Neuropsychological Dysfunction and Neuroimaging Abnormalities in Neurologically Intact Adult Patients with Sickle Cell Disease (SCD)

Phase II Pilot Intervention Study
(Neuropsych II)

STUDY INFORMATION MANUAL

July 2009

TABLE OF CONTENTS

1. INTRODUCTION

This Study Information Manual (SIM) is to be used as a reference document for the *Neuropsychological Dysfunction and Neuroimaging Abnormalities in Neurologically Intact Adult Patients with Sickle Cell Disease (SCD) - Phase II Pilot Intervention (Neuropsych II)* study.

All staff members participating in the conduct of this study should have access to the SIM and be familiar with its contents. The most recent version of the SIM is posted to the study website and may be downloaded as needed.

1.1. Neuropsych Contact Information

1.1.1. Protocol Development Committee

Name	Role	Position and Institution	Phone / E-mail
Elliott Vichinsky, MD	Protocol Chair	Medical Director, Hematology/Oncology Programs (Children's Hospital & Research Center at Oakland)	(510) 428-3651 evichinsky@mail.cho.org
Daniel Armstrong, PhD	Neurocognitive Investigator	Professor, Pediatrics & Psychology, and Associate Chair, University of Miami	(305) 243-6801 darmstrong@miami.edu
Jeffrey I. Gold, PhD	Neurocognitive Investigator	Assistant Clinical Professor of Anesthesiology (VA Medical Center); Assistant Clinical Professor of Pediatrics (USC Keck School of Medicine)	(323) 660-2450 ext. 6341 jgold@chla.usc.edu
Michael W. Weiner, MD	Neuroimaging Investigator	Director, Magnetic Resonance Unit (VA Medical Center, San Francisco**);** Professor of Medicine, Radiology, Psychiatry and Neurology (University of California at San Francisco)	(415) 387-0501 mweiner@itsa.ucsf.edu
Diana Truran Sacrey	Neuroimaging Investigator	Imaging Coordinator (VA Medical Center, San Francisco)	(415) 221-4810 x 3650 diana.truran@ucsf.edu
Barry Eggleston, MS	Biostatistician	Senior Biostatistician (Rho Federal Systems Division)	(919) 408-8000 ext. 278 barry_eggleston@rhoworld.com
Lynne Neumayr, MD	Care Coordinator	Administrative Director, Department of Hematology (Children's Hospital and Research Center at Oakland)	(510) 428-3698 lneumayr@mail.cho.org

1.1.2. Neuropsych SDMC Study Team

The SDMC is located at Rho Federal Systems, 6330 Quadrangle Drive, Suite 500, Chapel Hill, NC 27517. The telephone number is (919) 408-8000; the fax is (919) 287-0126. See below for a list of study contacts and telephone extensions.

Name / Role	Ext.	E-mail
Karen Kesler, PhD / Principal Investigator	244	Karen_Kesler@rhoworld.com
Barry Eggleston, MS / Biostatistician	278	Barry_Eggleston@rhoworld.com
Michele Cosgrove / Sr. Clinical Data Associate	445	Michele_Cosgrove@rhoworld.com
Cathie Snyder / Sr. Study Coordinator	291	Cathie_Snyder@rhoworld.com

2. STUDY OVERVIEW

The study is sponsored by the National Heart, Lung, and Blood Institute (NHLBI). The Statistics and Data Management Center (SDMC), located at Rho Federal Systems Division in Chapel Hill, North Carolina, provides project and data management, regulatory, statistical, and other services for this protocol.

The study was originally designed in 2 phases: In Phase I, approximately 156 subjects would participate in a cross-sectional study consisting of screening questionnaires, a neuropsychological testing battery, and MRI testing. In Phase II, a subset of approximately 30 participants will be asked to participate in a transfusion intervention. Half will be randomized to undergo a chronic transfusion regimen for six months, and the other half will be treated with standard care alone, guided by their disease symptoms.

The objectives for Phase II, which were linked to Phase I, were to determine the extent of neurocognitive dysfunction in neurologically asymptomatic adult patients with sickle cell disease (primary) and to determine the association between neurocognitive dysfunction and imaging abnormalities (secondary).

The primary hypothesis, also linked to Phase I, was that neurocognitive testing in neurologically asymptomatic adult sickle cell patients would be abnormal compared to community controls. Secondary objectives to address issues of estimation:

1) neurologically intact adults with SCD will have significantly lower scores on other neuropsychological tests of executive function when compared to adult controls;
2) a larger percentage of adult patients with abnormal MRI will have abnormal NP testing than those with normal MRIs;
3) neurocognitive dysfunction most likely develops earlier than conventional neuroimaging techniques can detect; and
4) patients with baseline WAIS III PIQ scores of one standard deviation or more below the norm (85 or less) will show at least a five point improvement when re-tested after six months of transfusion and compared to the group of patients that receives standard care alone.

Phase I, which is now completed and undergoing final statistical analysis, demonstrated significant neurocognitive impairment in asymptomatic adult patients.

