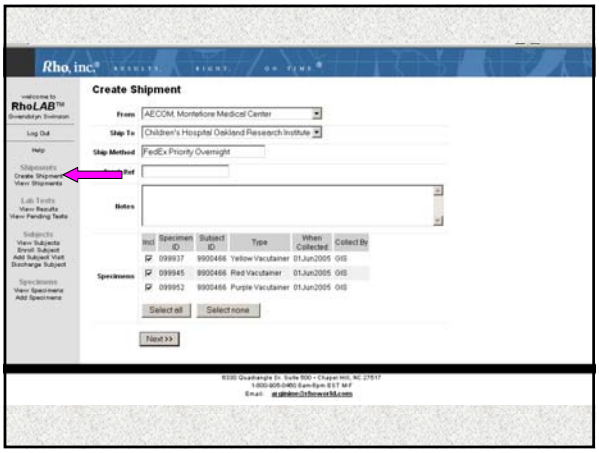


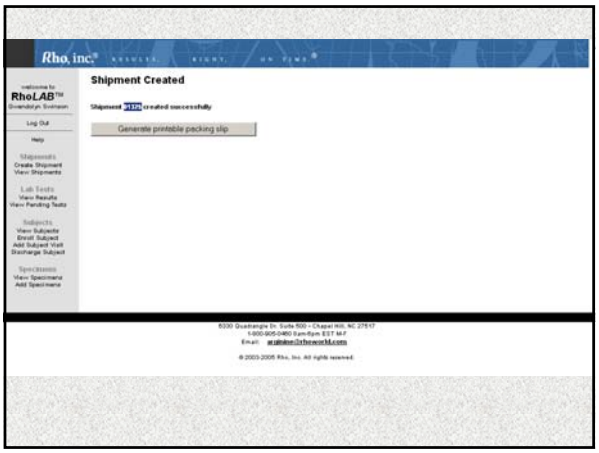
After confirming the information, select “Commit Shipment.”

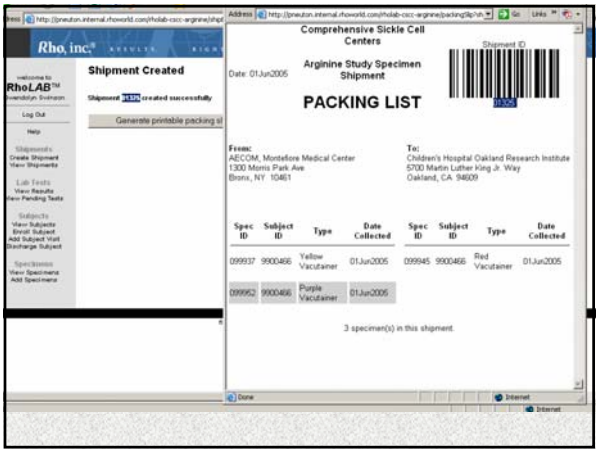


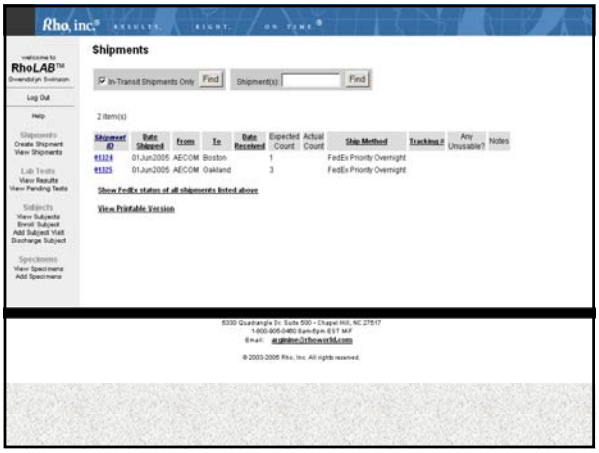
The packing slip and the shipment ID#s are the two pieces that communicate between the sites and the central labs.

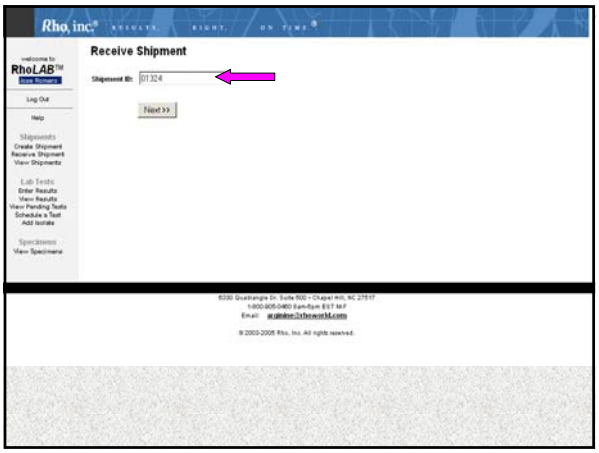


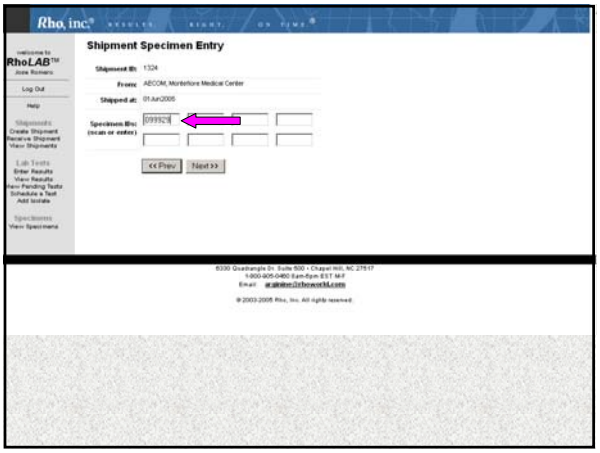


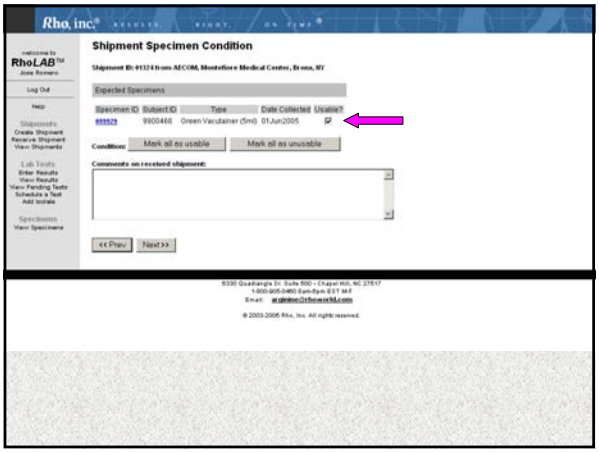

Rho, inc.
Shipment Created
Generate printable packing slip

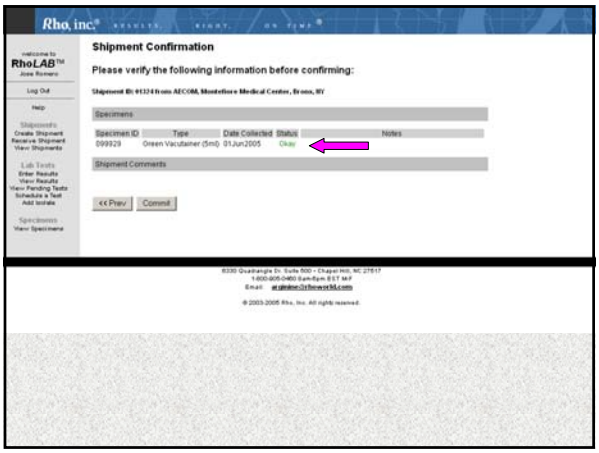

Rho, inc.
Shipment Created
Comprehensive Sickle Cell Centers
Arginine Study Specimen Shipment
PACKING LIST
Date: 01Jun2005
From:
AECOM, Montefiore Medical Center
1300 Morris Park Ave
Bronx, NY 10461
To:
Children's Hospital Oakland Research Institute
5700 Martin Luther King Jr. Way
Oakland, CA 94609
3 specimen(s) in this shipment

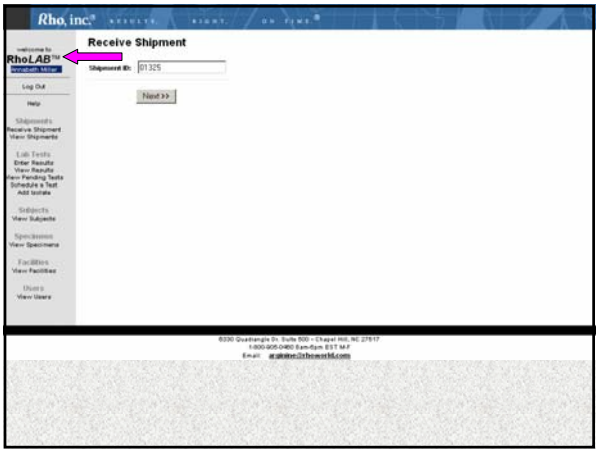

Rho, inc.
Shipments
In-Transit Shipments Only
Find
Shipment(s)
Find
2 item(s)
Show FedEx status of all shipments listed above
View Printable Version

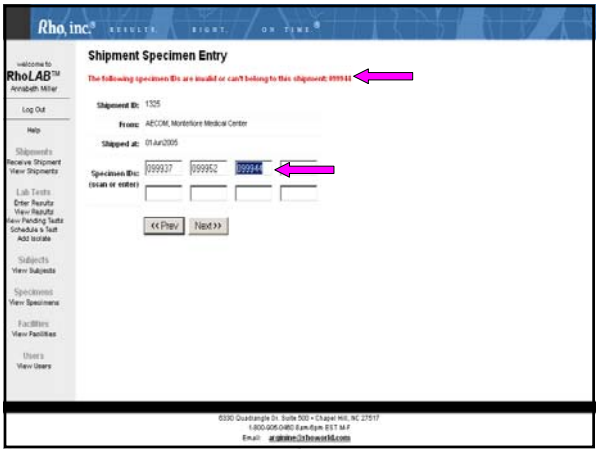

Rho, inc.
Receive Shipment
Shipment ID:
Next >>

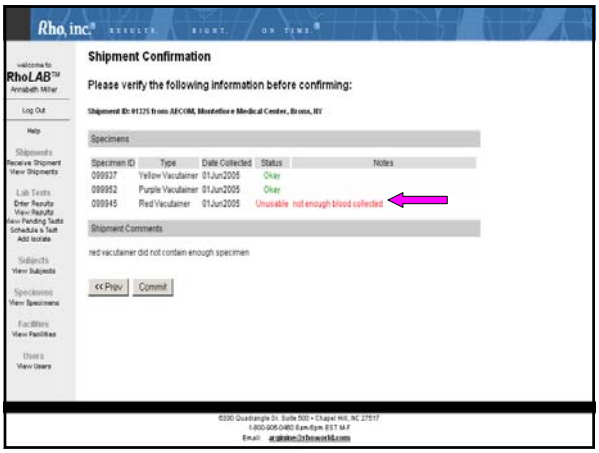

Rho, inc.
Shipment Specimen Entry
Shipment ID:
From:
Shipped at:
Specimen IDs:
<< Prev
Next >>

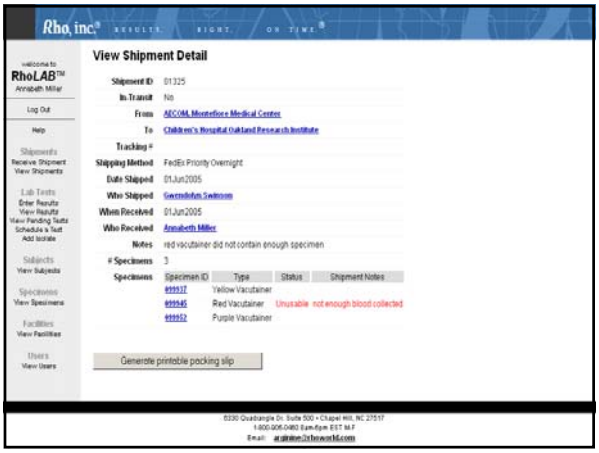

Rho, inc.
Shipment Specimen Condition
Expected Specimens
Specimen ID
Subject ID
Type
Date Collected
Usable?
Mark all as usable
Mark all as unusable
Comments on received shipment:
<< Prev
Next >>

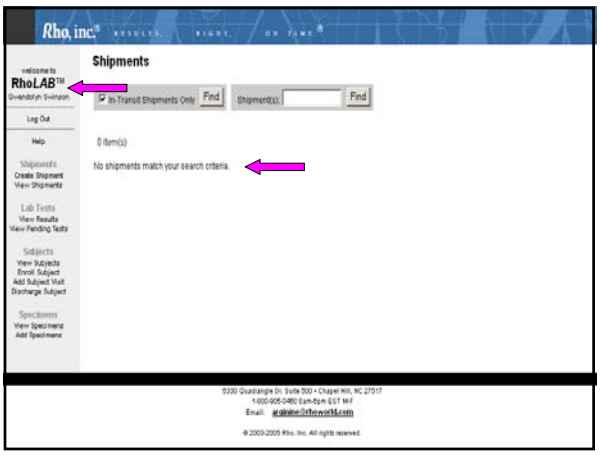

Rho, inc.
Shipment Confirmation
Please verify the following information before confirming:
Specimens
Specimen ID
Type
Date Collected
Status
Notes
099929
Green Vacutainer (5ml)
01Jun2005
Okay
Shipment Comments
<<Prev
Commit

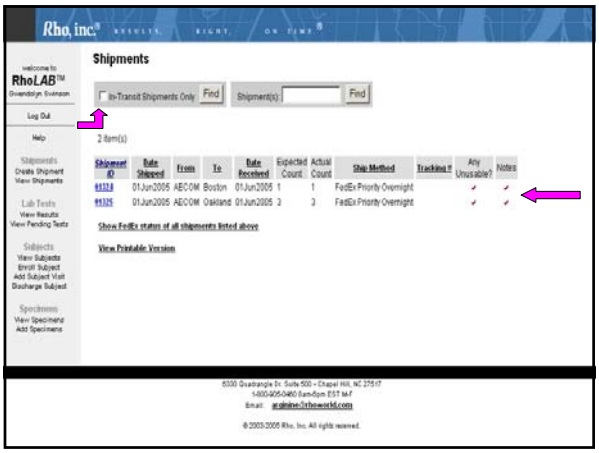

Rho, inc.
Receive Shipment
Shipment ID:
01325
Next >>


Rho, inc.
Shipment Specimen Entry
Shipment ID:
1325
From:
AECOM, Montefiore Medical Center
Shipped at:
01Jun2005
Specimen IDs:
(scan or enter)
<<Prev
Next>>


Rho, inc.
Shipment Confirmation
Please verify the following information before confirming:
Specimens
Specimen ID
Type
Date Collected
Status
Notes
000937
Yellow Vacutainer
01Jun2005
Okay
000952
Purple Vacutainer
01Jun2005
Okay
000945
Red Vacutainer
01Jun2005
Unusable not enough blood collected
Shipment Comments
red vacutainer did not contain enough specimen
<< Prev
Commit


Rho, inc.
View Shipment Detail
Shipment ID
01325
In Transit
No
From
AECOM, Montefiore Medical Center
To
Children's Hospital Oakland Research Institute
Tracking #
Shipping Method
FedEx Priority Overnight
Date Shipped
01Jun2005
Who Shipped
Gwendolyn Swinson
When Received
01Jun2005
Who Received
Annabeth Miller
Notes
red vacutainer did not contain enough specimen
Specimens
3
Specimens
Specimen ID
Type
Status
Shipment Notes
000937
Yellow Vacutainer
000945
Red Vacutainer
Unusable not enough blood collected
000952
Purple Vacutainer
Generate printable packing slip


Rho, inc.
Shipments
In-Transit Shipments Only
Find
Shipment(s)
Find
0 item(s)
No shipments match your search criteria.


