

## 1 STUDY ADMINISTRATION

### 1.1 Manual of Operations and Organizational Overview

This Manual of Operations (MOO) clarifies the walk-PHaSST study organization (Figure 1-1), policies, and procedures. The MOO describes procedures in more detail than does the protocol and is intended to promote high quality, and consistent research activities.

This chapter gives a brief overview of study logistics and defines the roles of all clinical and administrative participants. For a summary of the protocol design, please refer to the protocol synopsis.

Walk-PHaSST is a multicenter clinical trial being conducted through collaborative efforts among 10 clinical sites, the National Heart Lung and Blood Institute (NHLBI) and the Data Coordinating Center (DCC) at Rho, Federal Systems Division, Inc. The administrative organization of the study is designed to facilitate communication and cooperation, while providing scientific leadership and administrative guidance. The study is structured to include a Steering Committee, Executive Committee, Operations Committee, Data and Safety and Monitoring Board and Data Coordinating Center. In addition, NHLBI provides study oversight *via* the Project and Contracting Officers.

### 1.2 Study Logistics

This is a post-marketing, Phase II/III trial sponsored by NHLBI of the National Institutes of Health (NIH) and coordinated by Rho Federal Systems, Inc. The 10 participating clinical sites include:

- Site 01: Albert Einstein College of Medicine (AECOM)
- Site 02: Columbia University Medical Center
- Site 03: Children's Hospital of Oakland
- Site 04: Children's Hospital, Pittsburgh
- Site 05: Imperial College of London and Hammersmith Hospital (Hammersmith)
- Site 06: Howard University
- Site 07: Johns Hopkins University (JHMI)
- Site 08: NHLBI Intramural
- Site 09: University of Colorado
- Site 10: University of Illinois, Chicago

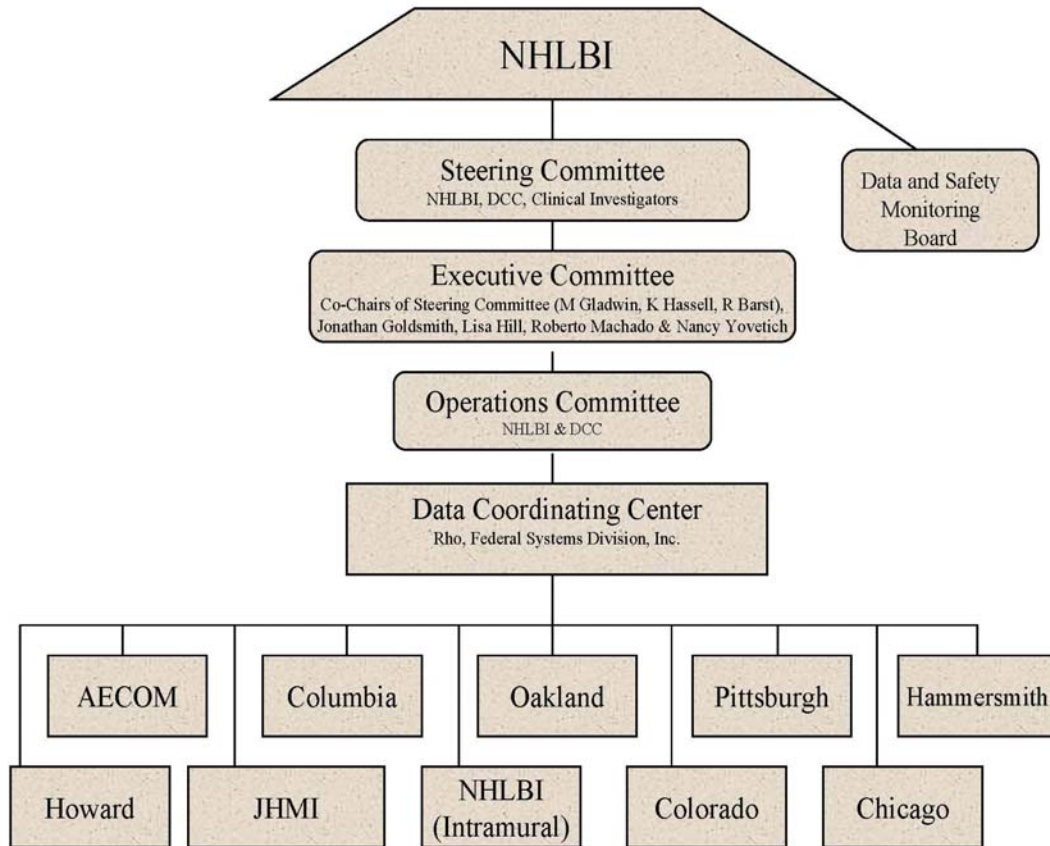
Underlining reflects the terms of reference for each clinical site in study documentation (e.g., status reports).

The study will be overseen by the Data and Safety Monitoring Board assigned to this study (see Figure 1-1 for structure of walk-PHaSST).

The 10 participating clinical sites will screen up to 1000 patients into the Screening Phase and randomize 132 of those patients into the 16-week Main Interventional Trial (MIT). Subjects completing the MIT will be offered an opportunity to participate in the Open-Label Follow-up Phase of the trial, during which time they may receive up to 1 additional year of open-label sildenafil. In addition to the MIT, subjects who a) do not qualify for MIT or b) who discontinue from or complete the MIT or Open-label Follow-up Phase may participate in the Observational Trial for up to 3 years.

### 1.3 Summary of the walk-PHaSST Consortium Organization

Figure 1-1 -- walk-PHaSST Organizational Chart



### **1.3.1 *National Heart Lung and Blood Institute (NHLBI)***

#### **1.3.1.1 NHLBI Project Officer**

The National Heart Lung and Blood Institute (NHLBI) is responsible for organizing and providing support for the walk-PHaSST trial. The Project Officer of the NHLBI will be responsible for review and approval of the protocol and of other key deliverables. In addition, the Project Officer will 1) monitor progress of the trial including technical progress of DCC and of the clinical sites; 2) interpret the Statement of Work and any technical performance requirements; 3) perform technical evaluations and inspections and 4) assist with technical performance problems.

#### **1.3.1.2 NHLBI Contracts Officer**

The Contracting Officer for this study is the only individual on the walk-PHaSST team who has the authority to act as an agent of the government. This individual has the ability to 1) direct or negotiate any changes in the Statement of Work associated with the contract; 2) modify or extend the performance period; 3) change the date of scheduled deliverables; 4) authorize reimbursements and 5) change any terms or conditions of the trial's contract. Therefore, any contract issues or questions about work scope should be directed to the study's Contracts Officer, Lisa Hill.

#### **1.3.1.3 Data and Safety Monitoring Board (DSMB)**

The DSMB is an advisory body convened and administered by NHLBI. It is composed of scientists/clinicians, statisticians, and ethicists who are independent from the walk-PHaSST clinical and administrative sites and who have no major financial interest in the study drug manufacturer (i.e., Pfizer). The DSMB reviews the conduct of the trial, evaluates screening and enrollment progress, and evaluates important safety information from the trial. The DSMB provides NHLBI with recommendations for conduct and continuation of the trial. NHLBI has the authority to modify any suggestions made by the DSMB.

The Executive Secretary of the DSMB is an NHLBI employee who is independent of the project (i.e., not the Project Officer, Contracts Officer, or an Investigator). The Executive Secretary provides the recommendations to the Project Officer who, in turn, provides to the study team.

### **1.3.2 *Steering Committee (SC)***

The walk-PHaSST Steering Committee (SC) includes the Project Officer, the DCC, and at least one Clinical Investigator from each of the clinical sites. The SC formulates and implements all policy decisions related to the study. The SC will fulfill the following responsibilities:

- Assist the Committee responsible for developing the Manual of Operations
- Ratify major changes in the Protocol or Manual of Operations
- Review concept proposals and appoint protocol teams
- Recommend to the NHLBI Project Officer changes or modifications to the protocol or other clinical activities that may be necessary or desirable
- Advise and assist the DCC and other committees on operational matters
- Resolve operational problems brought to the SC by investigators, study coordinators, clinical research associates, laboratories/repositories, or the DCC
- Review the performance of all participating centers based on information provided by the DCC. This evaluation includes the ability to enroll study participants, assessment of data quality collected by the participating centers and adherence to the protocol.

The Steering Committee meets once a month but may meet more frequently should the need arise. The SC does not have access to blinded study data.

### **1.3.3            *Executive Committee (EC)***

The walk-PHaSST Executive Committee (EC) members include: the Project Officer, Dr. Jonathan Goldsmith; the PI of the DCC, Dr. Nancy Yovetich; the Co-chairs of the Steering Committee (Dr. Mark Gladwin, Dr. Kathryn Hassell, and Dr. Robyn Barst), and Roberto Machado, MD. Additional team members attend on an as needed basis. The EC is primarily responsible for the scientific direction and administration of the study. The EC will meet monthly to fulfill the following responsibilities:

- Develop and maintain, with advice from other clinical sites, an organizational structure that meets the needs of the study and the NHLBI
- Remain informed of all operational aspects of the study and formulate policies that ensure the smooth operation of the study
- Advise the DCC on issues of importance to the overall conduct of the studies
- Appoint persons to appropriate committees
- Chair the Steering Committee meetings
- Represent the Steering Committee to the DSMB
- Amend the protocol when needed
- Evaluate requests for protocol waivers



### **1.3.4            *Operations Committee (OC)***

The walk-PHaSST Operations Committee (OC) includes the Project Officer, the DCC, and, on an as needed basis, other attendees that will work together to discuss the operational aspects of the study. The OC will determine the frequency of the meetings as enrollment increases. The OC will fulfill the following responsibilities:

- Review study enrollment at each site
- Review the efficiency and quality control of study procedures
- Review the process for central collection of the echocardiograms, blood, and right heart catheterizations
- Update and maintain the MOO on an as needed basis
- Respond to all questions and issues that may be brought up by the clinical sites during the course of the study
- Develop agenda topics for the Executive and Steering Committees

### **1.3.5            *Data Coordinating Center (DCC)***

The DCC plays a key role in developing and facilitating the study protocol and is responsible for providing statistical, epidemiologic, and scientific expertise to be used in designing the study. In addition, the DCC is responsible for ensuring the collection of quality and accurate data from participating centers. Specifically, the functions of the DCC include the following:

- Participate as members, create agendas, and finalize minutes for the Steering Committee, Executive Committee, Operations Committee, Publications Committee and Study Coordinator Committee
- Maintain a central website with up to date study materials and documents so that they are readily available to study staff
- Arrange for and participate in sub-committee meetings and generate meetings as necessary
- Maintain a roster of participants with relevant contact information, study roles and organizational affiliations
- Coordinate and facilitate communication via teleconference among participating centers and the NHLBI.
- Coordinate meetings and travel accommodations for participating centers
- Assist the Steering Committee in the development and finalization of the protocol
- Coordinate the development and distribution of the Manual of Operations (MOO)
- Develop secure, computerized data entry systems and case report forms