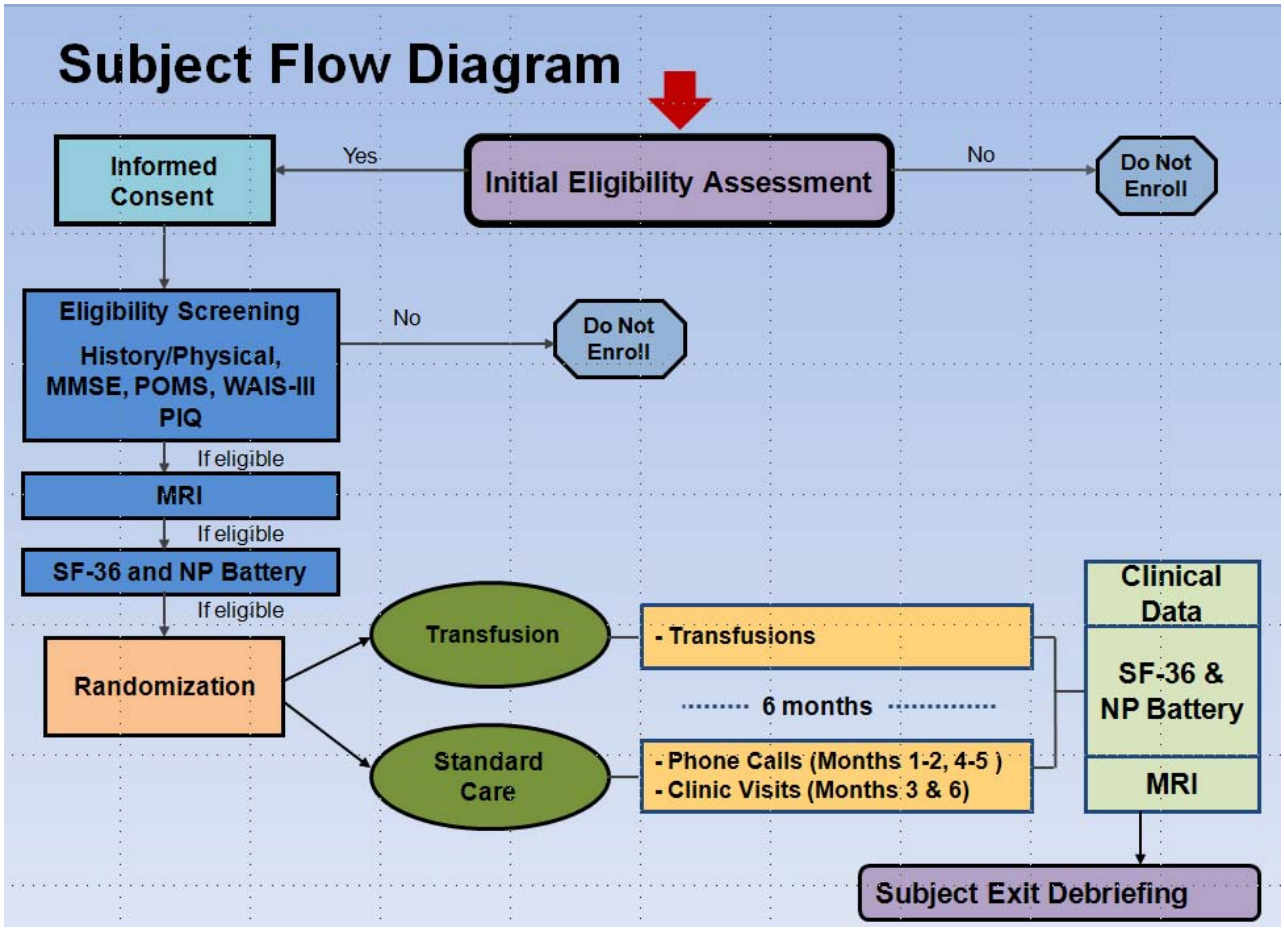
Currently, neurologically intact adult subjects aged 21-55 years, with a diagnosis of Hb SS/SB0, are eligible for Phase II eligibility screening. Approximately 36 patients will be randomized: half will undergo a chronic transfusion regimen for six months, and the other half will be treated with standard care alone, guided by their disease symptoms. A neurocognitive battery and MRI will be administered at baseline and again at the end of

the six-month period, and the mean change scores will be compared between the two groups.

Participating sites will recruit patients from their clinic populations. Enrollment is scheduled to be completed on December 31, 2009.

Refer to the study protocol, which may be downloaded from the study website, for additional information regarding the study, including the background and rationale.

2.1. Subject Flow Diagram



2.2. Study Visit Schedule

The study coordinator will conduct an initial eligibility assessment before beginning the consent process. Visit 1 (Screening Visit) is scheduled following the consent process. Visit 2 (MRI) should take place within 4 weeks of Visit 1, and Visit 3 (Neuropsych Battery/SF-36) should take place within 2 weeks of Visit 2. Subjects are then randomized into either a case group (transfusions) or a control group (standard care).

The first pre-transfusion visit or interval history telephone call should take place within 4 weeks of randomization. Randomized subjects are on study for 6 months.

The Neuropsych Battery and SF-36 are repeated within 2 weeks of the last treatment visit, and the MRI is repeated within 2 weeks of the Neuropsych Battery. Finally, subjects are asked to return for a debriefing visit.

	Visit 1 Screening Visit	**Visit 2 MRI**	**Visit 3 NP Battery/ Randomi-zation**	**Transfusion Visits [1] or Phone Calls/Visits [2]**	**Exit NP Battery Visit**	**Exit MRI Testing Visit**	**Exit Debriefing Visit**
Visit Windows		*w/i 4 wks of V1*	*w/i 2 wks of V2*	*1st w/i 4 wks of randomization*	*w/i 2 wks of last trans.*	*w/i 2 wks of NP Battery*	
- Consent - Elig.Screening - PIQ - MMSE - POMS	**X**						
- MRI Testing		**X**				**X**	
- SF-36 - NP Battery - Randomization			**X**		**X**		
- Transfusions or - Phone Calls/Clinic Visits				**X**			
- Exit Debriefing							**X**

[1] Number of transfusions during the 6-month period will vary between 6 and 8, and will occur at 3- to 4-week intervals.
[2] Phone calls will occur during Months 1, 2, 4, and 5. In-person clinic visits occur during Months 3 and 6.

3. PATIENT RECRUITMENT AND ELIGIBILITY

3.1. Inclusion Criteria

Individuals who meet the following criteria are eligible for enrollment:

1) WAIS III-PIQ score ≤ 90
2) Hemoglobin ≤ 9.0 g/dL
3) Capable of giving informed consent for the protocol
4) Willing to undergo transfusion therapy for 6 months
5) Adult between the ages of 21-55
6) African descent
7) Proficient/Fluent in English
8) Hemoglobin electrophoresis confirming hemoglobin SS or SB^0 (%A ≤15)
9) Mini-Mental Status Examination (MMSE) score of ≥ 20
10) Profile of Mood States (POMS) score on the Depression-Dejection Subscale ≤ 40

3.2. Exclusion Criteria

Individuals who meet any of the following criteria are disqualified from enrollment:

1) History of life threatening or serious transfusion complications
2) Lack of venous access
3) Pregnancy
4) Refusal of transfusion
5) History of unexplained severe hemolytic transfusion reaction
6) History of serious allergic, pulmonary transfusion reaction requiring hospitalization for the reaction
    a. Positive auto-immune hemolytic anemia (direct coombs with IGG and complement)
    b. Multiple (three or more) clinically significant allo-antibodies, due to common antigens (for example; EC, Kel)
    c. Uncommon, clinically significant antibody that results in difficulty in finding matched units (for example; anti-JKB)

d. Currently taking Hydroxyurea and not on a stable dose for ≥ 6 months

e. Creatinine > 1.7 mg/dL

f. Ferritin > 1,500 ng/mL or quantitative liver iron > 7 mg iron/g > dry weight and not currently on iron chelation therapy. (This is a pilot study in which only six months of transfusion will be utilized. The likelihood of iron overload induced toxicity from the transfusions over the six months is very small. Furthermore, ferritin is disproportionately elevated in SCD and overestimates the iron burden. Therefore, we have included a quantitative liver iron and/or ferritin as criteria for exclusion.)

g. Major infarct identified on previous MRI

h. Currently on Procrit or related drug that stimulates red blood cell production

7) Overt stroke

8) Previous evidence of an abnormal MRI or CT other than small periventricular or watershed lesions

9) History of head injury that resulted in neurological symptoms or medical visit

10) Abnormal neurological exam with focal findings

11) Alcohol consumption exceeding 14 drinks/weeks if female, 21 drinks/week if male

12) Drug abuse, as defined as using non-prescribed medication

13) History of claustrophobia and/or presence of metallic implants such as pacemakers, surgical aneurysm clips, or known metal fragments embedded in the body.

14) Baseline blood pressure > 140/90 on two repeated measurements. A second measurement is needed only if the first is > 140/90.