Rho, inc.
Shipments
RhoLAB
Log Out
Help
Shipments
Create Shipment
View Shipments
Lab Tests
View Results
View Pending Tests
Subjects
View Subjects
Enroll Subject
Add Subject Visit
Discharge Subject
Specimens
View Specimens
Add Specimens
In-Transit Shipments Only
Find
Shipment(s):
Find
2 item(s)
Shipment ID
Date Shipped
From
To
Date Received
Expected Count
Actual Count
Ship Method
Tracking #
Any Unusable?
Notes
01JUN2005 AECOM Boston 01JUN2005 1 1 FedEx Priority Overnight
01JUN2005 AECOM Oakland 01JUN2005 3 3 FedEx Priority Overnight
Show FedEx status of all shipments listed above
View Printable Version

CSCC Arginine Protocol CRF

The following pages will be used at Screening ("Week – 4") visit only.

Some forms in this section will be used at other visits as well, as indicated in the protocol:

- Urinalysis
- Pregnancy

Comprehensive Sickle Cell Centers	**Inclusion Criteria**	

Item	Instructions
Questions 1-7	• All questions must be answered 'Yes'. For question 1, fill in the date the informed consent was signed in the dd/mmm/yy format (ex. 25SEP04). • Subjects MUST be excluded from the study if any questions are 'No'.
Question 5	Question #5 may be 'NA' if subject is under 10 years of age.
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Inclusion Criteria**	
Protocol # 1 **Arginine**	Date of Visit: ☐☐ / ☐☐☐ / ☐☐ Day Month Year	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

For the subject to be considered eligible for this study, Questions 1 through 7 must be answered Yes. Question 5 may be NA.

1. Has the subject signed the informed consent? Yes ☐ No ☐

   Date of informed consent: ☐☐ / ☐☐☐ / ☐☐
   Day Month Year

2. Does the subject have an established diagnosis of Hb SS or S-beta0 thalassemia? Yes ☐ No ☐

3. Does the subject have a history of at least one documented vaso-occlusive pain event in the last 12 months? Yes ☐ No ☐

4. Does the subject have a regular compliance with comprehensive care? Yes ☐ No ☐

5. Does the subject have a history of a retinal exam in the last year? Yes ☐ No ☐ NA ☐
   (For subjects 10 years of age or more)

6. Is the subject at least 5 years of age? Yes ☐ No ☐

7. Is the subject in his/her steady state and not in the midst of any acute complication due to sickle cell disease at enrollment? Yes ☐ No ☐

Exclusion Criteria

Item	Instructions
Questions 1-11	• All questions must be answered 'No'. Subjects MUST be excluded from the study if any are marked 'Yes'. • Question 6 refers to any treatment, any time.
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Exclusion Criteria**	
Protocol # 1 **Arginine**	Date of Visit: ☐☐ / ☐☐☐ / ☐☐ Day Month Year	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

For the subject to be considered eligible for this study, Questions 1 through 11 must be answered No.

1. Does the subject have an inability to take or tolerate oral capsule medications?	Yes ☐	No ☐
2. Does the subject have a hepatic dysfunction (SGPT ≥ 2X normal OR albumin ≤ 3.2)?	Yes ☐	No ☐
3. Does the subject have a renal dysfunction (Creatinine ≥ 1.2 for children, ≥ 1.4 for adults)?	Yes ☐	No ☐
4. Is the subject allergic to arginine?	Yes ☐	No ☐
5. Has the subject had a history of priapism requiring treatment within the last year?	Yes ☐	No ☐
6. Has the subject had a history of retinopathy requiring treatment?	Yes ☐	No ☐
7. Is the subject pregnant?	Yes ☐	No ☐
8. Has the subject had a transfusion within the last 90 days?	Yes ☐	No ☐
9. Has the subject had ≥ 10 hospital admissions (overnight stay) for pain in the last 12 months, or is he/she currently using narcotics daily (adult who takes narcotics everyday, not meant for those who take narcotics for several days due to a crisis)?	Yes ☐	No ☐
10. Has the subject had treatment with hydroxyurea within the last 90 days?	Yes ☐	No ☐
11. Has the subject had treatment with any investigational drug within the last 90 days?	Yes ☐	No ☐

Comprehensive Sickle Cell Centers	**Demographics**	

Item	Instructions
Weight	Record the subject's weight in kilograms.
Height	Record the subject's height in centimeters.
Date of Birth	Record the subject's date of birth in the dd/mmm/yyyy format (ex. 25SEP1970).
Gender	Check the appropriate gender.
Diagnosis	Check the appropriate diagnosis. Either SS **or** $SB^{0.}$
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Demographics**	
Protocol # 1 **Arginine**	Date of Visit: ☐☐ / ☐☐☐ / ☐☐ Day Month Year	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Weight: ☐☐☐.☐ (kg) Height: ☐☐☐.☐ (cm)

Date of Birth: ☐☐ / ☐☐☐ / ☐☐☐☐
Day Month Year

Gender: ☐ Male ☐ Female

Diagnosis:
(choose one)

☐ **SS**

☐ **SB^0**

Comprehensive Sickle Cell Centers	**Baseline Health History**	

Item	Instructions
Have you been transfused in the last 2 weeks?	• If 'Yes', record dates in the dd/mmm/yy format (ex. 25SEP04) for all transfusions that occurred ***in the last 2 weeks***. Also, be sure to record the number of units or the number of cc's for each transfusion. • If more than one transfusion occurred, use the 'Add' button to record additional visits.
Questions	• Answer either 'Yes' of 'No' to each question on the page. Not sure may be recorded for the question about being unusually tired. • Each question refers to **the past 2 weeks**.
Have you had any unusual headaches?	If 'Yes', choose the <u>one</u> choice that best describes the frequency of the headaches being experienced by the subject.
Have you taken any new medications?	If 'Yes', be sure to record each new medication on the Concomitant Medications form.
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Baseline Health History**	
Protocol # 1 **Arginine**	Date of Visit: ☐☐ / ☐☐☐ / ☐☐ Day Month Year	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions refer to the past 2 weeks.

Have you been transfused in the last 2 weeks? Yes ☐ No ☐

If yes, record date and number of units or cc's for each transfusion.

Date transfused: ☐☐ / ☐☐☐ / ☐☐ (Day Month Year)

Number of units: _____
OR
cc's for pediatrics: _____

ADD

Have you had leg ulcers? Yes ☐ No ☐

Have you had blood in the urine? Yes ☐ No ☐

Have you had chronic pain in the hips or shoulders? Yes ☐ No ☐

Have you had chronic pain in other locations? Yes ☐ No ☐

Have you had any increase in problems with painful erections? Yes ☐ No ☐

Have you had a fever 101° or higher? Yes ☐ No ☐

Have you had vision problems? Yes ☐ No ☐

Have you had any problems with breathing, including asthma? Yes ☐ No ☐

Have you been unusually tired, or more tired than you usually are? Yes ☐ No ☐ Not sure ☐

Have you had any unusual headaches? Yes ☐ No ☐

If yes, frequency of headaches.

☐ Everyday ☐ 2-3 times/week ☐ Once a week ☐ More than once a week

Have you taken any new medications? Yes ☐ No ☐

If yes, add each to the CMED form.

Comprehensive Sickle Cell Centers	**History of Hospital, Clinic, & ED Visits**	

Item	Instructions
ALL FIELDS	All information for this page is to be obtained from the subject's medical record.
List all Hospital Admissions…	• Record all Hospital Admissions that occurred during the last year. Hospital Admission requires an overnight stay. • If more than one Hospital Admission occurred, use the 'Add' button to record additional admissions.
Date of admission/discharge	• Record the date of hospital admission in the dd/mmm/yy format (ex. 25SEP04). • Record the date of hospital discharge in the dd/mmm/yy format (ex. 25SEP04).
Reason	• Record the reason for hospital admission from the list provided. More than one reason may be checked for a given date. • If 'Other, specify' is chosen, be sure to specify in the space provided.
List all ED or Day Hospital visits	• Record all Emergency Department or "Day Hospital" visits that occurred during the last year. • If more than one visit occurred, use the 'Add' button to record additional visits.
Date of visit and location of visit	• Record the date of visit in the dd/mmm/yy format (ex. 25SEP04). • For each date, check whether the visit was to an Emergency Department or Day Hospital.
Reason	• Record the reason for the visit from the list provided. More than one reason may be checked for a given date. • If 'Other, specify' is chosen, be sure to specify in the space provided.
List all Clinic visits…	Record all clinic visits ***for acute pain*** that occurred during the last year. If more than one clinic visit ***for acute pain*** occurred, use the 'Add' button to record additional visits.
Date of clinic visit	Record the date of all clinic visits in the dd/mmm/yy format (ex. 25SEP04). For multiple dates, click the 'Add' button to enter a new row of data.
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**History of Hospital, Clinic, & ED Visits**	
Protocol # 1 **Arginine**	Date of Visit: ☐☐ / ☐☐☐ / ☐☐ Day Month Year	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Information for these questions is to be obtained from the subject's medical records.

List all Hospital Admissions that happened during the last year.

Date of admission: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Date of discharge: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Reason: *(check all that apply)* ☐ ACS ☐ VOC ☐ Non-Sickle Pain ☐ Other, specify _____

ADD

List all Emergency Department visits or "Day Hospital" visits that happened during the last year.

Date of visit: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Location: ☐ Emergency Department ☐ Day Hospital

Reason: *(check all that apply)* ☐ ACS ☐ VOC ☐ Non-Sickle Pain ☐ Other, specify _____

ADD

List all Clinic visits *for acute pain* that happened during the last year.

Date of clinic visit: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

ADD

Comprehensive Sickle Cell Centers	**Medication History**	

Item	Instructions
Medication	• Check 'Yes' if the medication was used by the subject **in the past year**. • Check 'No' if the medication was *never* used by the subject **in the past year**. • If 'Yes' and the medication is followed by 'If yes, specify' or 'If yes, type', be sure to specify in the space provided. • Use the subject's medical record for all medication information.
Length of Time Used	• Record the ***approximate*** number of months the medication was used by the subject in the past year. • Record the ***approximate*** number of days the medication was used by the subject in the past year.
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Medication History**	
Protocol # 1 **Arginine**	Date of Visit: ☐☐ / ☐☐☐ / ☐☐ Day Month Year	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Check all medications used by this subject in the **past year.** Information for these questions is to be obtained from the subject's medical records.

Medication **If yes, record the total approximate length of time used**			**Length of Time Used**	
			Months	Days
Hydroxyurea	Yes ☐	No ☐		
Prophylactic Penicillin	Yes ☐	No ☐		
Any other antibiotic **If yes,specify:** _____	Yes ☐	No ☐		
Folic Acid	Yes ☐	No ☐		
Narcotics **If yes, type:** _____	Yes ☐	No ☐		
NSAIDS	Yes ☐	No ☐		
Desferal	Yes ☐	No ☐		
Oxygen	Yes ☐	No ☐		
Any other pain medication **If yes,specify:**	Yes ☐	No ☐		
Specify 1: _____				
Specify 2: _____				
Psychiatric medications	Yes ☐	No ☐		
Other, or intravenous meds **If yes, specify:** _____	Yes ☐	No ☐		

Comprehensive Sickle Cell Centers	**Pain History**	

Item	Instructions
Number of Times	• Check the best response, as reported by the subject, *to the best of the subject's knowledge*, **in the past year**. • If any of the lead questions are yes, be sure to record the number of times in the space provided. • **Do not** record a range. • ***To avoid double-counting***, if an event could be reported in more than one category, report this event in the most serious category. (For example, if a subject had a painful event that was treated at home, but then went to the emergency room, this event should be recorded in the 'Visited an emergency room, not admitted to hospital' category.) If a subject called a doctor but did not go to the office, emergency room or hospital, this event should be recorded in 'Was treated at home'.
Information provided by	For each category, check the appropriate response on how the information for that category was obtained.
Usual Treatment	For each category, describe the usual treatment given to the subject in order to treat the painful episode **in the past year**.
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Pain History**	
Protocol # 1 **Arginine**	Date of Visit: ☐☐ / ☐☐☐ / ☐☐ Day Month Year	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Record the number of **painful episodes in the past year**, **as reported by the subject to the best of their knowledge**, for which the subject:

	Information provided by	**Usual Treatment**
Was treated at home? Yes ☐ No ☐ Declined ☐ *If yes, specify number of times* _____	☐ Patient ☐ Parent/Guardian ☐ Proxy	
Was treated in a clinic or doctor's office, not hospital? Yes ☐ No ☐ Declined ☐ *If yes, specify number of times* _____	☐ Patient ☐ Parent/Guardian ☐ Proxy	
Visited an emergency room, not admitted to hospital? Yes ☐ No ☐ Declined ☐ *If yes, specify number of times* _____	☐ Patient ☐ Parent/Guardian ☐ Proxy	
Was admitted to hospital? Yes ☐ No ☐ Declined ☐ *If yes, specify number of times* _____	☐ Patient ☐ Parent/Guardian ☐ Proxy	

Comprehensive Sickle Cell Centers	**Chemistry Labs**	

Item	Instructions
Collection date	Record the collection date in the dd/mmm/yy format (ex. 25SEP04).
Test/Value	Record a value for each test in the units provided on the form.
Normal Ranges / Lower Limit	Record the lower limit of the range that is considered normal for each test, as displayed on the lab report.
Normal Ranges / Upper Limit	Record the upper limit of the range that is considered normal for each test, as displayed on the lab report.
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Chemistry Labs**	
Protocol # 1 **Arginine**	Date of Visit: ☐☐ / ☐☐☐ / ☐☐ Day Month Year	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Collection date: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE	NORMAL RANGES (Please record the lower & upper limit for each lab value)	
		LOWER LIMIT	UPPER LIMIT
Sodium (mEq/L)	☐☐☐		
Potassium (mEq/L)	☐.☐		
Chloride (mEq/L)	☐☐☐		
CO_2 (mEq/L)	☐☐.☐		
Calcium (mg/dL)	☐☐.☐		
Creatinine (mg/dL)	☐☐.☐		
Glucose (mg/dL)	☐☐☐		
BUN (mg/dL)	☐☐☐		
ALT (IU/L)	☐☐☐☐		
Alk phosphatase (IU/L)	☐☐☐☐		
Total bilirubin (mg/dL)	☐☐.☐		
Total protein (gm/dL)	☐☐.☐		
Albumin (g/dL)	☐☐.☐		
LDH (u/L)	☐☐☐☐		