- Develop and implement edit checks and validation procedures to ensure high quality data
- Assist centers in addressing missing, erroneous or delayed data
- Identify laboratories and repositories to support the objectives of the walk-PHaSST study and coordinate contracts with these organizations
- Provide specimen tracking using RhoLAB
- Provide randomization procedures and manage study drug repackaging and distribution
- Develop the statistical analysis plan (SAP)
- Perform statistical analysis of study endpoints
- Attend the open portion of the DSMB meeting
- Prepare statistical reports to monitor study progress, data quality and site performance for the DSMB
- Provide monthly status reports of study progress to the NHLBI Project Officer
- Develop and submit the annual IND reports in conjunction with the NHLBI Project Officer and the IND holder (NHLBI Extramural)
- Monitor adverse events and reporting of serious adverse events
- Annual review of the data (for completeness, accuracy, and integrity) at the clinical sites by a trained clinical research associate (CRA)
- Assist in the development of presentations and publications
- Provide training and training materials for site staff regarding standard operating procedures for conducting the walk-PHaSST trial

## **2 SCHEDULE OF STUDY EVALUATIONS**

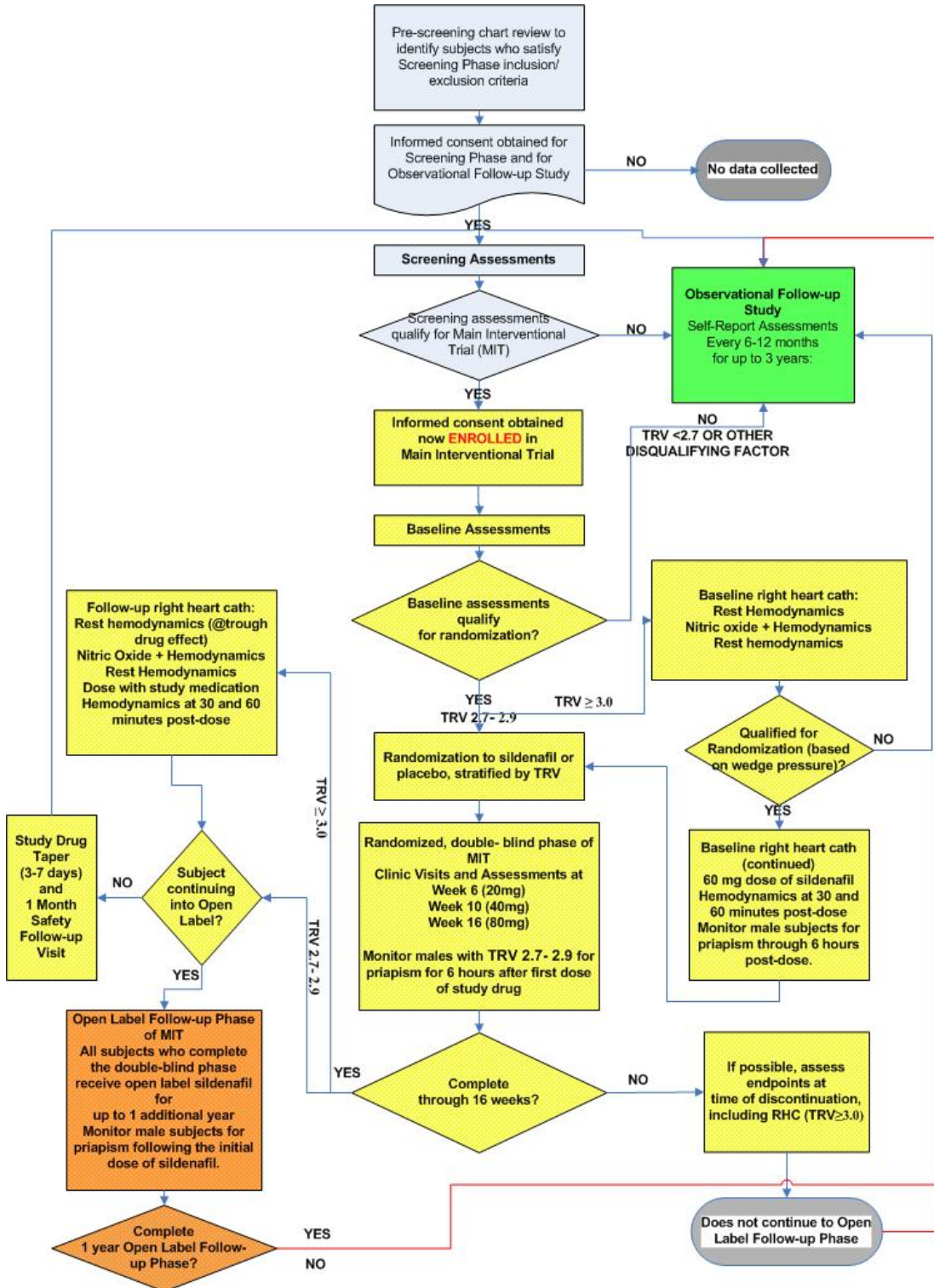
### **2.1 Summary of Evaluations**

This chapter provides a suggested schedule for a highly efficient administration of study procedures and evaluations. However, in some cases, sites may need to modify this order, based on individualized needs (e.g., scheduling challenges).

Details of the conduct of study procedures and evaluations are provided in Chapters 4 – 12.

For convenience of reference, several protocol items are duplicated herein. Figure 2-1 describes the study flow. This figure contains one administrative correction within the baseline right heart catheterization procedure (correct dosage= 60 mg). Table 2-1 and Table 2-2 Schedule of Events – Main Interventional Trial summarize the schedule of study evaluations.

Figure 2-1 Subject Flow



### **2.1.1 Screening and Observational Follow-up Study Procedures**

In the Screening Phase of the study, patients who are at least 12 years of age and who have sickle cell disease will be consented and then screened to determine qualification for the MIT.

The following screening assessments (done only while the patient is in steady state) will qualify subjects for enrollment into MIT:

- 1) TRV • 2.7 m/sec. (determined by the echocardiogram)
- 2) 6MW distance of 150-500 m (determined by 6 minute walk procedure)
- 3) If female, not pregnant (determined by local test)
- 4) For subjects whose screening measures satisfy the above criteria but who do not have prior electrophoretic documentation of sickle cell disease, a hemoglobin electrophoresis should be performed locally.

The following items will disqualify a subject for enrollment into MIT (refer to Protocol Section 5.3.2 for a full list of Exclusion Criteria of the MIT):

- 5) Patients who are < 12 years of age or > 70 years of age.
- 6) Female patients who are pregnant, lactating, or not on a reliable form of birth control.
- 7) Any of the following medical conditions:
  - a. Stroke within the last 6 weeks
  - b. New diagnosis of pulmonary embolism within the last 3 months
  - c. History of retinal detachment or retinal hemorrhage in the last 6 months
  - d. Non-arteritic anterior ischemic optic neuropathy (NAION) in one or both eyes
  - e. History of sustained priapism requiring medical or surgical treatment, unless currently impotent or on transfusion program within the last two years
  - f. Any unstable (or chronic or acute) condition that in the opinion of the investigator will prevent completion of the study
- 8) On any of the following concurrent medications:
  - a. Nitrate-based vasodilators
  - b. Prostacyclin (inhaled, subcutaneous, or intravenous)
  - c. Endothelin antagonists
  - d. Calcium channel blocker dose not stable for at least 3 months
  - e. Any other investigational drug (except HU)
  - f. Active therapy for pulmonary hypertension

- g. Protease inhibitor therapy for the treatment of HIV
- 9) Acute or chronic impairment (other than dyspnea), such as angina pectoris, intermittent claudication, symptomatic hip osteonecrosis that would significantly impact the ability to perform a 6-minute walk test
- 10) A tonsillectomy for sleep apnea in the past 3 months
- 11) If an eye exam has not been completed within a year of Randomization. Patients who are on anticoagulation therapy must have a repeat eye exam at baseline (prior to Randomization) even if the patient has had one in the past year.
- 12) Patients with systolic blood pressure • 140 mmHg OR diastolic blood pressure • 90 mmHg (refer to Section protocol 9.3.3 for qualifying blood pressure assessment instructions).

Subjects who do not meet all inclusion/exclusion criteria will be given the opportunity to participate in the Observational Follow-up Study (OFS). The OFS will consist of subject contact every 6-12 months to collect self-reported medical events since the previous visit or phone call. Information that will be collected includes: the frequency of hospitalization, ED, clinic visits, any occurrences of events associated with sickle cell disease (ACS, priapism, etc). The subject will also report any therapy received for sickle-cell related symptoms.

**Table 2-1 Schedule of Events – Screening and Observational Follow-up Study**

	Screening	Follow-up Study (Every 6-12 months, as possible)
Sign Informed Consent	X	
Medical history, physical examination, and vital signs (including weight)	X	
Standard laboratory tests (chemistry, CBC, urinalysis)	X	
Hemoglobin Electrophoresis	X <sup>1</sup>	
HIV test	X	
Echocardiogram (TRV for RV systolic function)	X	
6-minute walk test	X	
Genotype studies	X	
Pregnancy test	X	
Biomarkers (Central Labs [RBC pellets], e.g. NT-BNP)	X	
Adverse Events <sup>2</sup>	X	
Subject report of Hospitalizations/ED/Clinic visits		X
Subject report of Stroke / neurological events, surgical procedures, priapism, acute chest syndrome		X
Subject report of hydroxyurea therapy, pulmonary hypertension therapy, iron chelation therapy, renal replacement therapy, transfusion therapy		X

<sup>1</sup> Complete only for subjects who otherwise qualify for the MIT but for whom source documentation of hemoglobin electrophoresis is absent.

<sup>2</sup> AEs will be reported if they begin or worsen from the time a subject signs informed consent for the Screening Phase through 7 days after the last screening procedure and only if the investigator believes the event to be possibly associated with that study procedure.

### 2.1.2 **Main Interventional Trial**

Subjects who meet the inclusion criteria for the MIT (based on assessments completed during Screening) and who choose to sign informed consent will have their data entered into the Enrollment Eligibility function of RhoRAND. Successful subjects will then undergo additional testing to verify their eligibility for randomization and to establish baseline MIT values.

The Baseline window is **approximately** 28 days (4 weeks/1 month). This means that from the time the first assessment is done (blood draw, echo, x-ray, etc) to Randomization, no more than approximately one month should lapse. Baseline assessments can begin while the subjects are in clinic for their initial MIT visit. The results of these assessments will confirm whether or not each subject is eligible for randomization into the MIT. If more than 28 days passes from the time of completion of the baseline physical exam, baseline 6MW and/or the baseline echocardiogram, the assessment(s) may need to be repeated so that the patient's current data is used for comparison of endpoints at each study visit. The clinical site should contact the DCC with guidance for how to proceed if assessments need to be repeated.

If a subject receives a blood transfusion for an acute event during this screening period, study assessments should not be performed until after 2-3 weeks have passed and that subject has returned to a steady state. If a patient is not steady after 2-3 weeks have passed, the clinical site should contact the DCC for additional guidance regarding the scheduling of the patient's next visit.