15) History of uncontrolled hypertension

16) Any chronic disorder that may result in neurocognitive or brain dysfunction that is **not secondary to SCD** including:

a. Inflammatory arterial disorders (lupus, polyarteritis)

b. History of cancer requiring chemotherapy and/or radiation

c. Untreated hyperlipidemia

d. Diabetes

e. Ongoing active infection such as HIV, tuberculosis, sarcoidosis

f. History of chronic transfusion

g. Chronic renal failure/Dialysis

h. Chronic lung disease characterized by need for oxygen

i. Morbid obesity (weight >115 kg)

j. Heart disease: history of congestive heart failure, history of severe coronary artery disease characterized by angioplasty or surgery, or history of angina

k. Active hepatitis or liver failure

l. Acquired or congenital immune deficiency

m. History of psychoses (delusions, hallucinations) and/or schizophrenia

n. Neurodegenerative disorders

o. Genetic disorder associated with neurocognitive dysfunction such as Down Syndrome

p. Other chronic illness or disorder other than SCD that will adversely affect the subject's performance in the study

4. SITE SETUP AND TRAINING

4.1. Site approval process

Study sites for the Neuropsych study must meet certain minimum requirements in order to be certified to conduct the study. The certification requirements fall into three categories: Human Rights, Neuropsychological Testing, and Neuroimaging.

4.1.1. Human Rights

IRB/Informed Consent Approval

In summary, sites must obtain approval of their individual site-customized informed consent materials from the NP study informed consent review committee before submission to site IRBs. Any IRB-requested changes in the informed consents must be resubmitted to the informed consent review committee and approved before resubmission to site IRBs. Once site IRB approval is obtained, sites must forward any communications from site IRBs, including requests for revisions, as well as the actual approval letter to the SDMC at Rho, Inc. for inclusion in the study master file.

NIH Human Subjects Training Certificate

Any research study staff coming into contact with human subjects or research data related to human subject research must have completed the mandatory NIH Human Participant Protections: Education for Research Teams training. Certificates of completion of the training are provided for printout by the NIH website and should be kept in hard copy on file at each study site for each member of the research staff.

4.1.2. Neuropsychological Testing

Sites must identify a neuropsychologist who meets the neuropsychologist qualifications for the study listed below. It is acceptable for a site to identify a supervising psychologist and a psychologist who will actually administer the neuropsychological battery. The psychologist identified must be certified through Neuropsych study training at the SDMC before the site will be allowed to participate in the study.

The study neuropsychologist must be a licensed psychologist or a pre- or post- doctoral psychological fellow under the direct supervision of a licensed psychologist. The neuropsychologist must have documented experience administering, scoring and interpreting the designated neuropsychological battery with adults, including:

- The SF-36
- The Wechsler Adult Intelligence Scale-Third Edition (WAIS-III)

- The Woodcock Johnson Revised: Test of Achievement (WJ-R)
- The Wisconsin Card Sorting Test (WCST)
- Test of Everyday Attention (TEA)
- The California Verbal Learning Test- Second Edition (CVLT-II)
- The Wechsler Memory Scales - Third Edition (WMS-III)
- Delis-Kaplan Executive Function System ™ (D–KEFS™)

The identified neuropsychologist must submit curriculum vitae and complete a checklist that provides information regarding his/her experience with administration of the complete battery of neuropsych tests included in the study. This checklist is used to assess the amount and type of training required. If the identified neuropsychologist has not had experience with any of these measures, he/she will be expected to complete sample administrations with a colleague, and then score and forward the materials to the coordinating staff for review.

4.1.3. Neuroimaging

Sites participating in the study must also meet certain requirements for the Neuroimaging component of the study, including:

- **MRI data should be acquired from one site**. If your institution consists of multiple sites, one should be chosen for the acquisition of imaging data.
- **Only 1.5 Tesla scanners will be included in the MRI study**. If only a 3 Tesla scanner is available please contact us directly and we will assess inclusion on a case-by-case basis.

Please note that MRI sites planning to upgrade either their gradients or head coils over the course of the MRI study might need to be disqualified from the study, as changing the gradients or head coils will produce changes in the MR images. Therefore, sites need to verify that Radiology Department upgrades of gradients or head coils are not anticipated during the duration of this study. If such changes are anticipated, sites need to contact the SDMC staff to assess inclusion in the study.

Sites using a Phased Array head coil cannot be included in the MRI study because of the marked inhomogeneity of signal/noise, which make it difficult to measure brain structures. Accepted head coils include: Quadrature Birdcage Head Coil and TEM Birdcage Head Coil.

All MRI sites are strongly encouraged to follow the American College of Radiology's quality control procedures and perform quality control testing at the recommended intervals with the ACR phantom. If sites do not currently have an ACR

phantom, one may be obtained through the ACR. Information on the ACR Quality Control Manual and the ACR phantom can be found at the website for the American College of Radiology.

MRI sites are strongly encouraged to have ACR accreditation. However, this is not a requirement. Sites with this certification, or enrolled in the program, will receive priority for enrollment in the MRI study. Information on the accreditation process can be obtained at the website for the American College of Radiology.

Because of the requirements of the Health Insurance Portability and Accountability Act (HIPAA), it is highly desirable that data sent from sites is striped of patient identifiers including name, social security number, date of birth, address, etc. However, it may not be possible for sites to strip identifying information from the MRI header. **Therefore, sites must obtain explicit IRB approval to send MRI scans with identifiers.**

It is strongly recommended that sites have a radiologist perform a clinical read shortly after the MRI scans to check for brain abnormalities. Scans will not be read for the purpose of clinical diagnosis at UCSF, and UCSF is not responsible for reporting abnormalities. It should be explicitly stated in the IRB protocol and on the consent form that clinical reads are not a part of the study and that a radiologist will not be viewing the scans for diagnostic purposes at the central processing site.

Please e-mail all questions regarding study imaging procedures to Diana Truran Sacrey at diana.truran@ucsf.edu.

4.2. IRB/Informed Consent Approval

Informed consent is an ongoing process that begins with the first contact with a prospective subject and continues until the study is completed. 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 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 consent form also documents the subject's agreement to participate.

The investigator or a designee may present the information and administer the consent. The investigator/designee should be well versed in the protocol and able to answer questions about the study procedures. The investigator/designee presenting the study should encourage the prospective subject to ask questions during this introduction to the study and anytime during his/her participation. Following the information presentation, the administrator should feel confident that the subject understands the study before the consent form is signed and before final inclusion into the study.

A consent form template is provided for this protocol and may be downloaded from the study website. Sites may modify the sample consent form as necessary for submission to

the local IRB, but no information from the risk section may be deleted from the sample consent form. The site specific consent form will be reviewed and approved by the SDMC on behalf of the NHLBI, prior to submission to the site IRB. A copy of the approved version of the informed consent statements (with IRB stamp) must be provided to the SDMC after IRB approval.

The consent form must be signed by the subject before participation in any study-related activities. A copy of the signed and dated consent form must be provided to the subject. Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at all times. Subjects should be re-consented if information is changed that might have an impact on their continued participation.