Comprehensive Sickle Cell Centers	**Hematology Labs**	

Item	Instructions
Collection date	Record the collection date in the dd/mmm/yy format (ex. 25SEP04).
Test/Value	• Record a value for each test in the units provided on the form. • Record information for Absolute Retic Count ***or*** % Retic.
Normal Ranges / Lower Limit	Record the lower limit of the range that is considered normal for each test, as displayed on the lab report.
Normal Ranges / Upper Limit	Record the upper limit of the range that is considered normal for each test, as displayed on the lab report.
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Hematology Labs**	
Protocol # 1 **Arginine**	Date of Visit: ☐☐ / ☐☐☐ / ☐☐ Day Month Year	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Collection date: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE	NORMAL RANGES (Please record the lower & upper limit for each lab value)	
		LOWER LIMIT	UPPER LIMIT
Hemoglobin (mg/dL)	☐☐.☐		
Hematocrit (%)	☐☐		
RBC ($X10^3/mm^3$)	☐☐.☐		
WBC ($X10^3/mm^3$)	☐☐.☐		
MCV (fl)	☐☐☐.☐		
MCHC (gm/dL)	☐☐.☐		
Platelet count ($X10^3/mm^3$)	☐☐☐		
Absolute Retic Count	☐☐☐		
OR			
% Retic	☐☐.☐		

Comprehensive Sickle Cell Centers	**Met Hb**	

Item	Instructions
Collection date	Record the collection date in the dd/mmm/yy format (ex. 25SEP04).
Test/Value	Record a value in the units provided on the form.
Normal Ranges / Lower Limit	Record the lower limit of the range that is considered normal for the test, as displayed on the lab report.
Normal Ranges / Upper Limit	Record the upper limit of the range that is considered normal for the test, as displayed on the lab report.
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Met Hb**	
Protocol # 1 **Arginine**	Date of Visit: ☐☐ / ☐☐☐ / ☐☐ Day Month Year	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Collection date: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE	NORMAL RANGES (Please record the lower & upper limit)	
		LOWER LIMIT	UPPER LIMIT
Met Hb (%)	☐☐.☐		

Comprehensive Sickle Cell Centers	**Urinalysis**	

Item	Instructions
Specify gravity, pH, Microscopic RBC, and WBC	• Record the result for each test in the units provided on the form. If units are not provided, use the standard unit for that test. • For Microscopic RBC and WBC check only one response. For lab results that are in the 20-30 range, check the 25-50 box.
Protein	Select the one choice as reported by your lab.
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Urinalysis**	
Protocol # 1 **Arginine**	Date of Visit: ☐☐ / ☐☐☐ / ☐☐ Day Month Year	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Specific gravity: ☐.☐☐☐

pH: ☐☐.☐

Protein *(Select the one choice, as reported by your lab)*:

☐ Negative ☐ Trace ☐ 100 ☐ 200 ☐ 300 ☐ 1+ ☐ 2+ ☐ 3+

Microscopic RBC (#/mm^3): ☐ 0-5 ☐ 5-10 ☐ 10-25 ☐ 25-50 ☐ 50+

WBC (#/mm^3): ☐ 0-5 ☐ 5-10 ☐ 10-25 ☐ 25-50 ☐ 50+

Comprehensive Sickle Cell Centers	**Pregnancy Test**	

Item	Instructions
Pregnancy Test	• Check ***one*** of the following three choices: 'Not done, subject male' 'Not done, female subject not of menstruating age' 'Not done, female subject not of child-bearing potential' • If 'Not done, female subject not of child-bearing potential', check ***all*** reasons that apply. • If 'Other, specify' is chosen, be sure to specify. • If pregnancy test is not done, omit the rest of this page.
Date of Collection	Record the date of collection in the dd/mmm/yy format (ex. 25SEP04).
Result	Check the result of the pregnancy test, either 'Positive' or 'Negative'.
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Pregnancy Test**	
Protocol # 1 **Arginine**	Date of Visit: ☐☐ / ☐☐☐ / ☐☐ Day Month Year	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

☐ Not done, subject male ☐ Not done, female subject not of menstruating age ☐ Not done, female subject not of child-bearing potential **(check reason below)** ☐ Postmenopausal ☐ Hysterectomy ☐ Tubal ligation ☐ Other, specify: _____	Date of Collection: ☐☐ / ☐☐☐ / ☐☐ Day Month Year Result: ☐ Positive ☐ Negative

The following pages will be used at Visit Week – 2, and later, as indicated in the protocol.

Comprehensive Sickle Cell Centers	**Chemistry Labs**	

Item	Instructions
Collection date	Record the collection date in the dd/mmm/yy format (ex. 25SEP04).
Test/Value	Record a value for each test in the units provided on the form.
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Chemistry Labs**	
Protocol # 1 **Arginine**	Date of Visit: ☐☐ / ☐☐☐ / ☐☐ Day Month Year	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Collection date: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE
Sodium (mEq/L)	☐☐☐
Potassium (mEq/L)	☐.☐
Chloride (mEq/L)	☐☐☐
CO_2 (mEq/L)	☐☐.☐
Calcium (mg/dL)	☐☐.☐
Creatinine (mg/dL)	☐☐.☐
Glucose (mg/dL)	☐☐☐
BUN (mg/dL)	☐☐☐
ALT (IU/L)	☐☐☐☐
Alk phosphatase (IU/L)	☐☐☐☐
Total bilirubin (mg/dL)	☐☐.☐
Total protein (gm/dL)	☐☐.☐
Albumin (g/dL)	☐☐.☐
LDH (u/L)	☐☐☐☐

Comprehensive Sickle Cell Centers	**Hematology Labs**	

Item	Instructions
Collection date	Record the collection date in the dd/mmm/yy format (ex. 25SEP04).
Test/Value	• Record a value for each test in the units provided on the form. • Record information for Absolute Retic Count ***or*** % Retic.
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Hematology Labs**	
Protocol # 1 **Arginine**	Date of Visit: ☐☐ / ☐☐☐ / ☐☐ Day Month Year	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Collection date: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE
Hemoglobin (mg/dL)	☐☐.☐
Hematocrit (%)	☐☐
RBC ($X10^3/mm^3$)	☐☐.☐
WBC ($X10^3/mm^3$)	☐☐.☐
MCV (fl)	☐☐☐.☐
MCHC (gm/dL)	☐☐.☐
Platelet count ($X10^3/mm^3$)	☐☐☐
Absolute Retic Count **OR**	☐☐☐
% Retic	☐☐.☐

Comprehensive Sickle Cell Centers	**Met Hb**	

Item	Instructions
Collection date	Record the collection date in the dd/mmm/yy format (ex. 25SEP04).
Test/Value	Record a value in the units provided on the form.
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Met Hb**	
Protocol # 1 **Arginine**	Date of Visit: ☐☐ / ☐☐☐ / ☐☐ Day Month Year	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Collection date: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TEST	VALUE
Met Hb (%)	☐☐.☐

Comprehensive Sickle Cell Centers	**Echocardiogram**	

Item	Instructions
Date of most recent echocardiogram	Record the date of the **most recent** echocardiogram in the dd/mmm/yy format (ex. 25SEP04).
TR Jet **Ejection Fraction** **Shortening Fraction** **LVH** **RVH**	• Check 'Yes' or 'No' where applicable. • Record a value for each in the units provided on the form. • The TR Jet is a velocity. If TR Jet is undetectable, be sure to check that box. • The Ejection Fraction should be measured by the Simpsons method. • For Ejection Fraction and Shortening Fraction, not reported may be checked.
Right Ventricular to Right Atrial Difference	• If two values are received, subtract them. The subtracted value should then be entered into this field. • Not reported may be marked.
Has ECHO ever been abnormal?	• **If the values recorded in the first section are considered to be normal**, answer the questions 'has ECHO **ever** been abnormal?", Yes or No. • If 'Yes', answer the remaining questions on the page. • If 'No', skip the rest of the page.
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Echocardiogram**	
Protocol # 1 **Arginine**	Date of Visit: ☐☐ / ☐☐☐ / ☐☐ Day Month Year	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Date of most recent echocardiogram: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TR Jet: ☐☐.☐ ☐ TR Jet Undetectable

Ejection Fraction: ☐☐ (%) ☐ Not reported

Shortening Fraction: ☐☐ (%) ☐ Not reported

Right Ventricular to Right Atrial Difference: ☐☐☐ mm Hg ☐ Not reported

LVH: Yes ☐ No ☐

RVH: Yes ☐ No ☐

If above is normal, has ECHO **ever** been abnormal? Yes ☐ No ☐

If **Yes**, date of most recent **abnormal** ECHO: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

TR Jet: ☐☐.☐ ☐ TR Jet Undetectable

Ejection Fraction: ☐☐ (%) ☐ Not reported

Shortening Fraction: ☐☐ (%) ☐ Not reported

Right Ventricular to Right Atrial Difference: ☐☐☐ mm Hg ☐ Not reported

LVH: Yes ☐ No ☐

RVH: Yes ☐ No ☐

Comprehensive Sickle Cell Centers	**Interim Health History**	

Item	Instructions
Have you had any hospitalizations since your last visit?	• Check 'Yes' if the subject had any hospitalizations ***since the last study visit***. Otherwise, check 'No'. • If 'Yes', record the date of admission, date of discharge, and reason for admission. If more than one hospitalization occurred ***since the last study visit***, use the 'Add' button to record additional visits. • If 'No', go to the next section on the page.
Date of admission/discharge	• Record the date of hospital admission in the dd/mmm/yy format (ex. 25SEP04). • Record the date of hospital discharge in the dd/mmm/yy format (ex. 25SEP04).
Reason	• Record the reason for hospital admission from the list provided. More than one reason may be checked for a given date. • If 'Other, specify' is chosen, be sure to specify in the space provided.
Have you been to the ED or Day Hospital since your last visit?	• Check 'Yes' if the subject had any visits ***since the last study visit***. Otherwise, check 'No'. • If 'Yes', record the date of visit, reason, and location of visit. If more than one visit occurred ***since the last study visit***, use the 'Add' button to record additional visits. • If 'No', go to the next section on the page.
Date of visit and location of visit	• Record the date of visit in the dd/mmm/yy format (ex. 25SEP04). • For each date, check whether the visit was to an Emergency Department or Day Hospital.
Reason	• Record the reason for the visit from the list provided. More than one reason may be checked for a given date. • If 'Other, specify' is chosen, be sure to specify in the space provided.
Have you had any clinic visits for acute pain since the last study visit?	• If 'Yes', record dates in the dd/mmm/yy format (ex. 25SEP04) for all clinic visits ***for acute pain*** that occurred ***since the last study visit.*** • If more than one clinic visit ***for acute pain*** occurred, use the 'Add' button to record additional visits.
Have you been transfused?	• If 'Yes', record dates in the dd/mmm/yy format (ex. 25SEP04) for all transfusions that occurred ***since the last study visit***. Also, be sure to record the number of units or the number of cc's for each transfusion. • If more than one transfusion occurred, use the 'Add' button to record additional visits.
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Interim Health History**	
Protocol # 1 **Arginine**	Date of Visit: ☐☐ / ☐☐☐ / ☐☐ Day Month Year	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to changes since the last study visit

Have you had any hospitalizations since your last study visit? Yes ☐ No ☐

If yes, Date admitted: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year) Date discharged: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Reason: *(check all that apply)* ☐ ACS ☐ VOC ☐ Non-Sickle Pain ☐ Other, specify _____

ADD

Have you been to the Emergency Department or "Day Hospital" since your last study visit? Yes ☐ No ☐

If yes, record date, reason and check the location (emergency department or day hospital).

Date of visit: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Location: ☐ Emergency Department ☐ Day Hospital

Reason: *(check all that apply)* ☐ ACS ☐ VOC ☐ Non-Sickle Pain ☐ Other, specify _____

ADD

Have you had any clinic visits ***for acute pain*** since the last study visit? Yes ☐ No ☐

If yes, record date of clinic visit: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

ADD

Have you been transfused? Yes ☐ No ☐

If yes, record date and number of units or cc's for each transfusion.

Date transfused: ☐☐ / ☐☐☐ / ☐☐ (Day / Month / Year)

Number of units: _____

OR

cc's for pediatrics: _____

ADD

Comprehensive Sickle Cell Centers	**Interim Health History**	

Item	Instructions
Questions	• Answer either 'Yes' of 'No' to each question on the page. Not sure may be recorded for the question about being unusually tired. • Each question relates to changes ***since the last study visit***.
Have you had any unusual headaches?	If 'Yes', choose the <u>one</u> choice that best describes the frequency of the headaches being experienced by the subject.
Have you taken any new medications?	If 'Yes', be sure to record each new medication on the Concomitant Medications form.
Have you had any Adverse Events?	If 'Yes', be sure to record each adverse event on the Adverse Events form.
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Interim Health History**	
Protocol # 1 **Arginine**		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

All questions relate to changes since the last study visit

Have you had leg ulcers? Yes ☐ No ☐

Have you had blood in the urine? Yes ☐ No ☐

Have you had any increase in problems with painful erections? Yes ☐ No ☐

Have you had a fever 101° or higher? Yes ☐ No ☐

Have you had vision problems? Yes ☐ No ☐

Have you had any problems with breathing, including asthma? Yes ☐ No ☐

Have you been unusually tired, or more tired than you usually are? Yes ☐ No ☐ Not sure ☐

Have you had any unusual headaches? Yes ☐ No ☐

If yes, frequency of headaches.

☐ Everyday ☐ 2-3 times/week ☐ Once a week ☐ More than once a week

Have you taken any new medications? Yes ☐ No ☐

If yes, add each to the CMED form.

Have you had any Adverse Events? Yes ☐ No ☐

If yes, add each to the AE form.