After informed consent is signed and RhoRAND Enrollment Eligibility has been successfully completed, it is recommended that the Baseline assessments (Table 2-2) are performed in the following order:

- 1) Review of all inclusion/exclusion criteria (refer to Protocol Sections 5.3.1 and 5.3.2). If Screening Phase evaluations were based on subject self-report, it is preferable to verify these data via the medical record.
- 2) Pregnancy test for all females of childbearing potential.
- 3) Introduce the Brief Pain Inventory (BPI) to the subject, teaching him/her how to complete the form, and explain that the BPI must be completed for 7 days prior to receipt of study drug. The baseline BPI must be completed prior to the RHC, because any pain elicited by the RHC would confound self-reported pain captured in the BPI.
- 4) Physical exam, echocardiogram (to confirm: TRV • 2.7 m/sec.; left ventricular ejection fraction • 40%; no clinically significant ischemic, valvular or constrictive heart disease which includes LVEF < 40% or SF < 22% by echo), and 6 minute walk (all conducted on the same day, preferably in the morning).
- 5) An eye exam if one was not conducted within the year prior to Randomization. If the patient is on an anticoagulation therapy, an eye exam will be required at MIT baseline (after consent is signed).
- 6) RhoRAND Enrollment Verification



- 7) All other baseline assessments (e.g., Chest X-ray, O2 Saturation, Quality of Life, lab tests) with the exception of the RHC may be conducted any time during the Baseline MIT period, but must be conducted prior to distributing double-blind study drug.
- 8) It is best if the RHC is scheduled as the last assessment prior to randomization. RHC must be conducted on the qualified subgroup (baseline TRV • 3.0 m/sec) AFTER RhoRAND Enrollment Verification and after completion of the baseline BPI. See Section 2.1.2.2 for specific RHC interventions. Ensure you have 60 mg sildenafil from the local pharmacist on hand to give to subject undergoing RHC at Baseline. If unable to obtain adequate wedge, site must perform left heart cath to obtain LVEDP. Confirm pulmonary wedge pressure • 24 mmHg during procedure to qualify subject for randomization.

It is important from a methodological perspective to randomize only those subjects who will be treated. The longer the lag from randomization to treatment, the more likely it is that something will happen to keep the subject from being treated. Therefore, it is recommended that you randomize the subject in RhoRAND within a few hours of initiating a subject's first study treatment but no farther in advance than the day prior to first treatment.

On day of first treatment, give first dose of study drug in clinic. Observe males for AE's and priapism for 6 hours; observe females for 2 hours. During the observation period after study medication is taken, the patients should have vital signs taken at 30 minutes, 60 minutes, and 2 hours. In addition, male patients should have vital signs taken at 4 hours and at 6 hours. Patients should not lay or sit the entire observation period, seeing how the patient is in their normal activity state should be included as part of the assessment.

As a reminder, AE/SAEs are collected in MIT as soon as a patient signs consent for the study. Signing consent "enrolls" the subject into the study. Patients should not be enrolled into the MIT until they are in steady state (i.e., on a stable dose of HU or not in crises) and they are ready to begin study assessments in order to prevent a large time lapse between signing consent and Randomization/treatment initiation.

**Table 2-2 Schedule of Events – Main Interventional Trial**

	Randomized, Double-blind Phase				Open-Label Follow-up Phase <sup>8</sup>
	Baseline	6±1wk	10±1wk	16± wk / early term	
Sign Informed Consent	X				
Interim medical history, physical examination, and vital signs	X	X	X	X	
Standard laboratory tests (chemistry, CBC, urinalysis)	X	X	X	X	
Echocardiogram (LV systolic/diastolic function)	X <sup>1</sup>	X		X	
Right heart catheterization – Hemodynamic parameters at rest <sup>2</sup>	X			X	
6-minute walk test	X <sup>3</sup>	X	X	X	
Pulmonary function studies <sup>4</sup>	X				
Borg dyspnea index	X	X	X	X	
NYHA/WHO functional class assessment	X	X	X	X	
Pregnancy test	X	X	X	X	
Ophthalmologic Exam	X <sup>9</sup>				
Chest X-ray <sup>7</sup>	X				
O <sub>2</sub> saturation	X	X	X	X	
Quality of Life (SF-36 or Peds-QL)	X			X	
Biomarkers (Central Labs, e.g. NT-BNP)	X	X	X	X	
Symptoms documentation: hospitalizations, ED, Clinic, transfusions, ACS, priapism	X	X	X	X	
Prior/concomitant medications & narcotics	X	X	X	X	
Compliance evaluations		X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	
Pain Questionnaire (BPI)	X	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	
Adverse Events	X	X	X	X	X <sup>6</sup>

<sup>1</sup>Confirmatory (may be the second echo that confirms the screening echo).

<sup>2</sup>Only for subjects enrolled in the trial with TRV • 3.0 m/s.

<sup>3</sup>Confirmatory (<15% change from screening 6MW test distance).

<sup>4</sup>To evaluate and/or quantify the presence of restrictive or obstructive lung disease. If obtained with 3 months of signing the main study consent document, this test need not be repeated.

<sup>5</sup>Subjects will maintain a diary for 1 week between each study visit. The diary will capture study drug compliance and self-reported pain assessments.

<sup>6</sup>Monitoring interval every 1-3 months, based on each site's standard practice.

<sup>7</sup>If obtained with 3 months of signing the main study consent document, this test need not be repeated.

<sup>8</sup>Patients who complete the treatment phase of the MIT but who choose not to participate in the Open-Label Follow-up Study will have study drug tapered for 3-7 days and return to the clinic for a safety follow-up visit approximately 30 days after completing MIT.

<sup>9</sup>Required for qualifying CTEPH patients and for those with no available record of an exam within the past year. Ophthalmologic exams will provide baseline information for clinicians, but will not be captured in the clinical database.

### **2.1.2.1 Timing of Assessments for the Treatment Period of the Main Interventional Trial**

Efficacy assessments (6MW and echocardiogram) should be performed (per protocol) at peak levels of study medication (1-2 hours after drug is ingested). This will be accomplished by directly observed therapy followed by study assessments. In the event of VOC, ACS or transfusions, postpone assessments for  $14 \pm 3$  days after resolution of the acute event or transfusion. A patient's study visit can only be postponed one time due to the patient not being in steady state. If the patient is not in steady state a second consecutive time to complete their study assessments, the Executive Committee must be contacted to discuss how to proceed.

Patients who are on chronic blood transfusion therapy can participate in the MIT as long as the therapy started at least 1 month prior to randomization and is continued throughout the trial. Each efficacy assessment must consistently occur at least 1 week before or at least 1 week after each chronic blood transfusion.

For visits Week 6 and Week 10, and EOS/early termination:

1. Patient brings study medication to visit.
2. Study medication is administered with **direct observation** by study coordinator.
3. The study coordinator waits one hour before completing an assessment with the patient.
4. Patient undergoes echocardiogram (except for week 10 visit) followed by 6-minute walk test.
5. Only for patients undergoing RHC: Conduct RHC 4 hours after drug administration (see following section for RHC guidelines)

If echocardiogram and 6-minute walk test cannot be performed on the same day, the tests can be obtained in two separate days as long as the same timing guidelines above are followed. The physical exam must be completed the day of the echocardiogram to make sure that vitals are collected on each patient.

### **2.1.2.2 Timing of Assessments in Right Heart Catheterization**

The goal of the RHC is to obtain hemodynamic measurements at trough and peak levels of study medication.

Right heart catheterization will be done during baseline and at the end of the double-blind phase. The procedure is performed the same way at baseline and at the end of the study, with the exception of the use of 60 mg of open-label at baseline and the use of 80 mg of the patient's study drug at the end of the study.

This hemodynamic assessment will follow the guidelines below:

1. In advance of the procedure, provide subjects with routine pre-op instructions (i.e. NPO, hold coumadin, etc.).

2. Prior to the EOC/Early Term visit, subjects will take their nighttime dose of study medication but will not take their morning dose prior to the study visit. Subjects will bring study medication to the visit.
3. Study medication is administered with direct observation by study coordinator
4. Efficacy endpoint assessments, i.e. ECHO and 6MW test will be performed 1-2 hours after study medication is administered; however, if unable to do before right heart catheterization, may perform these after the RHC ONLY under the following circumstances: patient is not sedated during the RHC, and femoral vein/artery is not used as access, then ECHO and 6MW can be performed after catheterization -1-2 hours after the second dose of study medication (administered after a minimum of 4 hours after first dose of study medication).
5. Right heart catheterization will be performed 4 to 8 hours after study medication is administered (trough).
6. Baseline hemodynamic measurements (trough) will be performed as outlined in Table 2-3 (steps 1 and 2)
7. Study medication will be administered and hemodynamic measurements will be performed at 30 and 60 minutes post dosing as outlined in steps 4 and 5 of Table 2-3.

**Table 2-3 Inhaled NO and Oral Sildenafil Challenge**

Baseline	EOS	Intervention	Duration	Assessment
Step 1	Step 1	Baseline		Resting hemodynamics
Step 2	Step 2	Inhaled NO 40 ppm	10 minutes	Resting hemodynamics <sup>1</sup>
Step 3	Step 3	None	10 minutes	Resting hemodynamics
Step 4	Not Applicable	Sildenafil 60 mg orally at Baseline	30 minutes post oral dose	Resting hemodynamics
Not Applicable	Step 4	Double-blind study drug at EOS	30 minutes post oral dose	Resting hemodynamics
Step 5	Step 5		60 minutes post oral dose	Resting hemodynamics

<sup>1</sup> Resting hemodynamics assessed at the end of the 10 minute period of inhaled NO, while the subject is still inhaling the NO.

### 2.1.3 Open-label Follow-up Study (Open-label Study)

Upon completion of the 16-week MIT, patients will be offered the opportunity to receive open-label Sildenafil for up to one year. Patients should begin the open-label medication following their end-of-study assessments. During the Open-label Study, Sildenafil

should be distributed to patients every 1-3 months, and AE/SAE information should be collected simultaneously at each of these visits. After the patient has completed his/her participation in the study, he/she should be entered into the Observational Follow-up Study and followed every 6-12 months until the end of the 3-year study.

#### **2.1.4            *Observational Follow-up Study (OFUS)***

Patients who meet the following criteria are enrolled into the Observational Follow-up Study:

1. Are not eligible for the MIT based on Screening (includes choosing not to sign informed consent);
2. Discontinue early from the MIT;
3. Complete the MIT, but choose not to enroll into the Open-label Follow-up Study (refer to MOO Section 13.3 for suggested guidance for tapering patients off of the MIT study drug);
4. Complete the Open-label Follow-up Study.

Patients who are enrolled into the OFUS will be followed every 6-12 months. The follow-up questions were developed to ask patients about their self-reported health care utilization, episodes of ACS or priapism, and initiation/continuation of therapies for SCD or iron overload (see Table 2-1 for additional details).

### 3 SUBJECT RECRUITMENT, ENROLLMENT, RANDOMIZATION, VISIT REGISTRATION, AND DISCONTINUATION INSTRUCTIONS

#### 3.1 Overview of Screening through Randomization via RhoRAND™

There are four distinct stages in transitioning a subject from screening through randomization within the RhoRAND electronic system: Screening Registration, Enrollment Eligibility, Enrollment Verification, and Randomization.