4.3. Site Initiation and Training

Prior to site initiation, sites must have completed the IRB approval process and submitted their IRB approval, approval-stamped consent forms, and a signed protocol signature page to Cathie Snyder at the SDMC. These documents may be sent via fax (919-287-0126) or e-mail (Cathie_Snyder@rhoworld.com). Please remember to retain a copy of each in your site Regulatory Binder.

Additionally, site study staff, including the site psychologists, must receive study training. The SDMC provides study training via central training and via webcast. Training slides are also posted on the Neuropsych website.

4.4. Regulatory Documentation

All required regulatory paperwork must remain at the study site and must be accurately maintained; the regulatory binder may be reviewed during study monitoring visits.

Site Regulatory Documents should include the following:

1) Study Personnel Signature/Responsibility list
2) Monitor Log and Monitoring Reports
3) Subject Screening/Enrollment log
4) Subject ID List
5) Original Protocol and Revisions/Amendments
6) Consent Forms (all versions)
7) Blank Case Report Forms (CRFs)
8) Advertisements and Subject Information Materials

9) IRB Approval - Regulatory Review History

10) Copies of SAE Reports and Unanticipated Problem Reports

11) Copies of Protocol Deviation Reports

12) Sponsor Correspondence

13) Internal Correspondence

14) Notes to File

5. STUDY EVALUATIONS

5.1. Initial Eligibility Assessment

Prior to scheduling Visit 1, the study coordinator should conduct an initial eligibility assessment that includes a review of the potential subject's medical history for inclusion/exclusion criteria. Make sure to consider the patient's hemoglobin history; potential participants should have a stable state hemoglobin of <9.

5.2. Assessing Literacy

As part of the eligibility screening, literacy of potential study subjects must be assessed. Subjects' reading comprehension is dependent upon numerous factors including vocabulary, sentence structure, and content of the material presented. Obtaining informed consent in accordance with ICH guidelines and policies for clinical research requires that the subject has the ability to fully understand the benefits, risks, and the rationale behind the study in which he or she is being asked to participate. Additionally, the quality of the data collected depends in part on the ability of the subject to understand the questions that are included in self-administered surveys or asked by a study interviewer. If the subject is not proficient/fluent in English, he/she must be excluded.

5.3. Screening Evaluations (Visit 1)

After a potential study subject reads and signs the informed consent, the Study Coordinator or a trained research associate will conduct a brief screening to determine if the subject is eligible to participate. This involves the administration of the MMSE and the POMS; refer to the protocol for more information regarding these screening measures. During this time, the research assistant can conduct a medical chart review to assess whether the subject meets the inclusion and exclusion criteria. If the subject is not potentially eligible, he or she will be thanked for his or her time and dismissed and will not continue with any further assessments. If he/she is potentially eligible, the neuropsychologist will administer the WAIS-III PIQ. Those who score ≤ 90 are eligible to continue the screening process.

Two teaspoons of blood will then be drawn from eligible subjects to confirm a diagnosis of sickle cell disease. The blood drawn will also be used for a hematology and chemistry panel. For females of childbearing potential, a urine sample will be collected to ensure that the subject is not pregnant. A history and physical exam utilizing the neurologic exam protocol will be obtained by one of the study staff.

5.4. MRI (Visit 2)

All subjects will have an MRI at study entry (Visit 2) and again when they complete the study. Subjects with an abnormal MRI (CT other than small periventricular or watershed lesions) are excluded from participation. If you have questions about a scan, please contact Jeff Kasten at (415) 221-4810, ext. 2030 or Diana Truran Sacrey at (415) 221-4810, ext. 3650.

MRI images should be burned to a disk; no patient identifiers other than the participant ID should be on the disc. If necessary, strip out all identifying information from the disc before sending. Please also label whether the scan is for study entry or study completion.

Disks should be sent via FedEx (or other certified mail carrier) to:

Jeffrey Kasten
VA Medical Center
4150 Clement Street, Building 13, #213
San Francisco, CA 94121

Follow-up with an e-mail notification to:

- Jeff Kasten - Jeffrey.kasten@ucsf.edu
- Cathie Snyder - Cathie_Snyder@rhoworld.com

Please be sure your MRI data is archived to an appropriate storage medium. In the event there is a problem with the shipment, you may be asked to re-send participant scans.

5.5. Neuropsychological Battery and SF-36 (Visit 3)

The Neuropsychological Battery and SF-36 are administered at Visit 3 and again at the end of the study. Subjects are eligible for randomization when the baseline battery and SF-36 have been completed.

5.5.1. Neuropsychological Battery

A trained and supervised neuropsychologist will administer all neuropsychological battery tests as described below. This visit will take approximately 6 to 6 ½ hours to complete; these tests may be divided over 2 days if necessary.

The neurological test battery in this study consists of a wide range of tests that investigate several aspects of neurocognitive functioning. All measures are individually administered and have been standardized on normative populations. Refer to the protocol for additional information regarding these instruments.

- The Weschler Adult Intelligence Scale - Third Edition (WAIS-III) will be used to assess intellectual functioning. Measurement of estimates of both nonverbal and verbal reasoning ability as well as general cognitive ability is provided.
- The Woodcock Johnson Revised: Test of Achievement (WJ-R) will be used to measure academic achievement.

The following neuropsychological measures will be administered to examine language, memory, executive functioning, and sensorimotor perceptual skills.

- The Delis-Kaplan Executive Function System (D-KEFS) assesses vital executive functions such as flexibility of thinking, inhibition, problem solving, planning, impulse control, concept formation, abstract thinking, and creativity in both verbal and spatial modalities.
- The Wisconsin Card Sorting Test (WCST) is a measure of nonverbal concept formation that is considered to measure executive functioning
- The Test of Everyday Attention (TEA) examines attention and executive functioning.
- The California Verbal Learning Test - Second Edition (CVLT-II) assesses memory for discrete auditory material by having the participant learn a list of 16 words over five trials.
- The Wechsler Memory Scales - Third Edition (WMS-III) contains 11 subtests that assess aspects of memory and learning.

The neuropsychologist will score all test forms and send the study coordinator a copy of the completed Case Report Forms (CRFs) for entry into EDC and a copy of the original test forms. Original test forms should remain under the control of the neuropsychologist until notified of permission to destroy per the site IRB.

The copy of the test forms should be sent to Children's Hospital of Los Angeles, where 20% will be randomly rescored to determine accuracy of data. Copies should be labeled to indicate study entry or study completion and sent via FedEx to:

Angela Li
Anesthesiology Critical Care Medicine
Children's Hospital Los Angeles
4650 Sunset Blvd., MS #12
Los Angeles, CA 90027

Follow-up with an e-mail notification to:

- Angela Li - ali@chla.usc.edu
- Cathie Snyder - Cathie_Snyder@rhoworld.com

If you have questions, please contact Angela at (323) 361-7091.

5.5.2. SF-36 Quality of Life Measure

The SF-36 is a self-administered test that may be administered by the study coordinator or the neuropsychologist. The SF-36 assesses the following eight health concepts:

1) limitations in physical activities because of health problems;
2) limitations in social activities because of physical or emotional problems;
3) limitations in usual role activities because of physical health problems;
4) bodily pain;
5) general mental health (psychological distress and well-being);
6) limitations in usual role activities because of emotional problems;
7) vitality (energy and fatigue); and general health perceptions.