Comprehensive Sickle Cell Centers	**Discontinuation Checklist**	

Item	Instructions
Has the subject experienced any of the following events?	• Check all events that the subject experienced ***since the last study visit***. • If 'Other' is chosen, be sure to specify. **If you believe a subject should be discontinued, please contact Lori Styles @ Children's Hospital Oakland.*
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Discontinuation Checklist**	
Protocol # 1 **Arginine**	Date of Visit: ☐☐ / ☐☐☐ / ☐☐ Day Month Year	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Since the last visit, has the subject experienced any of the following events:

check all that apply

- ☐ Drop in hemoglobin below 5 gm/dL
- ☐ Pulmonary failure requiring intubation
- ☐ Hepatic dysfunction (SGPT $\geq$ 3X normal OR albumin $\leq$ 3.0)
- ☐ Renal dysfunction (Creatinine $\geq$ 1.4 for children, $\geq$ 1.6 for adults)
- ☐ Focal neurological changes
- ☐ Increase in methemoglobin level to > 2X normal level
- ☐ Apparent allergic reaction to arginine
- ☐ Episode of priapism requiring treatment
- ☐ Severe headache
- ☐ Pregnancy
- ☐ Episode of retinopathy requiring treatment
- ☐ Other Specify: _____

**** Please contact Lori Styles @ Children's Hospital Oakland if you believe this subject should be discontinued.***

Comprehensive Sickle Cell Centers	**Study Drug Record**	

Item	Instructions
Randomization Number	Record the correct randomization number for the subject. The pharmacist will give the randomization number.
Date	**Each time** pills are dispensed or returned, record the date in the dd/mmm/yy format (ex. 25SEP04).
# of Pills Returned / # of Pills Dispensed	• On the first day drug is dispensed the date should be recorded. For # returned, 0 should be entered. For number dispensed the number that was dispensed to the subject should be recorded. • For Visit 6 and Visit 7, along with the date, record the number returned and the number dispensed to the subject. • For Visit 8, along with the date, record the number returned and record 0 for the number dispensed. • Visit 3, 6, and 7 should all have the same number for “Number dispensed” since the subject will be receiving a fresh stock.
Add	Use the ‘Add’ button to record additional dispense or return dates.
Comment	Record any pertinent comments regarding each date if necessary.

Comprehensive Sickle Cell Centers	**Study Drug Record**	
Protocol # 1 **Arginine**	**Randomization Number:** ☐☐☐☐	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Each time that pills are dispensed or returned, record the date. The number of pills remaining is the number of pills left in the bottle(s) that the subject brought with him/her that day. The number of pills dispensed is the total of new pills plus the pills the subject returned.

Date **DD / MON / YY**	**# of Pills Returned**	**# of Pills Dispensed** **(on that day)**	**Comment**
☐☐ / ☐☐☐ / ☐☐ Day Month Year			

ADD

Comprehensive Sickle Cell Centers	**Concomitant Medications**	

Item	Instructions
Medication	• Record the ***generic*** name for each concurrent medication separately in the space provided. For multiple medications, click the 'Add' button to enter a new row of data. ***Hydroxyurea and Arginine require a 90 day washout period prior to study drug dosing.***
Indication	Record the indication for each medication.
Start date	Record start date in dd/mmm/yy format (25SEP04). Record the closest approximation for any portion of a date that is unknown.
Stop date	Record stop date in dd/mmm/yy format (25SEP04). Record the closest approximation for any portion of a date that is unknown. Leave stop date blank if medication is ongoing.
Ongoing	Check ongoing if the subject is currently taking the medication. Leave stop date blank.
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Concomitant Medications**	
CSCC Concomitant Medications Form		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

*Record all medications from baseline to termination of study. Include start dates prior to the study **only** if the medication continues to be taken at baseline visit.*

Medication	Indication	Start Date DD MON YY	Stop Date DD MON YY	Ongoing

Adverse Events

Item	Instructions
Serious Adverse Event	Check 'Yes' or 'No' to indicate if the adverse event was considered a serious adverse event. If yes, be sure to submit a SAE report.
Adverse Event	Record each adverse event separately in the space provided. For multiple events click the 'Add' button to enter a new row of data.
Onset date	Record the date the adverse event began using the dd/mmm/yy format (ex. 25SEP04). Month and year are required date parts. If day is unknown, please estimate.
Stop date	• Record the date the adverse event stopped using the dd/mmm/yy format (ex. 25SEP04). Month and year are required date parts. If day is unknown, please estimate. • If the adverse event is ongoing at the end of the study, leave the stop date blank. If the subject dies while an adverse event is ongoing, the stop date should be the date of death.
Outcome	• If adverse event is ongoing at end of study and subject is alive, outcome should be 3 (ongoing). • If adverse event is present at time of death, but did not contribute to subject's death, outcome should be 4. • If adverse event is present at time of death, and **did** contribute to subject's death, outcome should be 5.
Severity	Choose 1-5.
Relationship to study drug	Choose (1-5). ***Refer to section 11.2.2 of the protocol for additional information about relationship to study drug.***
Action(s) Taken	Check the action taken for each adverse event recorded. More than one box may be checked.
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Adverse Events**	
CSCC Adverse Events Form		CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Serious Adverse Event?	**Adverse Event**	**Onset Date** DD MON YY	**Stop Date** DD MON YY	**Outcome** 1=Resolved without sequelae 2=Resolved with sequelae 3=Ongoing 4=Present at death, not contributing to death 5=Death due to AE	**Severity** 1=Mild 2=Moderate 3=Severe 4=Life threatening 5=Death	**Relationship to Study Drug** 1=Unrelated 2= Probably not/ remote 3=Possibly related 4=Probably related 5=Definitely related	**Action(s) Taken** No action	Study drug interrupted	Study drug discontinued	Study drug dose adjusted	Medical intervention	Hospitalization
Yes ☐ Y No ☐ N												
Yes ☐ Y No ☐ N												
Yes ☐ Y No ☐ N												
Yes ☐ Y No ☐ N												
Yes ☐ Y No ☐ N												

Comprehensive Sickle Cell Centers	**Study Termination**	

Item	Instructions
Was the study blind broken for this subject?	• If 'Yes' is checked, record the date the blind was broken in the dd/mmm/yy format (ex. 25SEP04). Also, record the reason for the unblinding in the space provided. • If 'No' is checked, proceed to the next question.
Did the subject complete the study?	• If 'Yes', skip the rest of the page. • If 'No', record the date of last dose of study drug AND check one primary reason for study discontinuation. • If 'Adverse Event' is chosen, be sure to also check **all** adverse events that contributed to study discontinuation. • If 'Other' is chosen, be sure to specify.
Comments for page?	Record any pertinent comments for this page only.

Comprehensive Sickle Cell Centers	**Study Termination**	
Protocol # 1 **Arginine**	Date of Visit: ☐☐ / ☐☐☐ / ☐☐ Day Month Year	CSCC ID: ☐☐☐☐☐☐☐ Center code: ☐☐☐ Hospital code: ☐☐☐

Was the study blind broken for this subject? Yes ☐ No ☐

If yes, date blind broken: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Reason for unblinding: _____

Did the subject complete the study? Yes ☐ No ☐

If no, date of last dose of study drug: ☐☐ / ☐☐☐ / ☐☐
Day Month Year

Check **one** primary reason for study discontinuation:

- ☐ Adverse Event **(check all that apply)**
  - ☐ Drop in hemoglobin below 5 gm/dL
  - ☐ Pulmonary failure requiring intubation
  - ☐ Hepatic dysfunction (SGPT ≥ 3X normal OR albumin ≤ 3.0)
  - ☐ Renal dysfunction (Creatinine ≥ 1.4 for children, ≥ 1.6 for adults)
  - ☐ Focal neurological changes
  - ☐ Increase in methemoglobin level to > 2X normal level
  - ☐ Apparent allergic reaction to arginine
  - ☐ Episode of priapism requiring treatment
  - ☐ Severe headache
  - ☐ Other Specify: _____
- ☐ Pregnancy
- ☐ Non-compliance
- ☐ Withdrew consent
- ☐ Lost-to-follow-up
- ☐ Death
- ☐ Other Specify: _____

Source Documentation

Source documents are the original records, or source, from which data recorded on the Case Report Forms was obtained. For example, a lab report that provides information that is copied onto the Case Report Form (or into the "electronic case report form") is a source document. When source documents exist, they must be maintained in the participant's file, so that information on the Case Report Forms can be traced to, and verified from, the source.

In some instances, there is no separate source document. Examples include interviewer-administered questionnaires. In these cases, the data that is recorded on the Case Report Forms is also the source document.

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	CRF	Inclusion criteria and Exclusion criteria pages
Height, weight, gender, date of birth and sickle cell diagnosis	Medical Records	Demographics Page
Emergency Room, hospitalization and clinic visits	Medical Records and CRF	History of Hospital, Clinics and ED page, and Interim Health History page
Medications	Medical Records	Medication History page
Pain History	CRF	Pain History Page
Chemistry Labs	Lab results report	Chemistry Labs page
Hematology Labs	Lab results report	Hematology Labs page
Urinalysis	Lab results report	Urinalysis page
Pregnancy test	Medical records	Pregnancy Test page
ECG	ECG results report	Echocardiogram page
Check discontinuation criteria	Lab results report, medical records and CRF	Discontinuation Checklist page
Dispense medication	CRF	Study Drug Record page
Study termination	Lab results report, medical records and CRF	Study Termination page

Good Clinical Practice

Rho, inc.™

Basic Ethical Principles

- Respect for persons
  - Individuals should be treated as autonomous agents
  - Persons with diminished autonomy are entitled to protection
    - Capacity for self determination matures through life
    - Some lose this capacity through illness, mental disability or severely restricted liberty (prison)

Rho, inc.™

Basic Ethical Principles

- Beneficence
  - Do not harm
  - Maximize benefits while minimizing possible harms

Efforts taken to secure a subject's well being should go beyond strict obligation.

Rho, inc.™

Basic Ethical Principles

- Justice
  - "fairness in distribution"
  - Selection of research subjects needs to be scrutinized in order to determine whether some classes are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied

Rho, inc.™

1981: DHS and FDA Issue Regulations Based on Belmont

DHHS

- 45 CFR part 46 – Jan 16, 1981 – Protection of Human Subjects

FDA

- 21 CFR Part 50 – May 30, 1980 – Informed Consent
- 21 CFR Part 56 – Jan 27, 1981 – Institutional Review

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Elements of Informed Consent

1. A statement that the study involves research and;
   - Explains the purpose(s) of the research
   - Explains the expected duration of the subject's participation
   - Describes the procedures to be followed
   - Identifies all procedures which are experimental

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Elements of Informed Consent

2. A description of any reasonably foreseeable risks or discomfort to the subject
3. A description of any benefits to the subject or to others which may reasonably be expected from the research

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Elements of Informed Consent

4. A disclosure of appropriate alternative procedures or courses of treatment (if any) that might be advantageous to the subject
5. A statement describing the extent (if any) to which the confidentiality of records identifying the subject will be maintained and notes the possibility that the FDA may inspect records

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Elements of Informed Consent

6. In the event of injury, an explanation as to whether compensation and medical treatments are available, what they consist of, and where further information may be obtained

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Elements of Informed Consent

7. An explanation of whom to contact:
   - For answers to pertinent questions about the research
   - For answers to pertinent questions about the subject's rights
   - In the event of a research-related injury

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Elements of Informed Consent

8. A statement that participation is voluntary and that:
   - Refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled
   - The subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled

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CSCC PROTOCOL DEVIATION FORM

CSCC PROTOCOL: _____ IND NO: _____

CENTER NAME: _____ SUBJECT ID NUMBER: _____ _____

SUBJECT RANDOMIZED? ☐ **No** ☐ **Yes** ☐ **NA** STUDY DAY NUMBER: _____

Complete a new form for each deviation from the protocol.

Date of protocol deviation: _____ / _____ / ____ (MM/DD/YY)

Description of deviation from protocol:

_____

_____

Reason for deviation from protocol: _____

_____

_____

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? _____

What steps were taken to resolve this deviation and prevent recurrence?_____

_____

_____

COMPLETED BY (print and sign): _____

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

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

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

☐ **Site IRB** _____ / _____ / ____

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

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

CSCC Protocol Deviations

DEFINITION:
Protocol Deviations: 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
All deviations from the protocol must be addressed in study subject source documentation. 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.

Instructions for Documenting Deviations on Protocol Deviation Form

- Document protocol deviations as they occur.
- Include a description of the deviation, reason(s) it occurred and a corrective action plan to assure future protocol compliance.
- Complete a separate protocol deviation form for each occurrence.
- Investigator should sign form.
- Report all protocol deviations promptly to the SDMC Study Coordinator and to your 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 3 days
- Other deviations should be reported to the SDMC within 30 days of occurrence.

General Types of Typical Protocol Deviations

- Randomization errors
- Dosing errors
- Missed visits or mistimed visits
- Missed procedures
- Inclusion/Exclusion errors

CSCC PROTOCOL DEVIATION FORM

CSCC PROTOCOL: _Arginine_____ IND NO: _1234567_____

CENTER NAME: _ABC University_____ SUBJECT ID NUMBER: 999999_____

SUBJECT RANDOMIZED? ☐ **No** ☑ **Yes** ☐ **NA** STUDY DAY NUMBER: 18____

Complete a new form for each deviation from the protocol.

Date of protocol deviation: _03/ _14_ / _2004_ (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? _____

What steps were taken to resolve this deviation and prevent recurrence?_None_____

_____

_____

COMPLETED BY (print and sign): __Alice Lail_____

DATE: _03__ / _16__ / _2004_ (MM/DD/YY)

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

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

☐ **Site IRB** _____ / _____ / ____

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

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

CSCC PROTOCOL DEVIATION FORM

CSCC PROTOCOL: _*Arginine*_____ IND NO: _*1234567*_____

CENTER NAME: _*ABC University*_____ SUBJECT ID NUMBER: *888888*_____

SUBJECT RANDOMIZED? ☐ **No** ☑ **Yes** ☐ **NA** STUDY DAY NUMBER: *7*__

Complete a new form for each deviation from the protocol.

Date of protocol deviation: _*05*/ _*1*_ / _*2004*_ (MM/DD/YY)

Description of deviation from protocol: *Subject violated exclusion criteria. They were transfused on March 19, 2004 which is within 90 of enrollment.*__ _____

Reason for deviation from protocol: *Did not realize subject had been transfuse.d*_____

_____

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? _*In the annual report*_____

What steps were taken to resolve this deviation and prevent recurrence? _*None*__ _____

_____

_____

COMPLETED BY (print and sign): __*Alice Lail*_____

DATE: _*05*_ / _*15*__ / _*2004*_ (MM/DD/YY)

Investigator's Signature: ___*Signature here*____ _____ / _____ / ____ (MM/DD/YY)

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

☐ **Site IRB** ____ / _____ / ____

☐ **SDMC 919-408-0999** __*05*_ / __*15*_ / _*2004*_

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

CSCC PROTOCOL DEVIATION FORM

CSCC PROTOCOL: _*Arginine*_____ IND NO: _*1234567*__

CENTER NAME: _*ABC University*__ SUBJECT ID NUMBER: *777777*_____

SUBJECT RANDOMIZED? ☐ **No** ☑ **Yes** ☐ **NA** STUDY DAY NUMBER: 28___

Complete a new form for each deviation from the protocol.