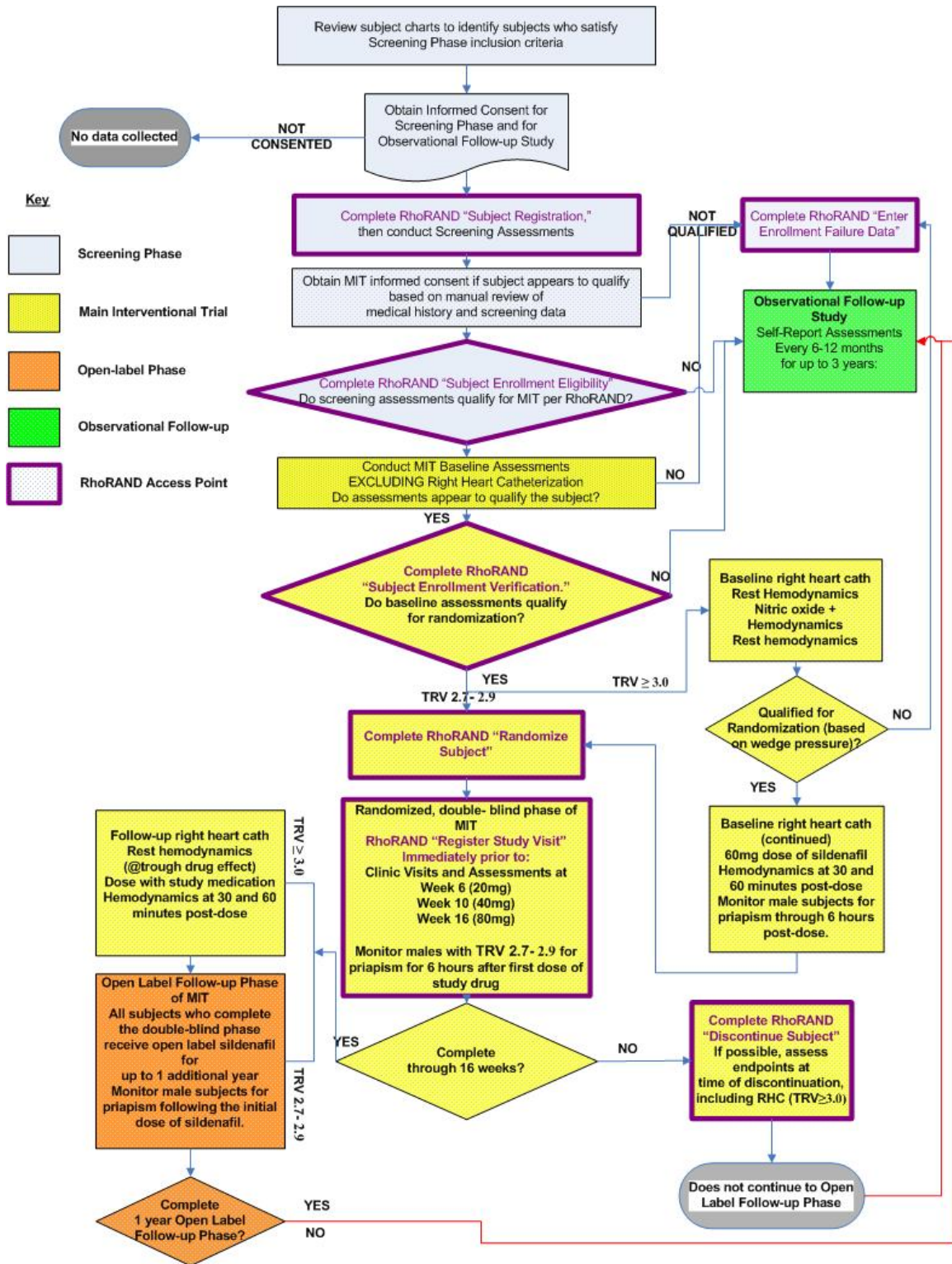
- 1) **Screening Registration:** RhoRAND evaluates the subject in accordance with the screening criteria, captures information about informed consent, and assigns a subject ID.
- 2) **Enrollment Eligibility:** RhoRAND evaluates the subject's qualification to enter the MIT based on the subject's medical history data and on the Screening Phase assessments.
- 3) **Enrollment Verification:** RhoRAND evaluates the second echo and second (and possibly third) 6MW, to confirm that these values qualify the subject for the right heart catheterization procedure (for subjects with TRV• 3.0m/sec) or randomization (for subjects with TRV• 2.7-2.9).
- 4) **Randomization:** RhoRAND provides the randomized, double-blind treatment assignment; for subjects with TRV• 3.0m/sec, acceptable wedge pressure is first confirmed.

Figure 3-1 is an adaptation of the protocol's study flow diagram. The figure includes purple text highlighting each RhoRAND system access point. For further emphasis, all boxes including a RhoRAND access point are outlined in purple. In addition to the RhoRAND functions associated with the four stages noted above, the figure reflects the functions of Visit Registration, Logging an Enrollment Failure, and Discontinuing a Subject.

One important advantage of RhoRAND is that it provides quality control gateways by evaluating whether or not the subject is qualified to advance through each stage. An additional advantage of RhoRAND is that it provides study administrators with all of the screening and enrollment data required for study status reporting; this means you will not have the added burden of faxing the screening and enrollment logs every week.

Please take advantage of the following tools to support your use of RhoRAND. The *Quick Reference Guide for Investigators and Study Coordinators* (see page 3-3) is a succinct clarification of the RhoRAND system as it relates to subject activities. There is also a set of annotated screen shots designed to support you as you practice the RhoRAND system). Requirements for practicing the system, along with these annotated screenshots, are included in Section 3.7.

**Figure 3-1 Study Flow including RhoRAND access points**







## Screening Registration, Enrollment, & Randomization System

Powered by RhoRAND™



### Quick Reference Guide for Investigators and Study Coordinators

#### WEB ADDRESS

<https://www.rhoworld.com/login/>

#### Website Access

To gain web access, please contact your Data Coordinating Center (DCC) study coordinator to obtain user access forms. Follow the instructions on the form and allow a few days for access to be granted.



#### Study Data Integrity

Please **do not share** your user ID or password. Also, remember to logout of the system and close your browser while away from your computer.

#### MENU OPTIONS

- Subject Registration**
- Subject Enrollment Eligibility**
- Subject Enrollment Verification**
- Subject Randomization**
- Enter Enrollment Failure Data**
- Register a Subject Visit**
- Subject Discontinuation from MIT**
- (Practice Functions (for all functions above))**
- Resend Notifications**

Brackets are used to provide additional clarification for the menu items described herein. The bracketed text does not appear on the menu item.

#### SYSTEM/PROCESS FLOW

- Log on to Website
- Select RhoRAND from software menu
- Enter User ID and Password
- Subject Registration [at Screening]**
  - Enter date of screening consent
  - Enter version of signed Informed Consent
  - Indicate the subject's willingness to permit genetic blood tests
  - Enter Screening information
  - Store system notification, containing the Subject ID, in subject's study file
- Subject Enrollment Eligibility [for Main Interventional Trial (MIT)]**
  - Enter Subject ID
  - Enter date and version of signed MIT Informed Consent

#### Subject Enrollment Eligibility (continued)

- Enter MIT inclusion/exclusion information
- Store system notification in subject's file

#### Subject Enrollment Verification [for MIT]

- Enter Subject ID
- Enter additional 6MW and TRV information from baseline assessments
- Store system notification in subject's file

#### Subject Randomization [into Treatment Phase of MIT]

- Enter Subject ID
- Confirm completion of RHC procedures *(when applicable)*
- Store system notification, containing the kit assignment, in the subject's file. A copy of the notification is also sent to the site pharmacist.

#### Enter Enrollment Failure Data

- Enter Subject ID
- Enter Screening Date
- Store system notification in subject's file

#### Register a[n MIT] Subject Visit

- Enter Subject ID
- Confirm Visit
- Enter comments for late and unscheduled visits
- Check for adverse event and drug titration
- Confirm dosage level
- Confirm participation in Open Label *(Week 16 Only)*

#### Register a[n MIT] Subject Visit (continued)

- Store system notification, containing the kit assignment, in subject's file. A copy of the notification is also sent to the site pharmacist.

#### Subject Discontinuation from MIT

- Enter Subject ID
- Enter date of discontinuation
- Enter reason for discontinuation
- Confirm participation in Open Label Follow-up Phase *(Week 16 Only)*
- Store system notification in subject's file

#### Resend Notifications

- Select the desired notification type to be re-sent
- Enter Subject ID
- Store re-sent notifications

#### PRACTICE FUNCTIONS

- Practice Subject Registration**
- Practice Subject Enrollment Eligibility**
- Practice Subject Enrollment Verification**
- Practice Subject Randomization**
- Practice Enter Enrollment Failure Data**
- Practice Register a Subject Visit**
- Practice Subject Discontinuation**

Use the Practice RhoRAND Worksheets stored in the Manual of Operations, to practice each system feature. You must perform all practice functions at least one business day prior to registering your first actual subject. You will receive a notification for each completed practice function. If you do not receive a notification within 15 minutes of completing a practice function, please contact the Help Desk.



## RhoRAND Frequently Asked Questions

- Q** *What is RhoRAND™ ?*
- A** RhoRAND™ is a Internet-based software system used for subject screening, enrollment, randomization, and visit tracking, as well as for study drug distribution and tracking.
- Q** *Is there a way to know exactly what the system will ask me, so that I can be ready with the data?*
- A** Yes. Rho has created worksheets that exactly reflect the data collected within the following functions: 1) Registration; 2) Enrollment Eligibility; 3) Enrollment Verification; and 4) Randomization. These worksheets are available in the MOO and on the walk-PHaSST website.
- Q** *Can everyone working at a site use the same user ID and password?*
- A** No. It is necessary for each person to use his/her individual user ID and password.
- Q** *How can I get a user ID and password?*
- A** You'll use the same ID and password that you use to access the walk-PHaSST website. If you do not have access to the website, please contact your DCC study administrator to receive access.
- Q** *What should I do if I have to terminate a session before I have entered all of the information?*
- A** The system will require you to log back in and start from the beginning. When leaving your computer, please log out for security purposes.
- Q** *Can I practice using the RhoRAND system?*
- A** In fact, you *must* successfully practice several functions within RhoRAND before you are approved to use the non-practice functions of the system. Practice worksheets are available in the MOO to facilitate this process.
- Q** *What should I do if I don't receive a RhoRAND notification?*
- A** First, please make sure that the email hasn't been delivered to your "junk" email folder. If it has, please adjust the email settings to recognize the system's emails as legitimate. If this isn't the problem and your email address has changed, you can call the Help Desk at 1-800-905-0460 or email walkPHaSST\_rhorand@rhoworld.com.
- Q** *Who should I contact if my email address or fax number changes?*
- A** You should notify the DCC study coordinator or the Help Desk.
- Q** *Will our site pharmacist receive the information about study drug assignments?*
- A** Each bottle of double-blind study medication contains a unique "kit number." Your pharmacist will be blinded to study treatment, and will receive blinded system notifications with subject ID and associated kit assignments. These notifications are generated by both the subject randomization and the register a subject visit functions in RhoRAND. The pharmacist will dispense the assigned kit number for the relevant subject. Please follow your standard site procedures when requesting study drug from the pharmacy. For instance, if a written prescription is required, please do so.
- Q** *What are the RhoRAND system hours of operation?*
- A** The RhoRAND system is available 24/7/365, with semi-annual pre-announced down time for system upgrades.