5.6. Other Assessments

Subjects randomized to the transfusion arm will receive 6 months of transfusions. The goal is to maintain a minimum of at least 2 g/dL rise of Hb over the baseline. Once transfusions are started, the pre-transfusion Hb obtained within 3 days prior to the transfusion should be 9.0 g/dL or greater, without exceeding a post-transfusion Hb concentration of 12.0 g/dL. All transfusions will be leukodepleted and Hb S negative. Phenotypically matched red blood cells for D, C/c, E/c, and Kell antigens are required, along with any known antibody. Only simple transfusion is allowed. Simple transfusion guidelines include the maximum delivery of 3.0 units of packed RBCs per transfusion at 3-4 week intervals.

Subjects randomized to the standard care arm will receive standard care for sickle cell disease. These subjects will visit the study site during months 3 and 6; they will receive telephone calls from study staff during months 1, 2, 4, and 5. The purpose of the visits and telephone calls is to collect and track information about new medications, neurological events, possible transfusions, and hospitalizations and/or emergency room visits. During the in-person clinic visits at months 3 and 6, controls will have blood drawn to measure Hb and ferritin levels.

6. GENERAL STUDY INFORMATION

6.1. Patient Study Log

A Patient Study Log should be maintained for all study subjects. This log, which may be downloaded from the study webpage, tracks all study activities from the time of consent.

6.2. Randomization

Participants will be randomized into either the case group (transfusions) or the control group (standard care). Cases will receive between transfusions every three to four weeks. Study controls will receive standard care for sickle cell disease during the six-month period.

A Randomization Request Form may be downloaded from the Neuropsych website. This form should be completed and sent via e-mail to Barry Eggleston (Barry_Eggleston@rhoworld.com) and Cathie Snyder (Cathie_Snyder@rhoworld.com).

Barry will conduct the randomization through an unblinded process. Within 2 business days, a Randomization Reply Form that provides the treatment assignment will be sent to the site.

6.3. Patient Compensation

Subjects will be compensated as follows:

- $50 for completion of the screening visit.
- $100 for completion of neuropsychological testing.
- $100 for completion of MRI testing.
- $80 per visit for each transfusion.
- $20 per visit for transportation and parking.

If the subject discontinues any aspect of the protocol he/she will receive reimbursement for the part(s) completed.

6.4. Subject Confidentiality

As in all medical research projects, personnel involved in the Neuropsych II pilot study should keep the confidentiality of study participants foremost in their minds. The

following list includes the basic issues that must be attended to at all research sites and the Statistics and Data Management Center (SDMC).

- 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.
- Neuropsych study participants provide us with very personal and sensitive medical and psychological 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 neuropsych 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.

6.5. Subject Study Withdrawal or Discontinuation

Subjects may decide to discontinue participation at any time during the study. Investigators may discontinue any subject at their discretion if, in their professional opinion, the subject's health, safety, and/or well-being is threatened by continued participation in the study.

Adverse events caused by participation in the study may necessitate modifications to the subject's level of participation or discontinuation from the study.

Subjects who discontinue prematurely from the study for any reason will be encouraged to complete, at a minimum, all safety follow-ups and, if willing, all efficacy endpoint visits for safety and intent-to-treat analysis.

6.6. 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.

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

- Randomization errors
- Missed visits
- Mistimed visits (visit falls outside the required timeframe)
- Missed procedures or assessments
- Inclusion/Exclusion errors
- Patient Safety

Source Documentation

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

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

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

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

Reporting Timeframes

Deviations that affect subject safety or integrity of the data should be reported to the SDMC within three days. Other deviations should be reported to the SDMC within 30 days of occurrence.

6.7. Neuropsychological and MRI Debriefings

Upon completion of all Phase II study activities, all participants should be debriefed about the results of the neuropsychological testing and the MRI.

The debriefing should include a face-to-face discussion about the results of the evaluation. The local PI should review the results of the MRI (comparing the entry MRI to the completion MRI) and the neuropsychologist should review any changes in neuropsych battery. The feedback session should include information about practical recommendations that may result in better adaptation to any problems identified. Furthermore, recommendations for additional testing and intervention should be considered if indicated. Following the discussion, the participant should receive a brief written summary of the findings.

Ideally, this meeting should include the subject, the local investigator, and the neuropsychologist; however, this meeting can be completed by the local investigator alone if the neuropsychologist is unavailable. In this case, the local PI should review the results with the neuropsychologist prior to the face-to-face meeting, and provide the subject with contact information for the neuropsychologist. Another option is to schedule 2 in-person debriefing meetings: 1 with the local PI and 1 with the neuropsychologist.

If a face-to-face meeting cannot occur, a phone meeting will be appropriate. If neither a face-to-face nor a phone meeting can occur due to the patient's lack of interest or availability, a brief summary should be sent out thanking them for their efforts, informing him/her of our attempts to schedule a face-to-face meeting and/or phone conference and of any previously unidentified clinically significant finding on MRI or neurocognitive testing that would require clinical intervention by standard of care guidelines outlined in the sickle cell disease NIH manual. This summary should underscore the need to have a phone conference for details and study review, and include contact information for the local PI and neuropsychologist.

Two templates for the neuropsychological debriefing are available via the study website: one for Average/Above Average results, and one for Average/Below Average results.

For participants whose performance on the neuropsychological testing is Below Average, Borderline, or Impaired on any measure, face-to-face interpretive feedback should include information about additional testing and intervention services that are available in the community. It should be explained that these services are not included as part of the study, and may require insurance or other out-of-pocket costs.

For the MRI debriefing, the Study PI should use the MRI Debriefing Checklist (included in the appendices) to meet with the Radiologist who will briefly read the MRI report to ensure there are no major problems identified by the MRI (e.g., major infarctions, watershed lesions, severe atrophy, etc.). The Study Coordinator or Study PI can then integrate these findings into the debriefing process.

Recommendations in regards to transfusion therapy based solely on the results of their participation in the six-month pilot trial are not justified. The benefit and risk should be

based on the clinical condition and the benefit of transfusions in general. The pilot study results will serve as a foundation for a definitive trial evaluating efficacy and risk.

All participants should be thanked for their participation. The results of a phase II/III trial establishing the efficacy and benefit of the pilot study would not have occurred without their participation in the pilot study. The results of future studies originating from this pilot trial will be made available to them. All patients have the right to ask the central study PI (Elliott Vichinsky) questions directly if needed. Dr. Vichinsky can be contacted at Children's Hospital Oakland, 747 52nd St. Oakland, CA 94609, (510) 428-3651.

6.7.1. Recommendations for Follow-up for the Neuropsychological Testing

The neuropsychological testing may show areas of functioning that are of concern to the study participant and/or the neuropsychologist. In these cases, simply having the information presented during a debriefing may be inadequate, and additional recommendations for follow-up may be necessary.

The following represent a limited set of recommendations that may be used for follow-up; however, these should not be substituted for the expert judgment of the neuropsychologist who completed the evaluation.