Date of protocol deviation: _*04*/ _*08*_ / _*2004*_ (MM/DD/YY)

Description of deviation from protocol:*Subject was given twice the dose that they should have received*

_____.

Reason for deviation from protocol: *Pharmacy error*

_____

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? __*Immediately*

What steps were taken to resolve this deviation and prevent recurrence? _*Subject was removed from study. Dosing guidelines were reviewed with the pharmacist.*

_____

_____

COMPLETED BY (print and sign): __*Alice Lail*_____

DATE: _*04*__ / _*08*__ / _*2004*_ (MM/DD/YY)

Investigator's Signature: ___ *Signature here*____ _____ / _____ / ____ (MM/DD/YY)

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

☐ **Site IRB** __*04*_ / __*08*_ / _*2004*_

☐ **SDMC 919-408-0999** __*04*_ / __*08*_ / _*2004*_

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

Regulatory Requirements Check List

Requirements before drug can be shipped (Filed with SDMC.)

- FDA form 1572 (Anyone who has conduct with the study.)
- CV for everyone listed on the FDA form 1572 along with a copy of medical license for doctors
- Protocol signature page
- IRB approval letter for protocol
- IRB approved informed consent
- List of IRB composition
- Investigators' Documentation on Training on Protection of Human Subjects in Clinical Trials (NIH Standard) (http://69.5.4.33/c01/)

Requirements during the study

- Any protocol amendments along with IRB approval
- Any changes to the informed consent along with IRB approval
- Revised 1572 with any personnel changes
- CVs and medical licenses for any new study personnel
- Documentation of CTM shipments (Shipping invoices)
- Documentation of all relevant communications (letters, faxes, memos, e-mail, meeting notes and records of phone conversations).
- Signed informed consent forms for all subjects entered into the study
- Source documents (See other section)
- Notifications from Lori Styles or Rho, Inc. of new safety information
- Interim and/or annual reports to the IRB
- Subject identification code list
- CTM accountability

Requirements after the study (Retain at site after study completion)

- CTM accountability
- Documentation of CTM destruction
- Completed subject identification code list
- Final report to IRB (Send to SDMC)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014.
Expiration Date: January 31, 2006.
See OMB Statement on Reverse.

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED.

☒ CURRICULUM VITAE ☐ OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.

If more than one site, enter them all.

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.

Endocrine, Diabetes & Hypertension Division, EBRC-201
Brigham and Women's Hospital
221 Longwood Avenue
Boston, MA 02115

Children's Hospital Oakland Research Institute
5700 Martin Luther King Jr. Way
Oakland, CA 94609

Enter Local Lab Here

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).

6. NAMES OF THE SUBINVESTIGATORS *(e.g., research fellows, residents, associates)* WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.

Arginine Supplementation in Sickle Cell Anemia: Physiological and Prophylactic Effects

8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:

☐ FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

☒ FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach curriculum vitae or other statement of qualifications as described in Section 2.
3. Attach protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND).

10. SIGNATURE OF INVESTIGATOR	11. DATE

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please **DO NOT RETURN** this application to this address.

Informed Consent

The 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 the alternatives. Each patient must be informed that participation in the study is voluntary and 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. Please see the attached checklist for specific requirements for the Arginine Study informed consent.

A template for the consent and assent form is included in this section. These forms must be modified according to the requirements of each institution. Before submitting the informed consent to that site's Institutional Review Board (IRB), the consent must be approved by the Arginine Protocol Committee. A copy of the approved version must be provided to Rho after IRB approval, with any IRB requested changes highlighted.

Informed consent must be obtained from each patient at the first screening 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/guardian is stating that he/she understands the information and is voluntarily giving informed permission 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. This form should be read to the child if they are unable to read.

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

IRB Approval Process for Informed Consent Statements for the Arginine Study

The informed consent statement 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 patient 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 CSCC Statistics and Data Management Center (SDMC) will track forms through this process; sites will not be allowed to enroll study subjects or controls until they have completed this process.

Site Consent Form Approval Process

Step	Action	Status
1	The Arginine Protocol Team develops an informed consent template	Completed
2	The template is 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:
	  o do not satisfy the requirements on the checklist
	  o 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.	

SAMPLE ADULT SUBJECT INFORMATION AND CONSENT FORM

[Yellow Highlighting indicates where site-specific information is needed]

Study Title:	**Arginine Supplementation in Sickle Cell Anemia: Physiological and Prophylactic Effects**
Sponsor:	**National Heart, Lung and Blood Institute, National Institutes of Health**
Principal Investigator:	Insert Center PI Name Here
Office Address:	Insert PI Office address Here
24-Hour Phone:	Insert Contact Phone Number Here

INTRODUCTION

You are being asked to take part in a clinical research study because you have sickle cell disease. Clinical trials include only individuals who choose to take part. If you do not want to take part in the study, just tell the study doctor. Please take your time to make your decision. You may discuss this study with someone you trust. It is important that you understand what will be done and the possible risks to you, so please ask questions at anytime.

WHY IS THIS STUDY BEING DONE?

This study is being done to see if adding the amino acid Arginine to your diet has a beneficial effect on your disease and if it is safe to do so for an extended time period. Arginine is a normal part of the proteins that make up the body.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 96 sickle cell patients (48 children and 48 adults) will be participating in this study. The study will be conducted at approximately 10 sites around the United States.

WHAT IS INVOLVED IN THE STUDY?

You will be randomly assigned, like flipping a coin, into one of the following groups:

- Placebo (an inactive substance)
- Arginine, 0.05 g/kg/day (low dose)
- Arginine, 0.10 g/kg/day (high dose)

Neither you nor your study doctor will be able to choose or know what group you will be in. Your chances to be in any of the groups are one in three. If you agree to be part of this study you will receive study drug (Arginine or Placebo) by mouth for twelve weeks.

If you agree to take part in this study and sign this form, the following tests and procedures will be done:

Before the treatment begins (will occur in two visits):

- A medical history

- A physical exam including blood pressure and heart rate measurements
- A blood sample will be taken (about 6 teaspoons) for laboratory records
- A urine sample will be collected
- If you are a woman of childbearing potential, a pregnancy test will be performed.

If your study doctor determines that you can take part in this study, you will receive study drug and you will return for several visits over the next 12 weeks (3 months).

The following will be done weekly during the first four weeks of treatment:

- Medical exam
- An echocardiogram (only at Visit 3)
- A blood sample will be taken (about 6 teaspoons) for laboratory tests to see if the study drug is working and safe
- A urine sample will be collected

The following will be done after 8 weeks of treatment:

- Medical exam
- A blood sample will be taken (about 6 teaspoons) for laboratory tests to see if the study drug is working and safe
- A urine sample will be collected

The following will be done after 12 weeks of treatment (End of Treatment):

- Medical exam
- A blood sample will be taken (about 6 teaspoons) for laboratory tests to see if the study drug is working and safe
- A urine sample will be collected
- If the earlier echocardiogram was abnormal, an additional echo cardiogram will be performed.

The following will be done 2 weeks and 4 weeks after you take your last dose of study drug:

- Medical exam
- A blood sample will be taken (about 6 teaspoons) for laboratory tests to see if the study drug is working and safe
- A urine sample will be collected

HOW LONG WILL YOU BE IN THE STUDY?

Your participation in the study will last 20 weeks (5 months). This includes 4 weeks of pre-treatment testing, 12 weeks of treatment and 4 weeks of follow-up time (2 visits).

WHAT ARE THE RISKS OF THE STUDY?

Risks Associated with Arginine

Rare side effects reported with Arginine given by mouth include nausea, vomiting, and occasional headaches. Arginine has not been given to sickle cell patients for long periods of time so the long-term risks of Arginine in sickle cell patients are not known. There is a concern that Arginine might cause priapism (a painful erection that will not go down) or changes in the retina (make your vision worse) when given to sickle cell patients. However, this has not been seen in any sickle cell patients to

date. If you have a recent history of priapism or retinal disease requiring treatment tell your study doctor about it.

Risks Associated with the Echocardiogram
The echocardiogram uses ultrasound to look at your heart and blood vessels. This procedure is painless and has no side effects.

Risks Associated with the Blood Draw
During the study a total of 54 teaspoons of blood will be drawn from your vein. There are no risks associated with the volume of blood to be drawn but there are some risks associated with drawing blood. These include experiencing pain, bruising or swelling at the site.

Risks Associated with Other Drugs
Since the interaction between different drugs may be harmful, tell your study doctor about any drugs you are taking such as over-the-counter or prescription medication, or herbals.

In addition, the study drug and procedures may have unknown, unforeseen, or unanticipated side effects, which could be serious, long-lasting or permanent. All drugs have the risk of causing an allergic reaction that could be life-threatening. It is important that you report any and all symptoms or possible reactions to your study doctor.

If you become severely ill during the course of this study, the doctors will be able to find out if you are taking the drug or the placebo.

You will be informed in a timely manner of any new information that may affect your willingness to continue in the study.

REPRODUCTIVE RISKS FOR WOMEN OF CHILDBEARING AGE:

We do not know if the study drug, Arginine, may cause problems to an unborn baby or to a nursing infant. It is not known if the study drug is safe during pregnancy. If you are pregnant, or are currently breastfeeding, you may not be in this study. If you are a woman of childbearing age, you may be in the study only if you are not pregnant (as shown by a blood or urine test for pregnancy done before the study). You must also agree to either not have sex, or use an appropriate form of contraception for as long as you receive study drug. If you are unable to have children, this does not apply to you. If you become pregnant while in this study, you will be counseled and have the study drug stopped. In this case, you can no longer be in the study and you will be referred to a qualified doctor for appropriate care. That doctor will follow the progress of your pregnancy until the birth or termination of the pregnancy. You may ask one of the study staff about counseling or for information about preventing pregnancy.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

You may or you may not have a medical benefit, if you take part in this study. The information learned from this study may benefit research and other people with sickle cell disease in the future.

WHAT WILL YOU DO WITH MY *BLOOD* AT THE END OF THE STUDY?

Blood and fluid samples collected during the study will be labeled with a subject identification number and will not have your name, your initials or other identifiable information on them.

The record linking the subject identification number to your medical file will be kept confidential by the study doctor. The samples will be sent to different laboratories for testing as discussed under "What is involved in the study?".

Your blood will not be used for other research without your permission, although we may ask for your consent later.

WHAT OTHER OPTIONS ARE THERE?

Your participation in this study is voluntary. You may choose not to be in this study and receive the usual standard care for your disease.

WHAT ABOUT CONFIDENTIALITY?

The study research records will be kept confidential and you will not be identified in any written or verbal reports. No information that identifies you will be released without your written permission unless required by law. Your study records will identify you by a subject identification number. Any information that identifies you, including your tests, will not be shared with anyone else (including your spouse or family or health providers) without your written permission. If a research article or publication comes from this study, you will not be identified by name. The research records will be kept in a secured area and locked in a file cabinet in the research offices of the Principal Investigator. Research personnel authorized by the Principal Investigator will have access to these records.

Organizations that may look at your research records and medical records (including your identification), and copy your research records for quality control and data analysis include the National Heart, Lung, and Blood Institute (NHLBI; the sponsor of the study) and it's appointed Data and Safety Monitoring Board that will oversee this study, the US Food and Drug Administration (FDA), and other organizations involved in the research study including: [Include organizations that may have access to files]. Your information will also be reviewed by a representative of the Statistics and Data Management Center for NHLBI's Comprehensive Sickle Cell Center program at Rho, Inc. in Chapel Hill, NC, who will check for errors in the recording of your information. All of these groups are required to maintain confidentiality. As part of this process, copies of your research records (without your identification) may leave the Principal Investigator's office and be sent to these groups at other locations.

By signing this form you authorize access to your medical files to the organizations listed above for the duration of the study.

WHAT ARE THE COSTS?

There will be no added costs to you or your insurance company for procedures and medications that are part of this study. Costs of your clinical care that are not related to this research will be charged to you or your insurance company in the usual manner.

WHAT IF I AM INJURED OR BECOME ILL AS A RESULT OF BEING IN THIS STUDY?

If you are physically injured as a direct result of the study drug, the Institution shall provide medical treatment to you for that injury. The Sponsor (NHLBI) shall not pay for the treatment of medical complications that are part of the natural course of your main illness. NHLBI shall provide no other compensation of any type to any study subject. If you have any questions about compensation or medical treatments available to you in the event of an injury, you may contact Dr. _____ at _____. In the event a research-related injury should occur, you may contact Dr. _____ at _____.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Being in the study is entirely voluntary. You may decide not to be in the study or you may quit at any time. In either case, there will be no loss of benefits to which you are otherwise entitled. You have the right to ask as many questions as you want about the study. Your study doctor will answer your questions to the best of his/her ability. If you drop out of the study, all the data collected on you as part of the study will still be used to determine if arginine is beneficial and safe.

There may be reasons why you may not be able to be a part of this study even if you want to. The Principal Investigator, FDA, or the Sponsor (NHLBI) may stop your participation in the study at any time. You may also be taken out of the study without your agreement if (1) your health or safety is at risk by continuing to be in the study, (2) you have a serious side effect or complication related or unrelated to the study drug, or (3) for administrative reasons.

By signing this form, you are not giving up any legal rights to which you are otherwise entitled.

WILL I BE PAID FOR BEING IN THE STUDY?

You may receive up to $500 if you participate in the study to reimburse you for your time and travel expenses. [Fill in site-specific details here as desired].

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have any questions about the study or want to report an adverse reaction or illness, call the study doctor <Insert Name> at <Insert Telephone Number>.

If you believe that your rights as a research subject have been violated or if you have any questions about your rights as a research subject, contact the Committee on the Protection of the Rights of Human Subjects at 718 430-2237.

VOLUNTEER'S STATEMENT

I volunteer to be in a research study entitled**,** "Arginine Supplementation in Sickle Cell Anemia: Physiological and Prophylactic Effects ". I have been told that I may quit the study at any time and my care will not be affected.

I have been told that Dr. _____ at _____ is the doctor responsible for the study and for me as a research participant. If I have questions regarding the study or I experience an adverse event I can contact him/her at any time at XXX-XXX XXXX.

I have been told that the Committee on the Protection of the Rights of Human Subjects is responsible for overseeing the study. If I believe that my rights as a research subject have been violated or if I have any questions about my rights as a research subject, I may contact the Committee at any time at 718-430-3347.

I have been told about the tests, the benefits, and the risks. I have been told that I may contact the study staff if I have further questions.

This version of the informed consent replaces all versions that I may have previously signed. I will receive a copy of this consent form for my own information.