**Help Desk Phone: 1-800-905-0460**  
**Help Desk Hours of Operation: Monday through Friday,**  
**9:00 am to 6:00 pm Eastern Time**  
**Email: walkphasst\_rhorand@rhoworld.com**

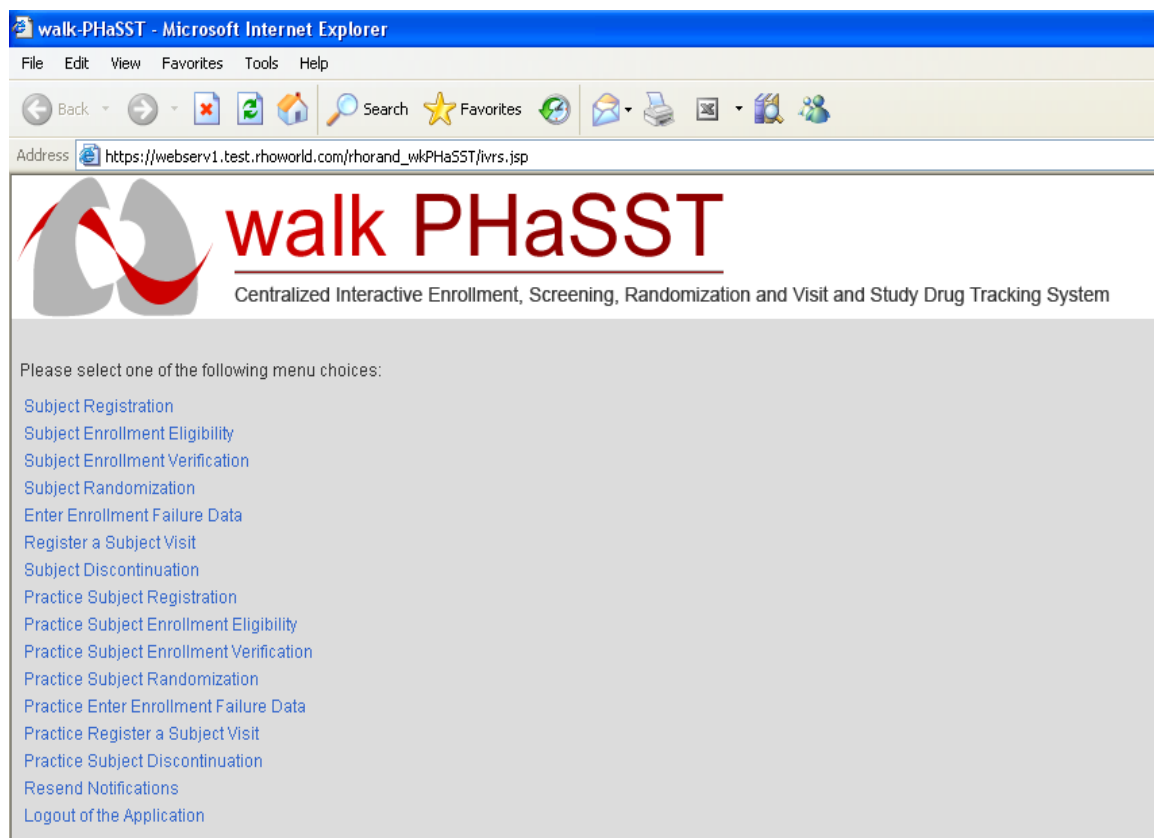
## 3.2 Subject Recruitment and Registration: Screening Study

The Screening Study identifies a pool of subjects with sickle cell disease who also may have pulmonary hypertension. Before conducting any screening assessments, you should confirm that the patient has a diagnosis of sickle cell disease and that the patient is greater than or equal to 12 years of age. Upon confirmation of Screening inclusion criteria, discuss the screening and MIT studies with the patient (and guardian, if applicable). If the patient signs informed consent for the Screening Study, access the Register a Subject function in RhoRAND system to receive a subject ID.

### 3.2.1 RhoRAND

The following graphics depict the screens displayed in the Register a Subject function. *(Please note: Slight differences between these screen shots and the actual system may exist when system update precedes a revision of the MOO.)*

#### Initial RhoRAND Menu Screen



The screenshot shows a Microsoft Internet Explorer browser window with the title "walk-PHaSST - Microsoft Internet Explorer". The address bar displays "https://webserv1.test.rhoworld.com/rhorand\_wkPhaSST/ivrs.jsp". The main content area features the "walk PHaSST" logo and the text "Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System". Below this, a message reads "Please select one of the following menu choices:" followed by a list of menu options:


- [Subject Registration](#)
- [Subject Enrollment Eligibility](#)
- [Subject Enrollment Verification](#)
- [Subject Randomization](#)
- [Enter Enrollment Failure Data](#)
- [Register a Subject Visit](#)
- [Subject Discontinuation](#)
- [Practice Subject Registration](#)
- [Practice Subject Enrollment Eligibility](#)
- [Practice Subject Enrollment Verification](#)
- [Practice Subject Randomization](#)
- [Practice Enter Enrollment Failure Data](#)
- [Practice Register a Subject Visit](#)
- [Practice Subject Discontinuation](#)
- [Resend Notifications](#)
- [Logout of the Application](#)

walk-PHaSST - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Refresh Home Search Favorites

Address [https://webserv1.test.rhoworld.com/rhorand\\_wkPHaSST/ivrs.jsp](https://webserv1.test.rhoworld.com/rhorand_wkPHaSST/ivrs.jsp)



# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

**You are about to register a subject into the walk-PHaSST study and obtain the subject's ID.**

Date of provision of informed consent for screening and observational follow-up study: MM:  DD:  YYYY:

Did the subject agree to permit genetic test on his/her blood?  Yes  No

Please enter the version of informed consent the subject has agreed to:


[Return to Main Menu](#)

walk-PHaSST - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Refresh Home Search Favorites

Address [https://webserv1.test.rhoworld.com/rhorand\\_wkPHaSST/ivrs.jsp](https://webserv1.test.rhoworld.com/rhorand_wkPHaSST/ivrs.jsp)



# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

Date of provision of informed consent for screening and observational follow-up study: **27 Nov 2007**

Is the information above correct?  Yes  No


[Return to Main Menu](#)

walk-PHaSST - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Home Search Favorites Refresh Print Mail Stop Help

Address [https://webserv1.test.rhoworld.com/rhorand\\_wkPHaSST/ivrs.jsp](https://webserv1.test.rhoworld.com/rhorand_wkPHaSST/ivrs.jsp)



# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

Has the subject been diagnosed with sickle cell disease (including, but not limited to SS, SC, SD, or Sβ<sup>+</sup>+ thalassemia)?  Yes  No

Subject's date of birth: MM:  DD:  YYYY:

Did subject agree to permit his/her genetic sample to be subjected to additional genetic tests related to his/her disorder but outside of the walk-PHaSST study?  Yes  No

Did subject agree to permit his/her genetic sample to be subjected to additional genetic tests **NOT** related to his/her disorder but outside of the walk-PHaSST study?  Yes  No

Did subject wish to be contacted with any important information about his/her health, based on future research involving his/her genetic materials?  Yes  No

What, if any agreement did subject provide in reference to contact for information about genetic information as it relates to other members of his/her family?

- Subject agreed to allow contact with him/her in the future  Yes  No
- Subject agreed to allow contact with other family members for participation in a future study  Yes  No
- Subject did not agree to permit contact with him/her and his/her family in the future  Yes  No


[Return to Main Menu](#)

walk-PHaSST - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Home Search Favorites Refresh Print Mail Stop Help

Address [https://webserv1.test.rhoworld.com/rhorand\\_wkPHaSST/ivrs.jsp](https://webserv1.test.rhoworld.com/rhorand_wkPHaSST/ivrs.jsp)



# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

The subject has been successfully registered into the walk-PHaSST study.

The subject has been assigned ID number: **990012** → This subject ID will be used in RhoLAB and EDC.B

Notifications have been generated and should be delivered to the appropriate study personnel shortly.

If you would like to perform additional operations, please click the menu link below. Otherwise, click the logout link or close your web browser to exit the system.

[Return to Main Menu](#)

[Logout of the Application](#)

Upon successful completion of the Register a Subject function, you will receive the following type of email notification (or fax --- if you prefer) with the assigned subject ID number. At that point, you may conduct the Screening Study assessments (see Table 3 of the protocol).

**Sample Screening Registration Notification Issued by RhoRAND**

walk-PHaSST)

Subject Registration Notification)

User ID: 9999)  
Site ID: )99)  
Site Name: Rho University)  
Subject ID: 990012)  
Date of Screening Consent: 28 November 2007)  
Date of Birth: 02 May 1984)  
Eligibility Screening Date: 30 November 2007)

The subject indicated above has been successfully registered into)the screening phase of walk-PHaSST. Please print this notification)and store in the study files.)

Generated 30-Nov-2007 12:16 Eastern Time)

**3.2.2 Subject ID Code List and Subject Screening and Enrollment Log**

Please record all subjects' names, contact information, and subject IDs in the **Subject ID Code List**, and maintain this form in a secure location. For purposes of convenience of recordkeeping, you may choose to use the **Subject Screening and Enrollment Log** provided. This is a tool to help keep track of the progress of all of subjects in a consolidated location. Use of this form is not required because subject status reports can be generated from the data captured in RhoRAND. However, please use it if you find it helpful.



## SAMPLE: Subject ID Code List

Investigator Name: \_\_\_\_\_ Site Number: \_\_\_\_\_

Include all subjects who have been registered into the Screening Phase of the walk-PHaSST protocol

Subject Study ID Number	Subject Name/Initials and/or Medical Record Number	Subject Contact Information

Page \_\_\_\_ of \_\_\_\_



**SAMPLE Screening and Enrollment Log**

Subject ID	Date of Screening/ Observational Follow-up ICF	Date of Subject Registration in RhoRAND	Date of MIT ICF	Date of Enrollment Eligibility	Date of Enrollment Verification	Date of Randomization	Date of Entry Into Open- Label	Date of Entry into Obs. Follow-up	Final MIT Disposition <sup>1</sup>

<sup>1</sup> FEE=failed Enrollment Eligibility; FEV=failed Enrollment Verification; FR=failed Randomization; RNT=randomized but not treated; DISC=treated but discontinued prematurely; COMP=Completed MIT.

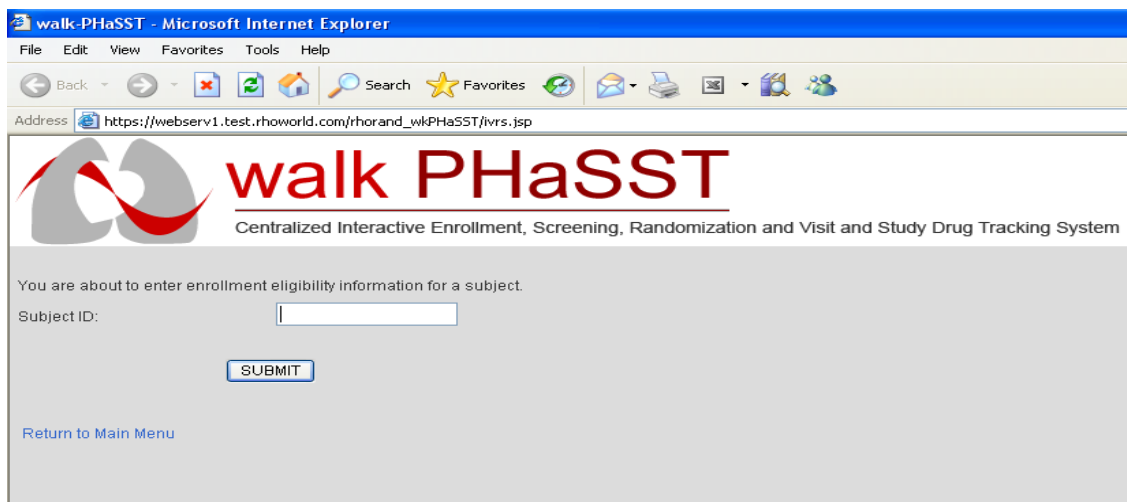
Subjects who fail any time prior to randomization may be “rescreened” up to 2 additional times if reassessment could qualify the subject to proceed in the MIT (e.g., if the screening TRV= 2.7 and the baseline TRV=2.6).