1) Scores on a battery of neuropsychological tests are descriptive of a range of abilities, but do not, in and of themselves, represent a disability for the individual participant. During the debriefing session, it should be determined whether any of the areas of concern represented by test performance actually result in functional difficulties for the participant. If the answer to this question is no, then pursuit of additional intervention, at this time, is not warranted.

2) Low scores in academic areas should also be discussed with the participant. Unless the participant is pursuing additional education, either to obtain better employment or retain current employment, specific recommendations to address low performance in math or reading are typically not indicated for adults. However, if the participant is interested, there are several recommendations that may be helpful:

    a. Adult education programs in local high school and community college systems that address adult literacy, and particularly health literacy, may be beneficial.

    b. If the participant's neuropsychological pattern suggests difficulty processing visual information, but indicates strengths in processing oral information, then the physician may complete an authorization form for the Lighthouse for the Blind or the National Library of Congress that will provide access to books on tape or disk. This may provide the participant

with access to content information in the face of a primary reading disability.

3) If there is evidence of significant problems with attention, and these difficulties interfere with activities of daily living, job performance, or social relationships, then the participant should be referred for further evaluation for adult attention deficit hyperactivity disorder. Use of a stimulant medication, under the supervision of a physician who is capable of monitoring benefit, may be very helpful to these individuals.

4) If there is evidence of significant problems with memory, referral to an adult memory disorders clinic is appropriate. The participant will be evaluated for early signs of Alzheimer's disease or other forms of dementia, and may receive treatment or become eligible for inclusion in clinical trials of new pharmaceutical approaches to memory deficits.

5) If the deficits interfere significantly with daily living and social relationships, referral to a clinical social worker or psychologist for counseling may be offered.

This list is not inclusive, and should be used as one set of possibilities for recommendations following the finding of abnormal results on the neurocognitive testing. Clinical decision-making regarding these results must include oversight from a licensed mental health professional with experience and training related to the interpretation of neurocognitive test results.

6.8. Site Documentation Filing

Sites must keep a site file on each subject participating in the Neuropsych study to include at least the following documents:

- Original Signed Informed Consent (or a copy if site IRB requires that original be filed in medical record)
- CSCC Registration Page (Assignment of ID Number via EDC)
- Randomization information
- Any AE/SAE reports
- WAIS-PIQ III w/ Score
- SF-36
- Records of Every Reimbursement Payment
- Neuropsych debriefing letter
- MRI debriefing letter

6.9. Good Clinical Practice

Good Clinical Practices (GCPs) are a standard for the design, conduct, performance, monitoring, analyses and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected. Below are characteristics of Good Clinical Practice to offer examples of the basic concepts of GCPs. To see a full listing of GCPs, see the Federal Register or go to http://www.fda.gov/cder/guidance/959fnl.pdf.

The basic principles of Good Clinical Practice include (but are not limited to):

- A trial should be conducted in compliance with the protocol that has received institutional review board (IRB) approval.
- The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician.
- Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task.
- Freely given informed consent should be obtained from every subject prior to clinical trial participation.
- All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.
- Confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

7. SAFETY MANAGEMENT

7.1. Adverse Events (AEs) and Serious Adverse Events (SAEs)

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

7.1.1. Definition of an Adverse Event

An AE is defined for this study as any untoward medical occurrence in a subject who is administered clinical study material. The occurrence of this event does not necessarily have a causal relationship with study product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study product, whether or not related to the study product.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency or intensity of the condition
- Significant or unexpected worsening or exacerbation of the condition/indication under study
- A new condition detected or diagnosed after study product administration even though it may have been present prior to the start of the study
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (e.g., invasive protocol-defined procedures, modification of a subject's previous drug treatment regimen).

An AE does not include:

- Medical or surgical procedures (e.g., colonoscopy or biopsy). The medical condition that leads to the procedure is an AE
- Social or convenience hospital admissions where an untoward medical occurrence did not occur
- Day-to-day fluctuations of a pre-existing disease or conditions present or detected at the start of the study that do not worsen

7.1.2. Definition of an SAE

An SAE is any adverse drug experience occurring at any dose that:

- Results in death
- Is life-threatening (at risk of death at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization

  NOTE: Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered to be an AE.

- Results in disability/incapacity

  NOTE: The term disability is defined as a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (i.e., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition

7.2. Clinically Significant Laboratory Abnormalities

All laboratory measurements will be evaluated for abnormalities. An abnormal laboratory finding is not by itself considered to be an AE or SAE unless the investigator considers the abnormal finding to be of clinical significance and should be reported in such a manner. The abnormal laboratory finding does not have to be associated with the use of the study product to be considered clinically significant.

For any significant changes noted by the investigator to be clinically significant or those that meet the criteria above, the clinical significance and relationship to the administration of study product will be established. This assessment will be recorded on the CRF. If the changes are clinically significant, the investigator will continue to monitor the subject until the parameter returns to baseline or until the investigator

determines that follow-up is no longer medically necessary.

7.3. Assessment of Adverse Event Severity

The investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the investigator's clinical judgment. The intensity of each AE and SAE should be assigned to one of the following categories:

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

An AE that is assessed as severe should not be confused with an SAE. Severity is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe. An event is described as 'serious' when it meets one of the pre-defined outcomes as described in "Definition of an SAE" section of this protocol.

7.4. Relationship of AEs and SAEs to Study Procedures

The investigator is obligated to assess the relationship between study mandated procedures and the occurrence of each AE/SAE. The investigator will use his/her clinical judgment to determine the degree of likelihood that the study design was responsible for the AE/SAE being reported. Alternative causes such as natural history of the underlying diseases (See Sickle Cell Related Conditions in the table below), concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated. The table below serves as a guide to conditions typically associated with sickle cell disease, not an exclusionary list of conditions. If the investigator feels that one of the following conditions is related to the study procedures, he/she should report it as related.

Sickle Cell Related Conditions

Expected AE	Expected AE	Expected AE
Acute chest syndrome Anemia Aplastic crisis Aplastic crisis/anemia Arthralgia Avascular necrosis of hip/shoulder Avascular necrosis of the femoral head Bone infarction Cardiomegaly Cerebrovascular accident Cholecystitis, hepatic sequestration Cranial nerve palsy Decreased kidney function Decreased lung function Delayed growth/puberty Depressed ESR	Development of autoantibodies associated with hemolysis Development of clinically significant alloantibodies Elevated urinary urobilinogen Fever Hand-foot syndrome Hematuria Hemiplegia Hemolysis Hemolytic transfusion reaction Hepatosplenomegaly Hyperplastic bone marrow Hyposthenuria Hypoxemia (PO2 < 65mmHg) Infection, pneumococcal Jaundice Leukocytosis Meningitis	Pain, joint Pain, long bone Pain, severe abdominal Priapism Pulmonary embolism Pulmonary hypertension Pulmonary parenchymal infiltrates on chest x-ray Pyelonephritis Renal failure Renal insufficiency/albuminuria Renal papillary necrosis Reticulocytosis (∃10%–20%) Retinal disease Retinal hemorrhage Rhabdomyolysis Sepsis Skin ulcers Splenic sequestration

7.5. Time Period, Frequency, and Method of Detecting AEs and SAE

AEs and SAEs will be recorded for all subjects from randomization through the Exit Debriefing visit. An interval history recording hospitalizations, emergency room visits, and clinical events will be collected at each monthly phone call (for subjects on standard care) or at the pre-transfusion visit (for subjects on the transfusion arm). Hemoglobin (Hb) and ferritin will be measured at study entry. Hemoglobin is measured again at each pre-transfusion visit, and ferritin is measured at Month 3, as well as at the end of the study. During the course of the six-month transfusion period complications related to transfusions will be recorded, as will any observations of new endocrine or cardiac problems, specifically any new arrhythmia or cardiomyopathy.