_____ _____
Signature of Study Participant Date

_____ _____
Printed Name of Participant Date

_____ _____
Signature of Witness Date

_____ _____
Printed Name of Witness Date

_____ _____
Signature of Investigator who Obtained Informed Consent Date

Principal Investigator: xxxxx, M.D.
Address
Weekday telephone number
24-hour phone number: (xxx) xxx-xxxx

SAMPLE CONSENT FORM FOR PARENTS OF STUDY SUBJECTS

[Yellow Highlighting indicates where site-specific information is needed]

Study Title:	**Arginine Supplementation in Sickle Cell Anemia: Physiological and Prophylactic Effects**
Sponsor:	**National Heart, Lung and Blood Institute, National Institutes of Health**
Principal Investigator:	Insert Center PI Name Here
Office Address:	Insert PI Office address Here
24-Hour Phone:	Insert Contact Phone Number Here

INTRODUCTION

Your child is being asked to take part in a clinical research study because he/she has sickle cell disease. Clinical trials include only individuals who choose to take part. If you do not want your child to take part in the study, just tell the study doctor. Please take your time to make your decision. You may discuss this study with someone you trust. It is important that you understand what will be done and the possible risks to your child, so please ask questions at anytime.

WHY IS THIS STUDY BEING DONE?

This study is being done to see if adding the amino acid Arginine to your child's diet has a beneficial effect on his/her disease and if it is safe to do so for an extended time period. Arginine is a normal part of the proteins that make up the body.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 96 sickle cell patients (48 children and 48 adults) will be participating in this study. The study will be conducted at approximately 10 sites around the United States.

WHAT IS INVOLVED IN THE STUDY?

Your child will be randomly assigned, like flipping a coin, into one of the following groups:

- Placebo (an inactive substance)
- Arginine, 0.05 g/kg/day (low dose)
- Arginine, 0.10 g/kg/day (high dose)

Neither you, your child, nor your study doctor will be able to choose or know what group you will be in. Your child's chances to be in any of the groups are one in three. If you agree to allow your child to be part of this study, your child will receive study drug (Arginine or Placebo) by mouth for twelve weeks.

If you agree to allow your child to take part in this study and you sign this form, the following tests and procedures will be done:

Before the treatment begins (will occur in two visits):

- A medical history
- A physical exam including blood pressure and heart rate measurements
- A blood sample will be taken (about 6 teaspoons) for laboratory records
- A urine sample will be collected
- If your child is a woman of childbearing age, a pregnancy test will be performed.

If your study doctor determines that your child can take part in this study, your child will receive study drug and you will return for several visits over the next 12 weeks (3 months).

The following will be done weekly during the first four weeks of treatment:

- Medical exam
- An echocardiogram (Only at Visit 3)
- A blood sample will be taken (about 6 teaspoons) for laboratory tests to see if the study drug is working and safe
- A urine sample will be collected

The following will be done after 8 weeks of treatment:

- Medical exam
- A blood sample will be taken (about 6 teaspoons) for laboratory tests to see if the study drug is working and safe
- A urine sample will be collected

The following will be done after 12 weeks of treatment (End of Treatment):

- Medical exam
- A blood sample will be taken (about 6 teaspoons) for laboratory tests to see if the study drug is working and safe
- A urine sample will be collected
- If the earlier echocardiogram was abnormal, an additional echocardiogram will be performed.

The following will be done 2 weeks and 4 weeks after your child takes the last dose of study drug:

- Medical exam
- A blood sample will be taken (about 6 teaspoons) for laboratory tests to see if the study drug is working and safe
- A urine sample will be collected

HOW LONG WILL YOUR CHILD BE IN THE STUDY?

Your child's participation in the study will last 20 weeks (5 months). This includes 4 weeks of pre-treatment testing, 12 weeks of treatment and 4 weeks of follow-up time (2 visits).

WHAT ARE THE RISKS OF THE STUDY?

Risks Associated with Arginine

Rare side effects reported with Arginine given by mouth include nausea, vomiting, and occasional headaches. Arginine has not been given to sickle cell patients for long periods of time so the long-term risks of Arginine in sickle cell patients are not known. There is a concern that Arginine might cause priapism (a painful erection

that will not go down) or changes in the retina (make your vision worse) when given to sickle cell patients. However, this has not been seen in any sickle cell patients to date. If your child has a recent history of priapism or retinal disease requiring treatment, please tell your study doctor about it.

Risks Associated with the Echocardiogram
The echocardiogram uses ultrasound to look at your heart and blood vessels. This procedure is painless and has no side effects.

Risks Associated with the Blood Draw
During the study a total of 54 teaspoons of blood will be drawn from your child's vein. There are no risks associated with the volume of blood to be drawn but there are some risks associated with drawing blood. These include experiencing pain, bruising or swelling at the site.

Risks Associated with Other Drugs
Since the interaction between different drugs may be harmful, tell your study doctor about any drugs your child is taking such as over-the-counter or prescription medication, or herbals.

In addition, the study drug and procedures may have unknown, unforeseen, or unanticipated side effects, which could be serious, long-lasting or permanent. All drugs have the risk of causing an allergic reaction that could be life-threatening. It is important that you report any and all symptoms or possible reactions your child experiences to your study doctor.

If you become severely ill during the course of this study, the doctors will be able to find out if your child is taking the drug or the placebo.

You will be informed in a timely manner of any new information that may affect your willingness to allow your child to continue in the study.

REPRODUCTIVE RISKS FOR WOMEN OF CHILDBEARING AGE:

We do not know if the study drug, Arginine, may cause problems to an unborn baby or to a nursing infant. It is not known if the study drug is safe during pregnancy. If your child is pregnant, or is currently breastfeeding, your child may not be in this study. If your child is a woman of childbearing age, she may be in the study only if she is not pregnant (as shown by a blood or urine test for pregnancy done before the study). She must also agree to either not have sex, or use an appropriate form of contraception for as long as she receives study drug. If she is unable to have children, this does not apply to her. If your child becomes pregnant while in this study, she will be counseled and have the study drug stopped. In this case, she can no longer be in the study and she will be referred to a qualified doctor for appropriate care. That doctor will follow the progress of your child's pregnancy until the birth or termination of the pregnancy. You may ask one of the study staff about counseling or for information about preventing pregnancy.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Your child may or may not have a medical benefit, if he/she takes part in this study. The information learned from this study may benefit research and other people with sickle cell disease in the future.

WHAT WILL YOU DO WITH MY *BLOOD* AT THE END OF THE STUDY?

Blood and fluid samples collected during the study will be labeled with a subject identification number and will not have your child's name, initials or other identifiable information on them.

The record linking the subject identification number to your child's medical file will be kept confidential by the study doctor. The samples will be sent to different laboratories for testing as discussed under "What is involved in the study?".

Your child's blood will not be used for other research without your permission, although we may ask for your consent later.

WHAT OTHER OPTIONS ARE THERE?

Your child's participation in this study is voluntary. You may choose not to be in this study and receive the usual standard care for your disease.

WHAT ABOUT CONFIDENTIALITY?

The study research records will be kept confidential and your child will not be identified in any written or verbal reports. No information that identifies your child will be released without your written permission unless required by law. Your child's study records will identify your child by a subject identification number. Any information that identifies your child, including your child's tests, will not be shared with anyone else (including healthcare providers) without your written permission. If a research article or publication comes from this study, your child will not be identified by name. The research records will be kept in a secured area and locked in a file cabinet in the research offices of the Principal Investigator. Research personnel authorized by the Principal Investigator will have access to these records.

Organizations that may look at your child's research records and medical records (including your child's identification), and copy your child's research records for quality control and data analysis include the National Heart, Lung, and Blood Institute (NHLBI; the sponsor of the study) and it's appointed Data and Safety Monitoring Board that will oversee this study, the US Food and Drug Administration (FDA), and other organizations involved in the research study including: [Include organizations that may have access to files]. Your child's information will also be reviewed by a representative of the Statistics and Data Management Center for NHLBI's Comprehensive Sickle Cell Center program at Rho, Inc. in Chapel Hill, NC, who will check for errors in the recording of your child's information. All of these groups are required to maintain confidentiality. As part of this process, copies of your child's research records (without your child's identification) may leave the Principal Investigator's office and be sent to these groups at other locations.

By signing this form you authorize access to your child's medical files to the organizations listed above for the duration of the study.

WHAT ARE THE COSTS?

There will be no added costs to you or your insurance company for procedures and medications that are part of this study. Costs of your child's clinical care that are

not related to this research will be charged to you or your insurance company in the usual manner.

WHAT IF MY CHILD IS INJURED OR BECOMES ILL AS A RESULT OF BEING IN THIS STUDY?

If your child is physically injured as a direct result of the study drug, the Institution shall provide medical treatment to you for that injury. The Sponsor (NHLBI) shall not pay for the treatment of medical complications that are part of the natural course of your child's main illness. NHLBI shall provide no other compensation of any type to any study subject. If you have any questions about compensation or medical treatments available to you in the event of an injury, you may contact Dr. _____ at _____. In the event a research-related injury should occur, you may contact Dr. _____ at _____.

WHAT ARE MY CHILD'S RIGHTS AS A PARTICIPANT?

Being in the study is entirely voluntary. You may decide not to allow your child to be in the study or your child may quit at any time. In either case, there will be no loss of benefits to which you or your child are otherwise entitled. You have the right to ask as many questions as you want about the study. Your study doctor will answer your questions to the best of his/her ability. If your child drops out of the study, all the data collected on your child as part of the study will still be used to determine if arginine is beneficial and safe.

There may be reasons why your child may not be able to be a part of this study even if you want him or her to. The Principal Investigator, FDA, or the Sponsor (NHLBI) may stop your child's participation in the study at any time. Your child may also be taken out of the study without your agreement if (1) his/her health or safety is at risk by continuing to be in the study, (2) he/she has a serious side effect or complication related or unrelated to the study drug, or (3) for administrative reasons.

By signing this form, you are not giving up any legal rights to which you or your child are otherwise entitled.

WILL I BE PAID FOR BEING IN THE STUDY?

You may receive up to $500 if your child participates in the study to reimburse you for your time and travel expenses. [Fill in site-specific details here as desired].

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have any questions about the study or want to report an adverse reaction or illness, call the study doctor <Insert Name> at <Insert Telephone Number>.

If you believe that your child's rights as a research subject have been violated or if you have any questions about your child's rights as a research subject, contact the Committee on the Protection of the Rights of Human Subjects at 718 430-2237.

VOLUNTEER'S STATEMENT

I grant permission for my child to be in a research study entitled**,** "Arginine Supplementation in Sickle Cell Anemia: Physiological and Prophylactic Effects ". I have been told that my child may quit the study at any time and his/her care will not be affected.

I have been told that Dr. _____ at _____ is the doctor responsible for the study and for my child as a research participant. If I have questions regarding the study or my child experiences an adverse event I can contact him/her at any time at XXX-XXX XXXX.

I have been told that the Committee on the Protection of the Rights of Human Subjects is responsible for overseeing the study. If I believe that my child's rights as a research subject have been violated, or if I have any questions about my child's rights as a research subject, I may contact the Committee at any time at 718-430-3347.

I have been told about the tests, the benefits, and the risks. I have been told that I may contact the study staff if I have further questions.

This version of the parental consent replaces all versions that I may have previously signed. I will receive a copy of this consent form for my own information.

_____ _____
Signature of Study Participant's Parent Date

_____ _____
Printed Name of Participant's Parent Date

_____ _____
Signature of Witness Date

_____ _____
Printed Name of Witness Date

_____ _____
Signature of Investigator who Obtained Informed Consent Date

Principal Investigator: xxxxx, M.D.
Address
Weekday telephone number
24-hour phone number: (xxx) xxx-xxxx

Arginine Supplementation in Sickle Cell Anemia:
Physiological and Prophylactic Effects
Assent Form

Introduction

You are being asked to take part in a research study because you have sickle cell disease. You don't have to be in this study if you don't want to. This is your decision to make. You can take as much time as you need to think about it. You can tell the study doctor that you do not want to be in the study. No one will be upset or mad at you if you say no. If you decide that you want to be in this study, there are things that you will have to do. We will explain these things. Please ask us any questions that you have.

Why is this study being done?

This study is being done to see if adding something to your diet (what you eat) will help your sickle cell disease. We want to see if it is okay to add this to your diet over a certain period of time.

How many people will be in this study?

Many children and adults will be in this study. The study will take place all over the country.

What will you have to do for the study?

You will be put into one of three groups. One group will get a pill to take that will not help or hurt them. Another group will get a pill with the stuff that we hope will help them in it. The last group will get a pill that has more of the stuff that we hope will help them in it. We do not know what group you will be in. You will not know either if you are in the study. If you are in the study, you will take a pill every day for three months.

Before you start taking the pill, several things will happen. A doctor will examine you and will ask you about your disease. We will do a test to look at your heart. This test will not hurt. You will have to have a little bit of blood drawn. This is so that we can if the study drug is working and is safe. Having your blood drawn may hurt a little and give you a bruise on your arm, but it will go away. You will also have to go to the bathroom in a cup.

If the doctor says that you can be in the study, you will get the pill to take. You will also come back to the treatment center several times for visits. At these visits, a doctor will examine you again. You will also have to have a little bit of blood drawn and will have to go to the bathroom in a cup again. We may also want to do the test where we look at your heart once more.

How long will you be in the study?

The study will last about 5 months (20 weeks). You will take the pill for 3 months. There is a month after that where we see how you are doing.

Will this study hurt you?
There is a chance that the pill you take may make you feel sick to your stomach or make your head hurt. There is also a chance that it will affect the eyes of people who have sickle cell disease. Tell your doctor if you have had any problem with your eyes before.

The test to look at your heart will not hurt you and will not make you feel bad afterwards. A device like a video camera is held up to your chest so that we can see your heart moving.

Having your blood drawn may hurt a little and give you a bruise on your arm, but it will go away.

Tell your doctor if there are any other medicines that you take. The pill that you take for the study may change how you feel or make you feel bad. If it does, be sure to tell your doctor.

Will this study help you?
There is a chance that the pill you take may make you have less painful sickle cell crises. What the doctors learn from the study may help other people with sickle cell disease.

Do I have to do this?
You do not have to be in this study if you do not want to. No one will be upset or mad if you decide you don't want to do this. Your doctor will still treat you the same whether you are in the study or not.

Your information will be kept secret:
Everything that you say and everything that is said about you will be kept private. To keep it that way, you will have a number that will be put on all of your forms instead of your name. All of the information that is collected about you will be put together with the information from other children. No one will be able to tell what any one child said or did.

We hope that you will want to be in this study. You can ask us any questions you want to about the study to decide whether or not you want to be in it.

Would you like to be in the study?

____ Yes **____ No**

_____ _____
Child's Name Date

_____ _____
Center Director or Study Coordinator Date

Confidentiality and Security

Patient Confidentiality

As in all medical research projects, Arginine Study personnel 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.

- Arginine Study participants provide us with very personal 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 Arginine Study 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.

- The SDMC will not have identifying information on each subject, like their name and address, only the CSCC subject identification code.

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 Arginine 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 Arginine Study analysis datasets format (SAS datasets). Displays of their data will be sent to the Centers to confirm the data have been incorporated.