### 3.3 Subject Enrollment: Main Interventional Trial (MIT)

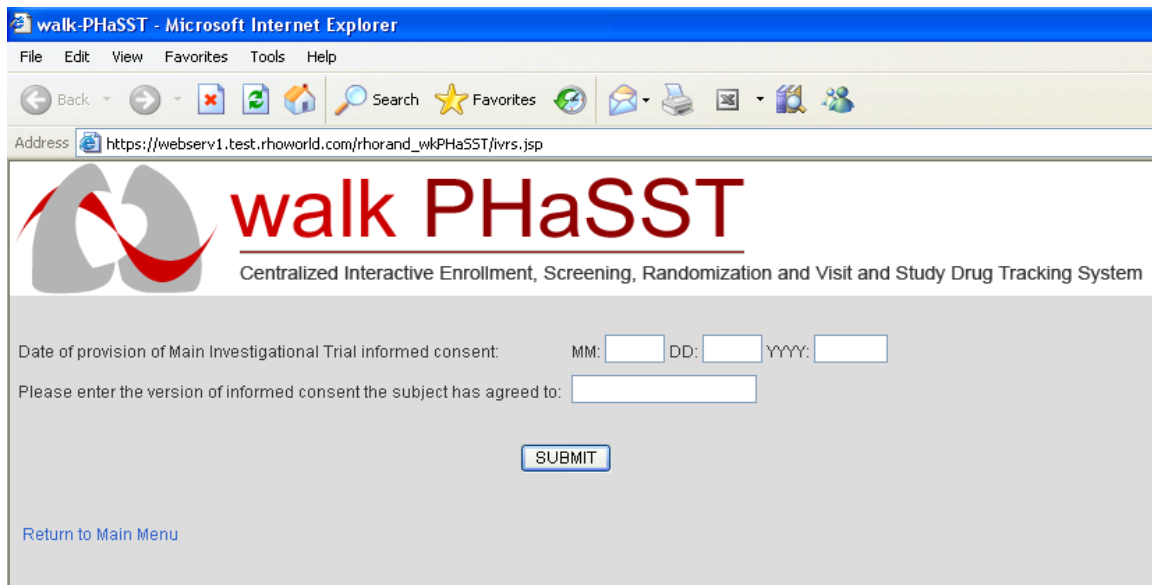
#### 3.3.1 Enrollment Eligibility

Evaluate the screening assessments and subject's medical history to determine eligibility for the MIT, and consent those qualified subjects. After a subject consents to the MIT, access the Subject Enrollment Eligibility function of RhoRAND to confirm the eligibility data.

The following graphics depict the screens displayed in the Enrollment Eligibility function. (*Please note: Slight differences between these screen shots and the actual system may exist when system update precedes a revision of the MOO.*)



The screenshot shows a Microsoft Internet Explorer browser window with the address bar displaying [https://webserv1.test.rhoworld.com/rhorand\\_wkPHaSST/ivrs.jsp](https://webserv1.test.rhoworld.com/rhorand_wkPHaSST/ivrs.jsp). The page header features the walk PHaSST logo and the text "Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System". The main content area contains the text "You are about to enter enrollment eligibility information for a subject." followed by a "Subject ID:" label and a text input field. Below the input field is a "SUBMIT" button. At the bottom left, there is a link labeled "Return to Main Menu".




The screenshot shows a Microsoft Internet Explorer browser window with the address bar displaying [https://webserv1.test.rhoworld.com/rhorand\\_wkPHaSST/ivrs.jsp](https://webserv1.test.rhoworld.com/rhorand_wkPHaSST/ivrs.jsp). The page header features the walk PHaSST logo and the text "Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System". The main content area contains the text "Date of provision of Main Investigational Trial informed consent:" followed by three input fields for MM, DD, and YYYY. Below this is the text "Please enter the version of informed consent the subject has agreed to:" followed by a text input field. At the bottom center, there is a "SUBMIT" button. At the bottom left, there is a link labeled "Return to Main Menu".

The system reflects certain responses back for purposes of confirmation.



walk-PHaSST - Microsoft Internet Explorer  
File Edit View Favorites Tools Help  
Back Forward Stop Home Search Favorites Refresh Print Mail Stop People  
Address https://webserv1.test.rhoworld.com/rhorand\_wkPhaSST/ivrs.jsp



# walk PHaSST


Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

Date of provision of Main Investigational Trial informed consent: **30 Nov 2007**

Is the information above correct?  Yes  No

[Return to Main Menu](#)

walk-PHaSST - Microsoft Internet Explorer  
File Edit View Favorites Tools Help  
Back Forward Stop Home Search Favorites Refresh Print Mail Stop People  
Address https://webserv1.test.rhoworld.com/rhorand\_wkPhaSST/ivrs.jsp



# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

## Inclusion Criteria

If the subject is female, is she on a reliable method of birth control or not physically able to bear children? (Please select 'Not Applicable' for male subjects.)  Yes  
 No  
 Not Applicable

Is there electrophoretic documentation of sickle cell disease (including, but not limited to SS, SC, SD, or Sβ<sup>+</sup>/+ thalassemia) for the subject?  Yes  
 No

TRV measurement #1 (m/s):   
Date of TRV measurement #1: MM:  DD:  YYYY:

Distance #1 walked (m):   
Date and time of walk distance evaluation #1: MM:  DD:  YYYY:  Hr(24):  Min:

In the opinion of the investigator, is the subject able to complete the protocol scheduled assessments during the 16 week, double-blind phase?  Yes  
 No


Again, the system reflects some responses back for purposes of confirmation.

walk-PHaSST - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Refresh Home Search Favorites Print Mail Stop

Address [https://webserv1.test.rhoworld.com/rhorand\\_wkPHaSST/ivrs.jsp](https://webserv1.test.rhoworld.com/rhorand_wkPHaSST/ivrs.jsp)


 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

Date of TRV measurement #1: **28 Nov 2007**  
Date and time of walk distance evaluation #1: **28 Nov 2007 09:25**

Is the information above correct?  Yes  No

[Return to Main Menu](#)

walk-PHaSST - Microsoft Internet Explorer  
File Edit View Favorites Tools Help  
Back Forward Stop Home Search Favorites Refresh Mail Print Mail New Tab  
Address [https://webserv1.test.rhoworld.com/rhorand\\_wkPHaSST/ivrs.jsp](https://webserv1.test.rhoworld.com/rhorand_wkPHaSST/ivrs.jsp)



# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

## Exclusion Criteria

Is the subject currently pregnant or lactating?  Yes  
 No

**Please indicate whether the subject is currently experiencing any of the following medical conditions:**

- Stroke within the last six weeks?  Yes  
 No
- New diagnosis of pulmonary embolism within the last three months?  Yes  
 No
- History of retinal detachment or retinal hemorrhage within the last six months?  Yes  
 No
- Non-arteritic anterior ischemic optic neuropathy (NAION) in one or both eyes?  Yes  
 No
- History of sustained priapism requiring medical or surgical treatment, unless currently impotent or on transfusion program within the last two years?  Yes  
 No
- Any unstable (chronic or acute) condition that in the opinion of the investigator will prevent completion of the study?  Yes  
 No

Is the subject currently taking nitrate-based vasodilators (including, but not limited to nicorandil [available in the UK only]), prostacyclin (inhaled, subcutaneous or intravenous) or endothelin antagonists?  Yes  
 No

If the subject is taking calcium channel blockers, have they been on a stable dose for less than 3 months?  Yes  
 No

Does the subject have a left ventricular ejection fraction of < 40% or clinically significant ischemic, valvular, or constrictive heart disease: LVEF < 40% or SF < 22%?  Yes  
 No

Is the subject involved in other research studies with investigational drugs with the exception of hydroxyurea?  Yes  
 No

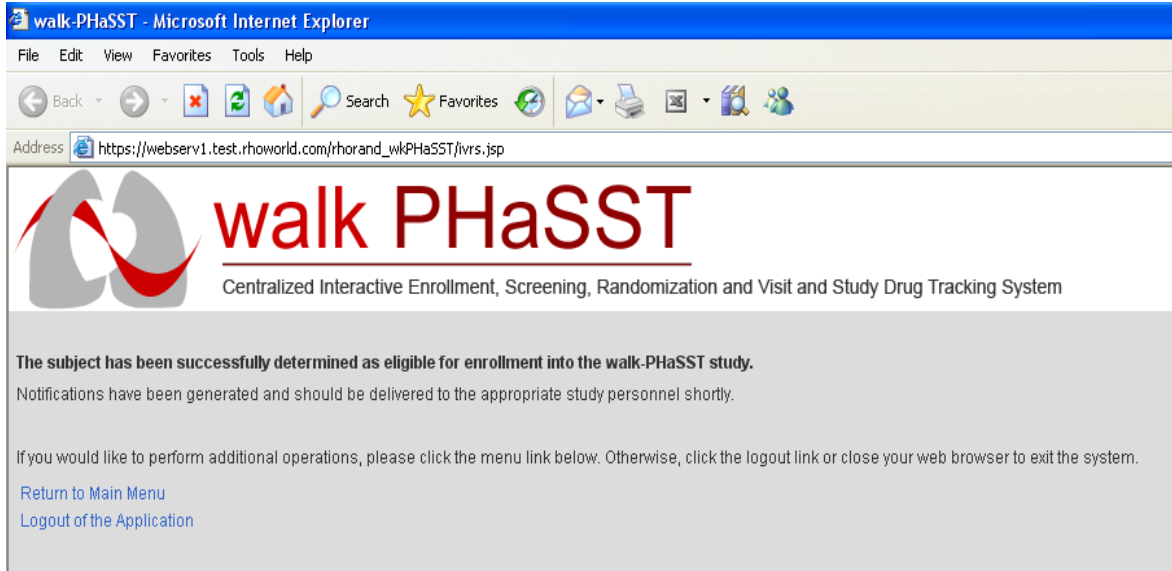
Does the subject have acute or chronic impairment (other than dyspnea), limiting the ability to comply with study requirements (in particular the 6MWT), e.g., angina, pectoris, intermittent claudication, symptomatic hip osteonecrosis?  Yes  
 No

Has the subject had a tonsillectomy for sleep apnea within the last three months?  Yes  
 No

Is the subject undergoing active therapy for pulmonary hypertension, including prostacyclin analog, endothelin-1 antagonists, or PDE-5 inhibitor?  Yes  
 No

Is the subject currently undergoing protease inhibitor therapy for the treatment of HIV?  Yes  
 No

Is the subject taking potent CYP3A4 inhibitors, including erythromycin, clarithromycin, saquinovir, or nefazodone?  Yes  
 No



**Sample Enrollment Eligibility Notification Issued by RhoRAND.**

Upon confirmation of eligibility for enrollment into the MIT, RhoRAND issues the following email (or fax, if preferred) notification.

```
      ) walk-PHaSST )  
  
      Enrollment Eligibility Notification )  
  
User ID:                               9999)  
Site ID:                               99)  
Site Name:                             Rho University)  
Subject ID:                            990012)  
Date of MIT Consent:                   28 November 2007)
```

The above subject has been deemed eligible for enrollment.  
Please print this notification and store in the study files.)