Information to be collected includes the nature, date and time of onset, intensity, duration, causality, and outcome of the event. Even if the AE/SAE is assessed by the investigator as related to the subject's underlying sickle cell disease, its occurrence must be recorded in the source documents and on the appropriate page of the CRF.

7.6. Recording of AEs and SAEs

When an SAE occurs, the investigator is responsible for reviewing all documentation (e.g., hospital progress notes, laboratory test results, and diagnostic reports) relative to the event. The investigator or designee will then record all relevant information about an AE/SAE onto the appropriate page of the CRF and SAE Report Form, as applicable. It is not acceptable for the investigator to send photocopies of the subject's medical records in lieu of completion of the appropriate CRF pages. Unless otherwise requested, transfer of subjects' medical records with the CRF should be restricted to hospital discharge

summaries and autopsy reports, if available. When sending medical records, all subject identifiers (i.e., name, subject initials, and medical record number) must be obliterated prior to faxing the documents to the data coordinating center.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

7.7. Reporting

7.7.1. Prompt Reporting of SAEs (sites to the SDMC)

The investigator or designee must report all SAEs to the data coordinating center via fax by the end of the next business day after becoming aware of the event. The SAE Report Form may be downloaded from the study website; the fax number is included on the form. This form should be completed as thoroughly as possible, with all available details of the event, signed by the investigator (or sub-investigator), and forwarded to the appropriate project contact within the designated time frames. If the investigator does not have all information about an SAE, he/she should not wait to receive additional information before notifying the SDMC of the event. The following information is a minimum set of information required for all initial SAE reports:

- Investigator name
- Subject identifiers
- Adverse event term(s)
- Reason why the event is serious

Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE CRF within the time frames outlined in the protocol.

7.8. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information on the subject's condition.

All AEs and SAEs documented at a previous visit/contact that are designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution (with or without sequelae), until the condition stabilizes, or until there is agreement between the investigator and the DSMB and/or NHLBI additional follow-up is not warranted.

New or updated information will be recorded on the originally completed SAE Report Form, with all changes initialed and dated. Once all updates have been made to the SAE report, the investigator must resign and date the report. The updated SAE CRF should be resent to the project contact for SAE receipt within the time frames outlined in the "Prompt Reporting of SAEs" section of the protocol.

8. WEBSITE OVERVIEW

8.1. Website Instructions

Study documents are posted to a secure website; users must be given access to this secure website. New users requesting access should submit a Web Access Form to Cathie Snyder via email (Cathie_Snyder@rhoworld.com) or fax (919-287-0126). You will be notified via e-mail when your access has been granted. To access the secure website, go to http://www.rhoworld.com and select "Login" button in the upper right corner. This will direct you to the RhoNET login page.

On the RhoNET login Page, you will type your username and password, and then select "Login" followed by "Comprehensive Sickle Cell Centers." This will take you to the secure homepage.

Announcements are displayed in the gray box in the center of the homepage. A link to the Staff Directory is on the left side of the screen. The staff directory contains contact information for study staff involved with any of the CTC studies who have access to the secure website.

Links to studies to which you have been given access are on the right side of the homepage. Select "Neuropsych" to access study documents.

8.2. Logging Off & Support

To log out, click the "Log Out" hyperlink on the bottom left side of the home page. Simply closing your browser or going to another URL will not log you off. If you have questions regarding content, updates, or technical issues, contact Cathie Snyder by telephone (919-595-6291) or e-mail (Cathie_Snyder @rhoworld.com). If you have forgotten your username or password, call the Help Desk at 1-800-905-0460.

8.3. Neuropsych Website Content

The study webpage organizes study materials by category:

- **General Protocol Documents** – Current version of the protocol; protocol deviation form and instructions; study budget, Protocol Signature Page, Certificate of Confidentiality, Patient Brochure, etc.
- **Case Report Forms** – Paper versions of the Case Report Forms (CRFs) and Completion Guidelines.

- **EDC Links** – Link to the EDC System, data entry information, and the NP Randomization Form.
- **Study Progress** – Enrollment reports, MRI/NP Battery tracker (shipment/receipt).
- **Training and Help Documents** – Debriefing Instructions, Visit Windows, MRI Debriefing Checklist, Psych Debriefing and Letter Templates, Frequently Asked Questions (FAQs), Study Information Manual, and Patient Study Log.
- **Informed Consent Documents** –Informed Consent Process, checklists, and templates.
- **Teleconference Minutes** – Minutes from Study Coordinator teleconferences.

9. DATA COLLECTION

9.1. Case Report Forms (CRFs)

A paper version of the CRFs may be downloaded from the study website. These include CRF completion guidelines explaining the various fields and responses found on the form. The table below lists CRFs that should be completed by visit and the location of the eCRF in the NP II EDC system.

ACTUAL STUDY VISIT	LOCATION IN EDC
Visit 1	
Demographics	Visit 1
Mini-Mental Status Examination	Visit 1
Profile of Mood States	Visit 1
WAIS III PIQ	Visit 1
Hematology and Chemistry	Visit 1
Intake and Chart Review	Visit 1
Intake and Chart Review Neurological	Visit 1
Focal Neurological Assessment	Visit 1
Physical Exam	Visit 1
Alcohol and Non-Rx Drug Use	Visit 1
Inclusion Criteria	Visit 1
Exclusion Criteria	Visit 1
Visit 2	
External MRI Data	Visit 2
Visit 3	
SF-36	Visit 3
NP Battery Observations	Visit 3 – NP Battery
WAIS III	Visit 3 – NP Battery
Woodcock-Johnson III	Visit 3 – NP Battery
Delis-Kaplan System	Visit 3 – NP Battery
Wisconsin Card Sorting Test	Visit 3 – NP Battery
Test of Everyday Attention	Visit 3 – NP Battery
CVLT-II	Visit 3 – NP Battery
WMS-III	Visit 3 – NP Battery
Randomization (following Visit 3)	Visit 3
6 Interval History Visits/Calls	
Interval History	Interval History
Month 3 – Mid-Phase Hematology /Chemistry	Mid-Phase Hematology and Chemistry Labs
Month 6 – Hematology/Chemistry	End of Study Visits
6-8 Transfusions/Pre-Transfusion Visits	
Transfusion	Transfusion