X. Site Visits

The Clinical Research Associate (CRA) will perform Interim Monitoring Visits in accordance with protocol specific requirements, Title 21 of the CFR, other applicable regulatory requirements, ICH/GCP guidelines, and the Rho, Inc. SOP CO 508: Interim Site Monitoring Visit.

The CRA from the Statistics and Data Management Center will make at least one visit to each site during the study. The CRA will provide a schedule of planned interim monitoring visits to the SDMC Study Coordinator for this study. In addition, this schedule will also be posted on the CSCC website. Additional monitoring visits will be conducted as necessary. The Interim Monitoring Report will be used to document the outcome of these visits.

Before each interim monitoring visit, the CRA will contact the SDMC Study Coordinator to determine if any special requirements/issues need to be addressed during that visit.

The CRA will send confirmation and follow-up letters to each site in conjunction with these visits. Confirmation letters should request that all necessary study related personnel be available, a workspace secured, and that all study related documents be available for all patients.

The CRA will conduct 100% review of the following:

- Selected EDC data elements (100% source verification of all pre-defined key data points)
- Informed consents
- Documentation to ensure that appropriate AE/SAE reporting procedures are being followed

The CRA will confirm that the following information for all subjects is present in the source documents and that the data on the CRFs are consistent with the following, <u>but not limited to</u>:

- Medical notes/source documents exist for each subject
- Sex and date of birth are verified from the medical record
- Documentation of diagnosis of Hb SS or SB°
- Verify that the subject and site staff properly signed and dated the correct version of the informed consent form
- A statement is present in the medical record that documents the date subject entered the clinical trial
- Confirm that the subject meets the inclusion/exclusion criteria
- Information concerning all adverse experiences
- Current therapy or concurrent medication
- Laboratory Data
- Confirm all SAEs were reported to the site IRB.
- Ensure that proper randomization procedures were followed
- Review and discuss enrollment and retention
- Review and discuss data management issues
- Discuss any site-specific issues, problems, or suggestions

Arginine Study SAE Reporting Procedure

What Is An Adverse Event?

- An adverse event is any undesirable sign, symptom or medical condition (including out of range laboratories) occurring once the consent form has been signed (Visit 1 – First Screening Visit) even if the event is not considered to be related to study drug.

Adverse Event Reporting

- Each adverse event should be entered onto its own line in the case report form (CRF).
- If the adverse event is serious then the serious box should be checked and a serious adverse event (SAE) form should be filled out.
- Enter the DIAGNOSIS or Medical conditions/disease in the adverse event form (eg. Influenza instead of each symptom – runny nose, fever, cough, etc.).

Adverse Event Must Haves

- Duration (start and end dates, if known)
- Outcome (Resolved without sequelae, Resolved with sequelae, Ongoing, Present at death and Death due to AE).
- Severity grade (1 – 5 with 1 being mild and 5 being death)
- Relationship to study drug (1 – 5 with 1 being unrelated and 5 being definitely related.
- Action taken – Check all that apply

Adverse Event Reporting

- Medical conditions/diseases present BEFORE starting study treatment will be considered adverse events if they worsen after starting the study (Visit 1).
- AEs during the screening phase should be captured. We will filter them out later.

Serious Adverse Event Definition

A SAE is defined as an undesirable sign, symptoms or medical condition which:

- Is fatal or life-threatening
- Requires or prolongs hospitalization
- Results in persistent or significant disability/incapacity

Serious Adverse Event Definition

- Constitutes a congenital anomaly or a birth defect
- Is medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.
- Is serious in the opinion of the investigator.

Serious Adverse Event Reporting - Pregnancy

Pregnancy is not itself a serious adverse event, however, it will be reported as a serious adverse event on the case report form and followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and presence or absence of any birth defects or congenital abnormalities.

Serious Adverse Events – Expected Events

The following are examples expected adverse events:

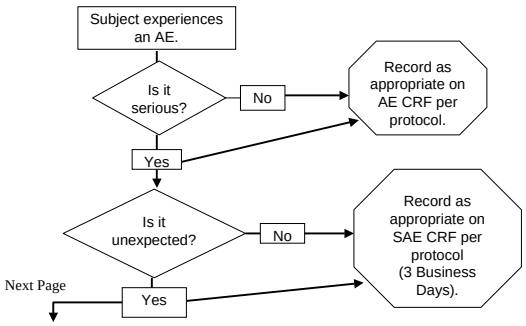
•Acute chest syndrome

•Aplastic crisis

•Pain, joint

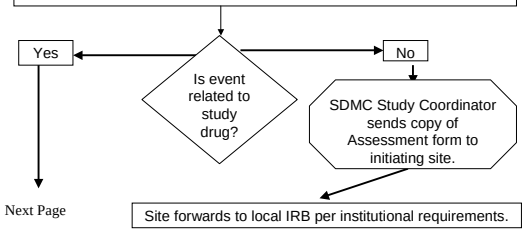
See protocol for a complete list.

SAE Reporting Procedure

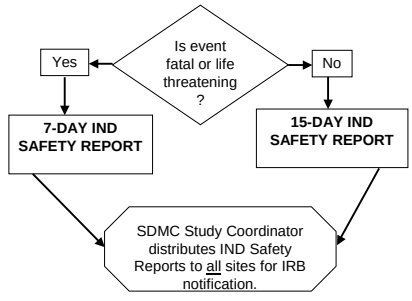


SAE Reporting Procedure

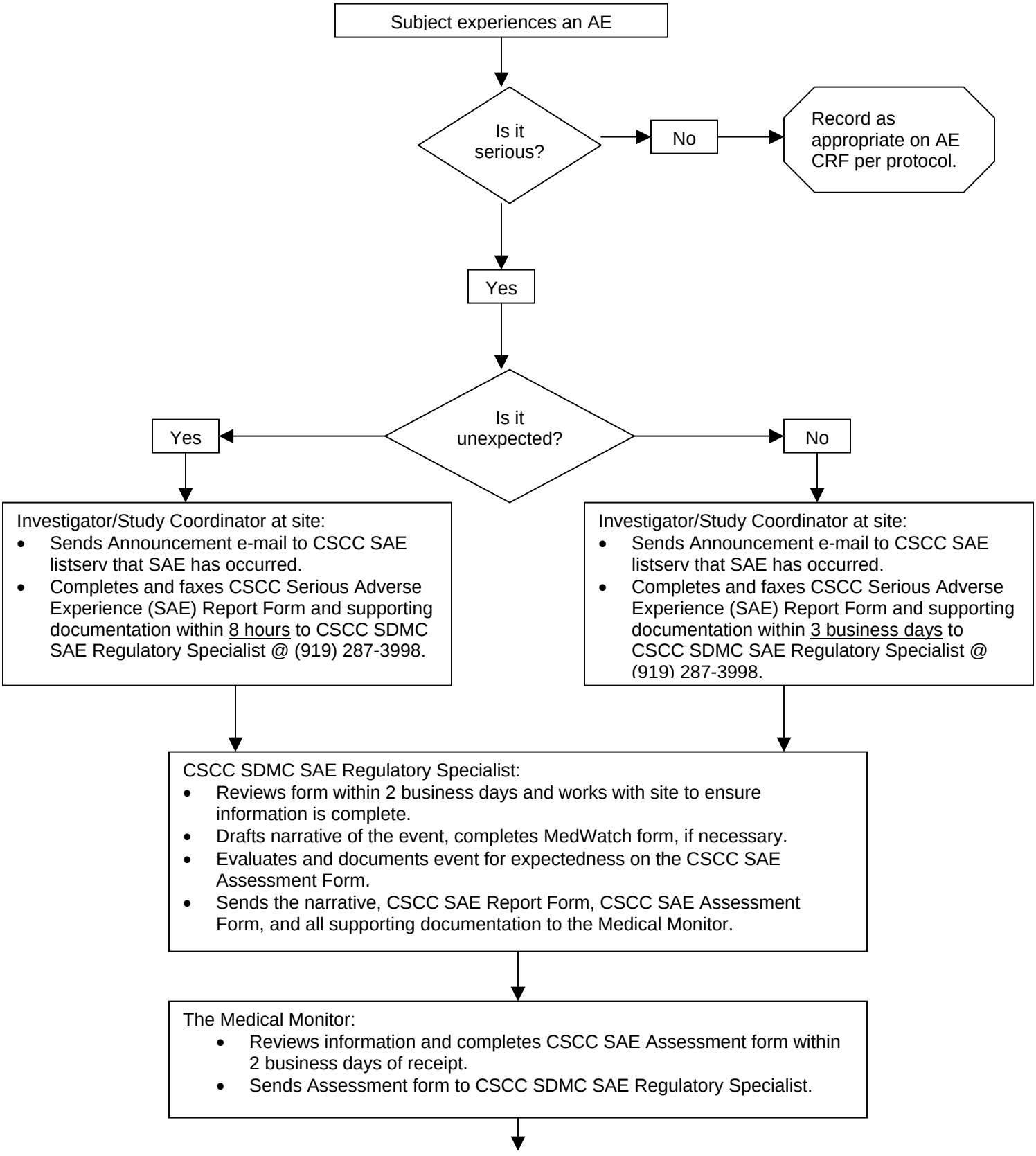
Principal Investigator at Site:
- Completes and faxes CSCC Serious Adverse Event (SAE) report and supporting documentation within 8 hours to RhoFed SDMC @ (919) 287-3998
- Sends Announcement E-mail to the CSCC SAE listserv (argininesae@RhoWorld.com) that an SAE occurred.

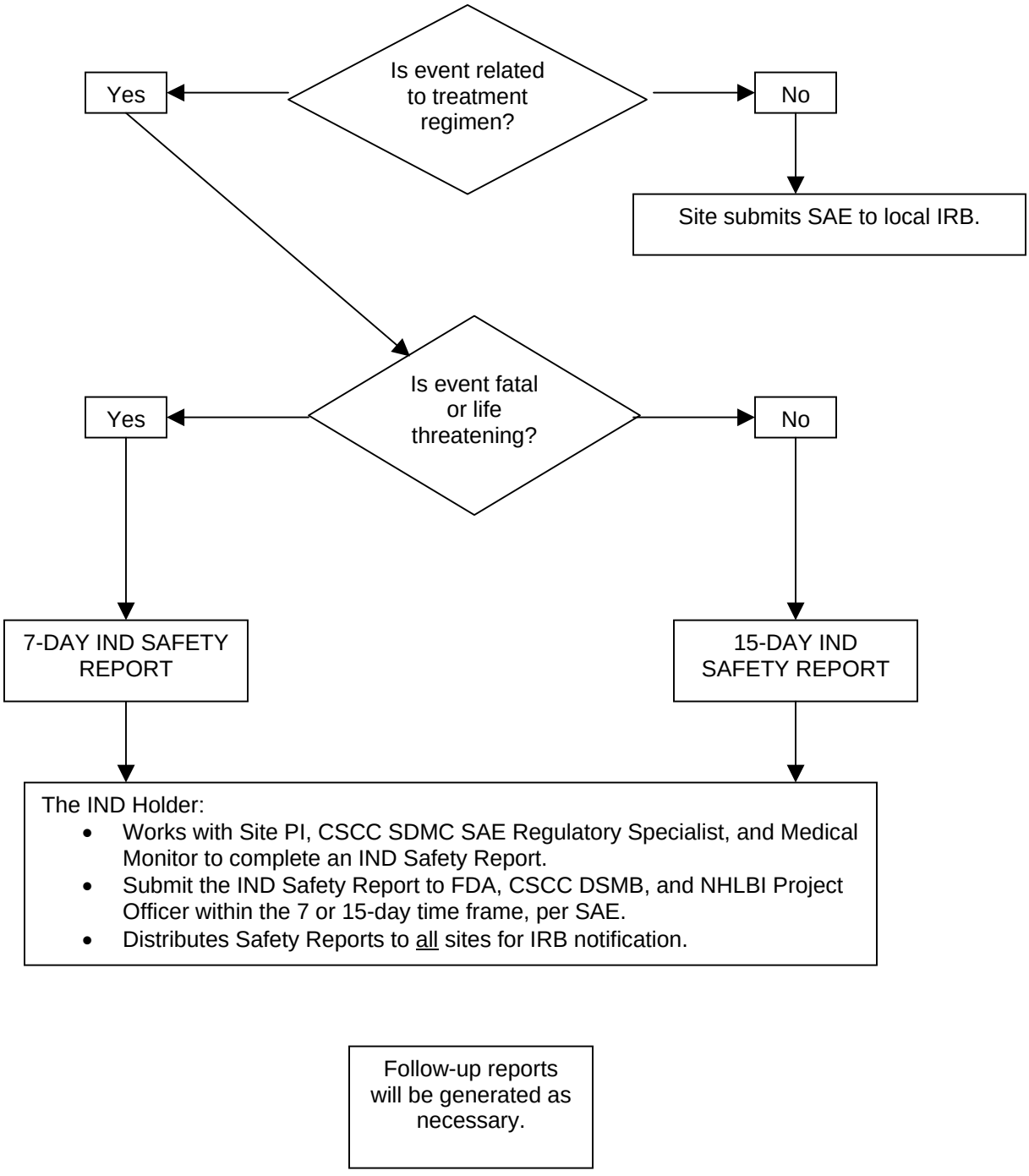


SAE Reporting Procedure



CSCC ARGININE SDMC
SERIOUS ADVERSE EXPERIENCE (SAE) REPORTING FLOW





Every 3 Months
•MedDRA: code everything
•All SAEs

Every 6 Months
•Report to DSMB
•SAEs
•AEs
•Labs

☐ Initial Report
☐ Follow-up Report

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CSCC ID: | | | | | | | |

Center code: | | |

Hospital code: | | |

SERIOUS ADVERSE EXPERIENCE REPORT

"Arginine Supplementation in Sickle Cell Anemia: Physiological and Prophylactic Effects"

Report Date (DD/MMM/YYYY)

Site Name: _____ _____/_____/_____

Subject's Age in Years:_____

Subject's Weight: ___ ___ ___ o lbs./ kgs. Subject's Gender: ☐ Male ☐ Female

Please indicate SAE category from the following choices:

☐ Death
☐ Immediately Life-Threatening
☐ Persistent/Significant Disability/Incapacity
☐ Hospitalization/Prolonged Hospitalization
☐ Congenital Anomaly/Birth Defect
☐ Serious as assessed by the Investigator

STUDY PRODUCT DATA

Complete the Table below.