Generated 30-Nov-2007 12:24 Eastern Time)

**Sample Enrollment Eligibility Failure Notification Issued by RhoRAND.**

If the subject does not pass the Enrollment Eligibility evaluation, the following notification will be issued:

```
                                walk-PHaSST)

                                Enrollment Eligibility Failure Notification)

User ID:)                        9999)

Site ID:                          99)

Site Name:)                       Rho University)

Subject ID:                       990035)

Failure Reason(s):
    -)Exclusion #7:  Tonsillectomy for sleep apnea within the
      previous 3 months)
```

The subject identified above has been determined to be currently ineligible for randomization. Please print this notification and store in the study files.)

-----

Some of the reasons for failing enrollment eligibility are temporary exclusions, and the subject may be re-evaluated at a later time. For instance, if the subject had a tonsillectomy for sleep apnea 2 months ago, you can access the Enrollment Eligibility function again in 1 month to reevaluate the subject at that time.


After confirmation of enrollment eligibility by RhoRAND, conduct baseline assessments (see Table 4 of the protocol) with the EXCEPTION of the right heart catheterization procedure. Approval to conduct the right heart catheterization occurs within the Enrollment Verification function.

### 3.3.2 **Enrollment Verification**

Upon completion of the MIT baseline assessments, access the Enrollment Verification function of the RhoRAND system. If a) the baseline TRV and 6MW (in conjunction with their screening counterparts) qualify the subject for randomization and b) the subject is in the lower TRV stratum, the system will approve the subject for randomization. If the subject otherwise qualifies but is in the upper TRV stratum ( $\bullet$  3.0 m/sec), the system will instruct you to conduct the right heart catheterization procedure. Please do so and confirm that the wedge pressure is within the protocol specified limits.

Based on protocol Version 6.0 (12September2008), the RhoRAND system was updated to include questions about the use of anticoagulation therapy (including a general question about use as well as a specific question regarding vitamin K antagonists and heparin) and an eye exam in the past year. Patients who are on anticoagulation therapy

---



**walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

Is the subject currently on anticoagulant therapy consisting of vitamin K antagonists or heparin?  Yes  
 No

[Return to Main Menu](#)



# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

Is the subject currently on any anticoagulant therapy?  Yes  No

SUBMIT

[Return to Main Menu](#)



# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

Has the subject received an ophthalmological exam within the past year?  Yes  
 No

SUBMIT

[Return to Main Menu](#)


---

walk-PHaSST - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Home Search Favorites Refresh Print Mail Stop

Address [https://webserv1.test.rhoworld.com/rhorand\\_wkPhaSST/lvrs.jsp](https://webserv1.test.rhoworld.com/rhorand_wkPhaSST/lvrs.jsp)



# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

Please enter the recorded subject data below. The second walk distance measurement on this page is optional unless the first measured measurement (in Enrollment Eligibility) differ by greater than 15%.

TRV measurement #2 (m/s):


Date of TRV measurement #2: MM:  DD:  YYYY:

Distance #2 walked (m):

Date and time of walk distance evaluation #2: MM:  DD:  YYYY:  Hr(24):  Min:

Distance #3 walked (m):

Date and time of walk distance evaluation #3: MM:  DD:  YYYY:  Hr(24):  Min:



# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

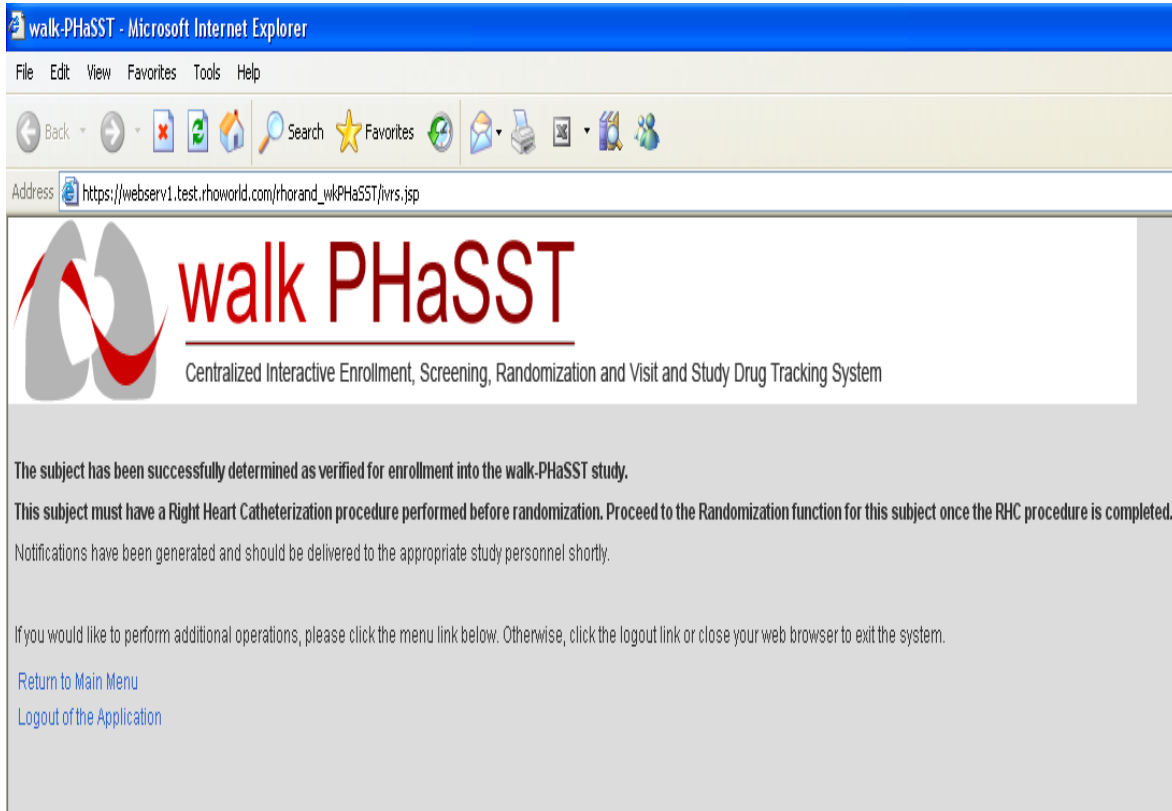
Date of TRV measurement #2: **30 Nov 2007**

Date and time of walk distance evaluation #2: **30 Nov 2007 09:00**

Date and time of walk distance evaluation #3: **Not entered.**

Is the information above correct?  Yes  No





The system issues the following notification upon successful completion of enrollment verification.

**Sample Enrollment Verification Notification Issued by RhoRAND**

walk-PHaSST)

Enrollment Verification Notification)

User ID: 9999)  
Site ID: 99)  
Site Name: Rho University)  
Subject ID: 990012)  
Date of MIT Consent: 01 November 2007)  
Baseline TRV: 3.1 m/sec)  
Next step: Right Heart Catheterization  
and then Randomization)

Enrollment data have)been verified for the above subject. Please  
print this notification and store in the study files.)

Generated 30-Nov-2007 12:27 Eastern Time)

### 3.4 Subject Randomization

It is important from a methodological perspective to randomize only those subjects who will be treated. The longer you randomize in advance of first treatment, the more likely it is that something will happen to keep the subject from being treated. Therefore, it is recommended that you access the Randomize a Subject function in RhoRAND within a few hours of initiating a subject's first study treatment. If the subject required a RHC, this is the only additional data you'll be asked to provide within the function. The system will randomize the subject and deliver notifications with the assigned kit number (i.e., study drug label number) to all of your site users and to your pharmacist.


The following graphics depict the screens displayed in the Enrollment Verification function. *(Please note: Slight differences between these screen shots and the actual system may exist when system update precedes a revision of the MOO.)*

walk-PHaSST - Microsoft Internet Explorer

File Edit View Favorites Tools Help


Back Forward Stop Refresh Home Search Favorites Mail Print Mail Stop Help

Address [https://webserv1.test.rhoworld.com/rhorand\\_wkPHaSST/ivrs.jsp](https://webserv1.test.rhoworld.com/rhorand_wkPHaSST/ivrs.jsp)

 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

You are about to randomize a subject.

Subject ID:

 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

Has the subject's Right Heart Catheterization procedure been completed? If not, please select 'No' - the patient's data entered up to this point will be saved and randomization can be completed for the subject by returning to the Enrollment and Randomization function once the procedure has been performed.  Yes  No

If you have answered 'Yes' above, please fill in the following fields:

Date of Right Heart Catheterization procedure (leave blank if you wish to go back): MM:  DD:  YYYY:

Wedge pressure as obtained by the Right Heart Catheterization procedure (mmHg):

[Return to Main Menu](#)



# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

Date of Right Heart Catheterization procedure: **30 Nov 2007**

Is the information above correct?  Yes  No

SUBMIT



# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

**The subject has been successfully randomized.**

Notifications have been generated and should be delivered to the appropriate study personnel shortly.

If you would like to perform additional operations, please click the menu link below. Otherwise, click the logout link or close your web browser to exit the system.

[Return to Main Menu](#)

[Logout of the Application](#)

The system issues the following notifications upon successful randomization. The Drug Dispensation Notification is also sent to the site pharmacist(s).

---

**Sample Randomization Notification Issued by RhoRAND**

walk-PHaSST )  
Randomization Notification )

User ID:) 9999)  
Site ID:) 99)  
Site Name:) Rho University)  
Subject ID:) 990012)  
Date of MIT Consent:) 30 November 2007)  
Baseline TRV:) 3.1 m/sec)  
Date of Randomization:) 10 December)2007)

Please print this notification and store in the study files.)

Generated 10-Dec-2007 11:31 Eastern Time)

**Sample Drug Dispensation Notification Issued by RhoRAND**

walk-PHaSST )  
Drug Dispensation Notification )

User ID:) 9999)  
Site ID:) 99)  
Site Name:) Rho University)  
Subject ID:) 990012)  
Date of Assignment:) 10 December 2007)  
Visit:) Randomization)  
Dosing Instructions:) 20 mg dose)  
1 tablet --3 times daily)  
Kit ID(s): 123456)  
123457)

The kits listed should be distributed to this subject.)

Please print this notification and store in the study files.)

Generated 10-Dec-2007 11:31 Eastern Time)

If it is your site practice to issue a prescription to the pharmacist for distribution of study drug, please do so at this time.

### 3.5 Registering Treatment Visits


It is necessary to access RhoRAND immediately prior to - OR at the time of - each MIT treatment visit. Visit registration is the mechanism for receiving the kit numbers for those bottles of study drug being dispensed at that visit.

The following graphics depict the screens displayed in the Enrollment Verification function. (*Please note: Slight differences between these screen shots and the actual system may exist when system update precedes a revision of the MOO.*)

walk-PHaSST - Microsoft Internet Explorer

File Edit View Favorites Tools Help


Address [https://webserv1.dev.rhoworld.com/rhorand\\_wkPHaSST/ivrs.jsp](https://webserv1.dev.rhoworld.com/rhorand_wkPHaSST/ivrs.jsp) Go

 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

**You are about to enter visit information for a subject.**

Subject ID:


[Return to Main Menu](#)

 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

The next visit to be registered for this subject is the **Week 6 visit** . Please confirm that this is the visit you are registering for the subject.

Yes, I am registering the **Week 6 visit** for subject 100267 .