ACTUAL STUDY VISIT	LOCATION IN EDC
1st End of Study Visit – MRI	
External MRI Data	End of Study Visits
ACTUAL STUDY VISIT	**LOCATION IN EDC**
2nd End of Study Visit – NP Battery	
SF-36	End of Study Visits
NP Battery Observations	End of Study Visits – NP Battery
WAIS III	End of Study Visits – NP Battery
Woodcock-Johnson III	End of Study Visits – NP Battery
Delis-Kaplan	End of Study Visits – NP Battery
Wisconsin Card Sorting Test	End of Study Visits – NP Battery
Test of Everyday Attention	End of Study Visits – NP Battery
CVLT-II	End of Study Visits – NP Battery
WMS-III	End of Study Visits – NP Battery
As Needed	
Adverse Experience	Adverse Experience
Transfusion Reaction	Transfusion Reaction
Neurological Event	Neurological Event
Adverse Experience	Adverse Experience
Concomitant Medications	Concomitant Medications
Death	Death
Debriefing	
Phase II Debriefing	End of Study Visits
Study Completion CRF	Phase II Completion

9.2. Introduction to Electronic Data Capture (EDC)

Rho, Inc.'s internet-based remote data entry system will be used to capture site data for the Neuropsych 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 (CRFs). Univariate data validation tests are performed as the data are keyed, and most implausible data values are resolved immediately.

Data are not stored on the site's computer. At the end of each "page," data are submitted to Rho, Inc.'s secure web server using SSL (128 byte public key encryption methodology) and stored in the study's operational database, which is the database used for capturing, validating, updating, and storing site data. The database is backed up nightly, and 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, or key additional data.

The pages will be accessible via the Neuropsych EDC system website and require specific user ID and password privileges. The data will be converted to intermediate datasets prior to incorporation into the Neuropsych study format (SAS datasets).

If you experience problems with the Rho Electronic Data Capture system, contact the Rho Help Desk at 1-800-905-0460 between the hours of 8 AM and 6 PM Eastern time.

9.2.1. Assignment of ID Numbers

Each patient enrolled in any CTC study (both multi-center and within-center) will be registered as a study subject and assigned a unique seven-digit ID number through Rho, Inc.'s electronic data capture (EDC) system. This ID number will be used to identify subjects in the Neuropsych study, and any other study in which they were previously enrolled. As such, the ID number is not study specific and can be used to track a patient's progress in multiple CTC studies. The first two digits of the ID number identify the institution at which the patient is enrolled, and the next five digits uniquely identify the patient.

To enroll a new subject, go the study-specific EDC system and select "New"; this will direct you to the Registration Form screen. Complete the form and an ID number will be assigned. To link a patient who already has a CSCC ID number to a new study, go to the study-specific EDC system and select "Import"; then select the subject's ID number and select "Import" (now at the bottom of the screen) once more. This will enroll the subject into the study and EDC System will advance to the study Case Report Forms.

9.3. Data Validation

Data entered via RhoEDC will be validated against a series of automatic and manual checks designed to test whether the data are correct and complete. Automatic checks are computer-driven and run within RhoEDC at the time of data entry. Manual checks are performed by the SDMC data managers periodically after the data are entered.

9.4. Automatic Checks ("pinks")

<u>During Data Entry</u>

When the system detects a possible error during data entry, an automatic query will pop up on the screen immediately after you exit the field that contains the suspect value, and the field where it appears will turn pink.

You have three options:

1) 'Continue' – Use this option if you're not sure whether the suspect value is right or wrong. Choosing 'Continue' will return you to the form without addressing the suspect value; you can come back to it later. The field with the suspect value will remain pink.

2) ‘Fix It Now’ – Use this option if you know the suspect value is wrong – for example, if you accidentally entered a year in the future. Choosing ‘Fix It Now’ will return your cursor to the field with the suspect value so you can correct it.

3) ‘Override’ – Use this option if you can confirm that the suspect value is right – for example, if a blood pressure reading was outside the range anticipated by the system, but in fact is correct according to the source document. If you choose ‘Override’, the system will prompt you to provide a reason for overriding the automatic query. If you do not enter a reason when prompted, the automatic query will not be overridden and the field with the suspect value will remain pink.

Note: If you override an automatic query, the override applies only to the form currently displayed. It does not apply to other forms of the same type for the current subject or for other subjects in the study.

After you have entered a reason, click ‘Submit Reason’ to save it. NOTE: Once a reason has been submitted for overriding an automatic query, that reason cannot be edited. If you decide to provide a reason later, click ‘Cancel’ to return to the original form. The field with the suspect value will remain pink.

When a field on the form is highlighted to show that it contains a possible error, you can manually open the corresponding automatic query to see an explanation. Click on the highlighted field to see the explanation.

Some possible errors cannot be detected until you submit the form. For example, a discrepancy between data entered in two different fields within the same form will produce automatic queries only when the form is submitted. If there are any of these possible errors present when you submit the form, a warning box will pop up on the screen immediately after you submit the form.

This warning box will list all the automatic queries for the page, including both the ones generated when you submitted the form and any that occurred while you were completing the form and were not either corrected or overridden.

These automatic queries are listed as links. To answer a query, click the link for the one that you want to correct. A box will pop up with the ‘Continue’, ‘Fix It Now’, or ‘Override’ options described above.

To submit the form without correcting the errors, click **Submit as is**. To return to the form and continue editing, click **Return to form**.

9.4.1.1. Status of Automatic Queries

The forms menu for each subject displays the query status of each form with an icon.

- The red exclamation point indicates outstanding queries. It appears next to:

- A link that leads to one or more forms that contain validation errors.
- A link to an individual error on a form or page.

- The green check indicates a form or group of forms with no outstanding queries. It appears next to:
  - An individual form that is complete and contains no validation errors.
  - A link under which all subordinate forms are complete and contain no errors.

9.5. Manual Checks

Some data elements are not suited to automatic computer checks. SDMC data managers will programmatically identify inconsistencies in data that may have been reported over time, or across forms. Such checks may include the following:

- Comparing the dates and times of all assessments to confirm that they occur in an appropriate sequence. For example, Visit 2 should come before Visit 3.
- Confirming that all screening eligibility and baseline assessments occur before treatment initiation (an exception being neurocognitive testing, which can occur up to a month after treatment initiation).
- Confirming that the recorded onsets of all treatment emergent adverse experiences are after treatment initiation.

Any issues detected by manual review of the data will be communicated to the clinical site in writing via a manual query spreadsheet. The site will review the data issue and resolve it either by changing the errant data in RhoEDC or by documenting that the data is correct as entered. The site will be responsible for updating the manual query spreadsheet with the resolution and returning it to the study data manager at the SDMC. SDMC data managers will review the resolutions to verify that the data issue has been closed.

9.6. Monitoring Visits

Monitoring Visits will be performed in accordance with protocol specific requirements, Title 21 of the CFR, other applicable regulatory requirements, ICH/GCP guidelines, and the Rho, Inc. SOPs.

Monitoring visits will be conducted as necessary; each site should have at least 1 visit. 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 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, but not limited to:

- 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