Study Product Name	Dose, Route, Schedule of Study Product(s) at SAE Onset	Date Study Product First Started (DD/MMM/YYYY)	Date Study Product Last Taken (DD/MMM/YYYY)
Arginine/ Placebo			

Event (Keyword or Cause of Death)	Date of Onset (DD/MMM/YYYY)	Severity	Relationship to Study Product	If NOT RELATED, is the event related to:
_____	____/_____/_____	☐ Grade 1 (Mild) ☐ Grade 2 (Moderate) ☐ Grade 3 (Severe) ☐ Grade 4 (Life-Threatening) ☐ Grade 5 (Death)	☐ Unrelated ☐ Probably not/Remote ☐ Possibly ☐ Probably ☐ Definitely	☐ study procedure? specify_____ ☐ other condition/illness? specify_____ ☐ other drug? specify_____

Study Product Status (as a result of the event described above)	Subject Status/Outcome
☐ Study Product Administration Complete ☐ Study Product Administration Continuing ☐ Study Product Administration Deferred ☐ Dose Adjust, *specify*: _____ _____ ☐ Participation terminated by Investigator ☐ Other, *specify:* _____	☐ Ongoing ☐ Resolved without sequelae Date ____/_____/_____ (DD/MMM/YYYY) ☐ Resolved with sequelae Date_____/_____/_____ (DD/MMM/YYYY) State sequelae: _____ ☐ Death Autopsy: ☐ Not Done ☐ Done (Provide Report) ☐ Planned ☐ Status Unknown

☐ Initial Report
☐ Follow-up Report

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CSCC ID: | | | | | | | |

Center code: | | | |

Hospital code: | | | |

SERIOUS ADVERSE EXPERIENCE REPORT

"Arginine Supplementation in Sickle Cell Anemia: Physiological and Prophylactic Effects"

Report Date (DD/MMM/YYYY)

Site Name: _____ _____/_____/_____

EVENT SUMMARY

Include clinical history of event, associated signs and symptoms, alternative etiologies being considered, medical management and relevant past medical history below, or attach summary (Use additional pages if necessary.)

LABORATORY TESTS (EX: CBC, Chemistry)

List relevant abnormal lab results AND attach copies of the lab results AND indicate pertinent results on the copy. (Use additional pages if necessary.)

Test	Collection Date (DD/MMM/YYYY)	Abnormal Result	Normal Range	Lab Value Previous to this SAE	Collection Date

DIAGNOSTIC TESTS (EX: MRI, CT Scan, Ultrasound)

List abnormal diagnostic test results AND attach copies of the diagnostic results AND indicate pertinent results on the copy. (Use additional pages if necessary.)

Test	Date Performed (DD/MMM/YYYY)	Results/Comments

☐ Initial Report
☐ Follow-up Report

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CSCC ID: | | | | | | | |

Center code: | | |

Hospital code: | | |

SERIOUS ADVERSE EXPERIENCE REPORT

"Arginine Supplementation in Sickle Cell Anemia: Physiological and Prophylactic Effects"

Report Date (DD/MMM/YYYY)

Site Name: _____ _____/_____/_____

CONCOMITANT MEDICATIONS

☐ No relevant concomitant medications

List relevant concomitant medications the subject was taking up to 1 month prior to SAE onset. If the subject was taking more than 6 medications, please make additional copies of this form and report all concomitant medications.

Medication	Start Date	Stop Date	Dose	Indication	Suspect
1.	____/_____/_____ DD/MMM/YYYY	____/_____/_____ DD/MMM/YYYY	☐ Unknown		☐ Yes ☐ No
2.	____/_____/_____ DD/MMM/YYYY	____/_____/_____ DD/MMM/YYYY	☐ Unknown		☐ Yes ☐ No
3.	____/_____/_____ DD/MMM/YYYY	____/_____/_____ DD/MMM/YYYY	☐ Unknown		☐ Yes ☐ No
4.	____/_____/_____ DD/MMM/YYYY	____/_____/_____ DD/MMM/YYYY	☐ Unknown		☐ Yes ☐ No
5.	____/_____/_____ DD/MMM/YYYY	____/_____/_____ DD/MMM/YYYY	☐ Unknown		☐ Yes ☐ No
6.	____/_____/_____ DD/MMM/YYYY	____/_____/_____ DD/MMM/YYYY	☐ Unknown		☐ Yes ☐ No

Completed by (signature): _____ Completed by (print): _____ Date: __/__/____

Investigator(signature): _____ Investigator (print): _____ Date: __/__/____

Date Submitted/Faxed To:	(DD/MMM/YYYY)	
☐ Local IRB:	____ / ____ / _____	☐ Not Applicable
☐ CSCC SDMC SAE Regulatory Specialist:	____ / ____ / _____	☐ Not Applicable
☐ CSCC – DSMB:	____ / ____ / _____	☐ Not Applicable
☐ Other, *specify:*_____	____ / ____ / _____	☐ Not Applicable

CSCC SERIOUS ADVERSE EXPERIENCE REPORT FORM COMPLETION GUIDELINES FOR Arginine Study

"Arginine Supplementation in Sickle Cell Anemia:
Physiological and Prophylactic Effects"

1.0 Definitions

1.1 Adverse Experience:

An adverse experience, as defined for this study, is any untoward medical occurrence in a patient of 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 temporarily associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (ICH, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, 1994).

1.2 Serious Adverse Experience:

Complete the CSCC Serious Adverse Experience (SAE) Report Form when a subject participating in the Arginine study experiences an adverse event that:

- Results in death;
- Is life-threatening (i.e., an experience in which the subject was at risk of death at the time of event; it does not refer to an experience 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; or
- Results in a congenital anomaly/ birth defect.

In the opinion of the Investigator, important medical experiences that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above may be considered serious. Examples of such experiences are intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. (ICH, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, 1994 and 21 CFR 312.32).

The SAE must be reported regardless of whether the SAE is deemed related to the use of the treatment regimen.

1.3 Treatment Regimen:

For this study, the treatment regimen includes all doses of arginine or placebo administered to a study subject during the 20-week study period.

2.0 SAE Reporting Time Period

All SAEs occurring after informed consent is obtained through **30 days** after the last dose of the treatment regimen must be recorded on the Adverse Event CRF in addition to reporting the event as a SAE. Any SAE ongoing 30 days after the last dose of the treatment regimen must be followed to resolution or until stable.

2.1 Adverse Experience Follow-Up

All AEs occurring after informed consent is obtained, all untoward medical events will be documented as AEs throughout the study treatment period. AEs occurring within **30 days** after discontinuation of the treatment regimen will also be collected. Adverse events will be monitored with relevant clinical assessments as determined by the Investigator. The Investigator will also determine the outcome of the event, which is defined as the outcome of the reaction/event at the time of the last observation. Outcome will be described as:

- Ongoing
- Resolved without sequelae
- Resolved with sequelae
- Death

Any unresolved AE or SAE that is considered to be related to study drug will be followed as clinically indicated until its resolution, or, if non-resolving, until considered stable. Subjects who become pregnant while on the treatment regimen will be instructed to discontinue study product and will be followed until birth or termination of pregnancy.

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

2.2 General Instructions:

1. Complete all fields/boxes on the SAE form.
2. It is important to provide as much information as possible on the initial SAE report.
3. **If not all information is available at the time the initial SAE report is completed, please provide the CSCC ID, Center Code, Hospital Code, Site Name, Report Date, SAE Category, Study Product Data, Event Name, Date of Onset, and Relationship of the event to the treatment regimen.**
4. Write legibly.
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 follow-up.
7. **Note:** The Protocol Chair, Lori Styles, must be consulted prior to permanent premature discontinuation of study medication.

2.3 Initial Report

1. Check the Initial Report box, located in the upper left corner, on all three pages of the SAE form.
2. Enter the CSCC ID, Center Code, Hospital Code, Site Name, and the Report Date on all three pages of the SAE form.
3. Enter the subject's age in years, gender, and weight.
4. **SAE category:** check all that apply.
5. **Study Product Data:** enter only the dose that the subject received at the onset of the event (i.e. the number of pills per day). Enter the date the subject was administered the first dose of study product and enter the date the product was last administered prior to the event's date of onset. If the patient was not randomized record that the patient did not receive study drug and N/A for the date fields.
6. **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). Only report one SAE per SAE Report Form.
7. **Date of Onset:** provide the date that the SAE event began. Record the date that the event became serious.
8. **Severity:** check one box only.
9. **Relationship:** check one box only. If the event is not related to study product administration, indicate if the event was related to another condition, drug, or procedure.
10. **Study Product Status:** check one box only. 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 other course of action was utilized, please specify.
11. **Subject Status/Outcome:** check on box only. 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.)
12. **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. Provide any medical history that is relevant to the event. **Be sure to include the site number and the subject ID number on all supporting documentation. Delete or**

completely obscure all personal information (name, subject initials, medical record number, etc.).

13. **Laboratory Tests:** include relevant abnormal lab results that contribute to an understanding of the event. Include normal ranges and previous lab results, which may be relevant to the event. **Please attach the lab reports to the SAE form and indicate relevant results.**
14. **Diagnostic Tests:** list relevant tests and test results for the event. **Please attach the diagnostic report to the SAE form and indicate relevant findings.**
15. **Concomitant medications:** list all medications the subject was taking from one month prior to SAE onset, up to the time of SAE onset. Enter the start date, stop date, dose, route, frequency, indication, and whether the medication was suspected in the causality of the SAE.
16. **Completed by/Investigator's signature:** the study staff member who completed the SAE form and the Investigator must sign and date the form.
17. Note: All Adverse Event CRFs must reflect similar criteria reported on SAE form.

3.0 SAE Reporting Guidelines

1. Report SAEs that are fatal or life threatening to the CSCC SDMC SAE Regulatory Specialist within 8 hours of the event.
2. Report all other SAEs within 3 business days of discovery.
3. Forward a SAE Announcement Email to the CSCC SDMC SAE Regulatory Specialist and the CSCC SAE Team, alerting them that a SAE has occurred. The email address is: ArginineSAE@RhoWorld.com

CSCC SAE Team:

Name	**Study Role**
Lori Styles, MD	Protocol Chair
Ken Ataga, MD	Medical Monitor
Karen Kesler, PhD	Rho, Inc. SDMC Lead
Mary Pierson, BA, RN	Rho, Inc. SAE Regulatory Specialist
Alice Lail, MPH	Rho, Inc. Unblinded Statistician

4. Fax the completed SAE Report form and supporting documentation to the attention of the CSCC SDMC SAE Regulatory Specialist, Rho Clinical Trials Safety Center, at: 919-287-3998.

4.0 Follow-up SAE reports

1. Please complete a new CSCC SAE Report form promptly when new significant information is obtained regarding the SAE.
2. Check the Follow-up Report box, located in the upper left corner, on all three pages of the SAE form.

3. Complete the CSCC ID, Center Code, Hospital Code, Site Name, and the Report Date on all three pages of the SAE form.
4. Enter only information that is new or changed from the information previously submitted.
5. The study staff member who completed the SAE form and the Investigator must sign and date the form.
6. Follow the SAE Reporting Guidelines listed above.

For questions about completing this form, please contact the CSCC SDMC SAE Regulatory Specialist at (919) 408-8000 extension 229. Hours of availability are Monday-Friday, 8am-4:30 pm, United States Eastern Standard Time.

Contact Information:
CSCC SAE Regulatory Specialist
Rho Clinical Trials Safety Center
6330 Quadrangle Dr.
Suite 500
Chapel Hill, NC 27517
Phone: (919) 408-8000 x 229
Fax: (919) 287-3998

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CSCC SAE Assessment Form:

"Arginine Supplementation in Sickle Cell Anemia: Physiological and Prophylactic Effects"

☐ INITIAL OR ☐ FOLLOW-UP REPORT

REPORT #_____

CSCC Medical Monitor:			**CSCC ID #:**	**SAE #:**	**Date** / /
IND #: ☐ **N/A**	**Protocol:** Arginine	**Hospital Code:**	**Center Code:**	**Site Name:**	**PI Name:**

Event Term:	**Date:**
➢ **SAE Onset**	/ /
➢ **Received from Safety CRO**	/ /
➢ **Reviewed by Medical Monitor**	/ /

Questions:	**Safety CRO:**	**CSCC Medical Monitor:**
➢ **Expedite Reporting to FDA?**	☐ **YES*** ☐ **NO** ☐ **N/A** * Must answer 'yes' to the following criteria: Serious Event? ☐ **YES** ☐ **NO** Related to Therapy? ☐ **YES** ☐ **NO** Unexpected Event? ☐ **YES** ☐ **NO**	☐ **YES*** ☐ **NO** ☐ **N/A** * Must answer 'yes' to the following criteria: Serious Event? ☐ **YES** ☐ **NO** Related to Therapy? ☐ **YES** ☐ **NO** Unexpected Event? ☐ **YES** ☐ **NO**
➢ **Expedite Reporting to DSMB?**	☐ **YES** ☐ **NO** ☐ **N/A**	☐ **YES** ☐ **NO** ☐ **N/A**
➢ **Recommend Unblinding Subject?**	☐ **YES** ☐ **NO** ☐ **N/A**	☐ **YES** ☐ **NO** ☐ **N/A**
➢ **Follow-Up Needed?**	☐ **YES** ☐ **NO** ☐ **N/A**	☐ **YES** ☐ **NO** ☐ **N/A**
➢ **Subject Withdrawn from Study?**	☐ **YES** ☐ **NO** ☐ **N/A**	☐ **YES** ☐ **NO** ☐ **N/A**

Safety CRO's Action Plan:	
Safety CRO: Rho, Inc (SCSS SDMC)	
Signature:	**Date:**

Medical Monitor Request:

➢ **Follow-up Information?** ☐ **Yes** ☐ **No**	➢ **Modification?** ☐ **Yes** ☐ **No**
If 'Yes', Additional Information:	**If 'Yes', Modification:**

Medical Monitor's Action Plan:	
Medical Monitor:	
Signature:	**Date:**

Please return this form via fax to the CSCC SDMC SAE Regulatory Specialist within two business days at: (919) 287-3998

Subject Discontinuation

The following are requires discontinuation of a subject's participation in the arginine study:

- Drop in hemoglobin below 5 gm/dL
- Pulmonary failure requiring intubation
- Hepatic dysfunction (SGPT ≥ 3X normal and albumin ≤3.0)
- Renal dysfunction (Creatinine ≥1.4 for children and ≥1.6 for adults)
- Focal neurological changes
- Increase in methemoglobin level to > 2X normal level
- Apparent allergic reaction to arginine
- Episode of priapism requiring treatment
- Severe headache
- Pregnancy
- Episode of retinopathy requiring treatment

Subjects may choose to discontinue from the study at any time. The local principal investigator may wish to discontinue the patient for another reason that is not listed above. Before discontinuing the patient, the investigator must contact Dr. Lori Styles to discuss the withdrawal of the subject.

A subject may experience adverse events, other than those listed above, which may necessitate a modification to the arginine dose. The investigator must call Dr. Lori Styles to discuss changes in the arginine dose.

Upon study discontinuation, the study termination page of the case report form must be completed. In addition, the subject will be encouraged to complete at a minimum all safety follow-ups and, if willing, all efficacy endpoints (this data will be used for an intent-to-treat analysis). If the subject agrees, these follow-up evaluations will be conducted at the scheduled study evaluation points.

Subjects who discontinue early from the study will be replaced.

CSCC ID Number Assignment Log

Center Name: _____ Hospital: _____

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