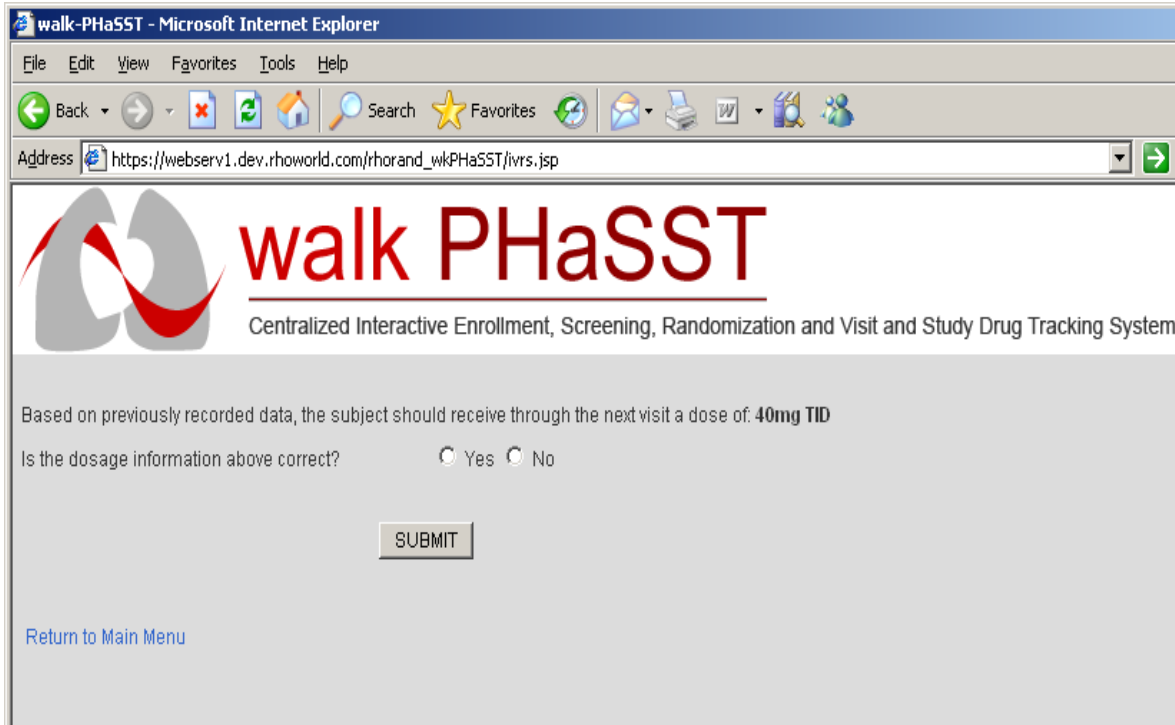
No, I am attempting to register a different visit for subject 100267 .

 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

Since the last visit, has the subject's drug dose been down-titrated to the previously tolerated level for the remainder of the trial?

Yes

No



Upon successful visit registration, you will receive a Visit Registration Notification (sample below) and both you and the site pharmacist(s) will receive Study Drug Dispensation Notifications (see Section 3.4 for a sample of this notification).

### **Sample Visit Registration Notification**

walk-PHaSST)

Visit Notification)

User ID:) 9999)  
Site ID: 99)  
Site Name: Rho University)  
Subject ID: 990014)  
Visit:) Week 6)  
Visit Date:) 04 May 2007)

Please print this notification and store in the study files.)

Generated 20-Dec-2007 12:22 Eastern Time)

### **Sample Visit Out of Range Notification**

If the study visit will fall outside of the protocol specified window, you may also receive a Visit out of Range Notification such as:

```
                walk-PHaSST)
Visit Out of Range Notification)

User ID:)                9999)

Site ID:                 99)

Site Name:              Rho University)

Subject ID:             100014)

Visit:)                 Week 6)

Visit Date:)            04 July 2007)

Randomization Date:)   15 May 2007)

Visit Window:)         19 Jun 2007 -)03 Jul 2007)
```

The subject's visit occurred outside of the protocol-accepted date range. You may need to record a Protocol Deviation in the EDC system.)

### **Dose Titration**

When registering each visit, the system will ask if the subject has been down titrated due to an adverse event for the remainder of the trial. If the subject has been down-titrated for the remainder of the trial, a yes response will step the subject's dosage down 1 level and save that dosing as the expected dosage for the remainder of the trial.

After responding to the above question, the system calculates the subject's expected dosage based on which visit is being logged and whether the subject has been down-titrated for the remainder of the trial. The system then presents the expected dosage and asks the user whether it is correct. If the user indicates the dosage is not correct, the system provides the opportunity to select the appropriate dosage. A dosage of 80mg is not available for the Week 6 visit.

Drug is assigned based on the dosage that is entered/confirmed by the user. Enough drug is assigned to the subject (in whole bottle increments) to last the subject through the last acceptable day of the next visit window.

## Unscheduled Visit

A patient may have to complete an unscheduled visit for the walk-PHaSST study for the following reasons:

- 1) The patient has been hospitalized and has forgotten to bring the study drug with him/her.
- 2) The patient has lost the study drug or has run out of the study drug and needs additional study drug in order to have enough medication to last to the next scheduled visit.
- 3) The patient may need to be TEMPORARILY down-titrated from the 80 mg dosage. (Down titrating from 40 to 20 merely requires taking fewer pills per day and does not require action on the part of RhoRAND.)
- 4) Other more complicated scenarios may require a phone call to the RhoRAND Help Desk (1-800-905-0460).



# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

The next visit to be registered for this subject is the **Week 6 visit**. Please confirm that this is the visit you are registering for the subject.

- Yes, I am registering the **Week 6 visit** for subject 123456 .
- No, I am attempting to register a different visit for subject 123456 .

SUBMIT

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### **3.6 Discontinuing Subjects Due to Enrollment Failure or Post-Randomization Premature Discontinuation**

All patients who receive a subject ID and then do not qualify for randomization into the MIT must ultimately be logged as enrollment failures in RhoRAND. RhoRAND automatically logs subjects as enrollment failures if they fail based on data entered in the Enrollment Eligibility or Enrollment Verification function. However, if a manual evaluation of the subject's data indicates that the subject does not qualify for the study, you may prefer to log the failure using the Enter Enrollment Failure Data function. This function requires significantly less data entry in cases where you are certain the subject does not satisfy the enrollment/randomization criteria.

Please note, that subjects who fail prior to randomization may be re-evaluated if their qualification status changes (e.g., if an additional 6MW test qualifies them for randomization). You should access the Enrollment Eligibility function to have a subject's new data evaluated.

Subjects who discontinue after they have been randomized must be discontinued via the Subject Discontinuation function in RhoRAND. Only use the Subject Discontinuation function after the subject has been enrolled into the MIT (signed consent). If you've inadvertently used the Subject Discontinuation function after enrollment into the MIT, but BEFORE the completion of the Enrollment Eligibility function, contact the Rho Help Desk so that the date of MIT consent can be entered manually.

### **3.7 Practicing RhoRAND**

All study coordinators who wish to access the RhoRAND system must successfully complete each practice function. Clinical Investigators are only required to practice the "Enter Blind Break Data" function. For your convenience, this section includes screen shots of completed system functions for a "test subject." You may use these responses to practice the system, or you may create your own "test subject." It is a good idea to introduce some temporary errors into your practice RhoRAND data entry, so that you can see how the system communicates errors. Please be aware, however, that in order to pass each practice function, the responses you provide must ultimately qualify the "test subject." That is, you can enter an incorrect value, then when the system asks you to confirm you provide the corrected, qualifying value.

### 3.7.1 Practicing Subject Registration

walk-PHaSST - Mozilla Firefox


File Edit View History Bookmarks Tools Help

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https://www.rhoworld.com/rhorand\_wkPhaSST/ivrs.jsp

Getting Started Latest Headlines

walk-PHaSST

 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

You are about to practice registering a subject into the walk-PHaSST study and obtaining the subject's ID.

Date of provision of informed consent for screening and observational follow-up study: MM:  DD:  YYYY:

Did the subject agree to permit genetic test on his/her blood?  Yes  No

Please enter the version of informed consent the subject has agreed to:

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walk-PHaSST - Mozilla Firefox


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Getting Started Latest Headlines

walk-PHaSST

 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

Has the subject been diagnosed with sickle cell disease (including, but not limited to SS, SC, SD, or Sβ<sup>0</sup>/+ thalassemia)?  Yes  No

Subject's date of birth: MM:  DD:  YYYY:

Did subject agree to permit his/her genetic sample to be subjected to additional genetic tests related to his/her disorder but outside of the walk-PHaSST study?  Yes  No

Did subject agree to permit his/her genetic sample to be subjected to additional genetic tests **NOT** related to his/her disorder but outside of the walk-PHaSST study?  Yes  No

Did subject wish to be contacted with any important information about his/her health, based on future research involving his/her genetic materials?  Yes  No

What, if any agreement did subject provide in reference to contact for information about genetic information as it relates to other members of his/her family?

- ◆ Subject agreed to allow contact with him/her in the future  Yes  No
- ◆ Subject agreed to allow contact with other family members for participation in a future study  Yes  No
- ◆ Subject did not agree to permit contact with him/her and his/her family in the future  Yes  No

### 3.7.2 Practicing Subject Enrollment Eligibility

walk-PHaSST - Mozilla Firefox


File Edit View History Bookmarks Tools Help

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https://www.rhoworld.com/rhorand\_wkPHaSST/ivrs.jsp

Getting Started Latest Headlines

walk-PHaSST

 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

You are about to practice entering enrollment eligibility information for a subject.

Subject ID:

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walk-PHaSST - Mozilla Firefox


File Edit View History Bookmarks Tools Help

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https://www.rhoworld.com/rhorand\_wkPHaSST/ivrs.jsp

Getting Started Latest Headlines

walk-PHaSST

 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

Date of provision of Main Investigational Trial informed consent: MM:  DD:  YYYY:

Please enter the version of informed consent the subject has agreed to:

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walk-PHaSST - Mozilla Firefox

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https://www.rhoworld.com/rhorand\_wkPHaSST/jvrs.jsp

Getting Started Latest Headlines

walk-PHaSST

# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

## Inclusion Criteria

If the subject is female, is she on a reliable method of birth control or not physically able to bear children? (Please select 'Not Applicable' for male subjects.)

Yes  
 No  
 Not Applicable

Is there electrophoretic documentation of sickle cell disease (including, but not limited to SS, SC, SD, or Sβ\*+ thalassemia) for the subject?

Yes  
 No

TRV measurement #1 (m/s):

Date of TRV measurement #1: MM:  DD:  YYYY:

Distance #1 walked (m):

Date and time of walk distance evaluation #1: MM:  DD:  YYYY:  Hr(24):  Min:

In the opinion of the investigator, is the subject able to complete the protocol scheduled assessments during the 16 week, double-blind phase?

Yes  
 No

walk-PHaSST - Mozilla Firefox


File Edit View History Bookmarks Tools Help

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https://www.rhoworld.com/rhorand\_wkPHaSST/ivrs.jsp

Getting Started Latest Headlines

walk-PHaSST



# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

## Exclusion Criteria

Is the subject currently pregnant or lactating?  Yes  
 No

**Please indicate whether the subject is currently experiencing any of the following medical conditions:**

- ◆ Stroke within the last six weeks?  Yes  
 No
- ◆ New diagnosis of pulmonary embolism within the last three months?  Yes  
 No
- ◆ History of retinal detachment or retinal hemorrhage within the last six months?  Yes  
 No
- ◆ Non-arteritic anterior ischemic optic neuropathy (NAION) in one or both eyes?  Yes  
 No
- ◆ History of sustained priapism requiring medical or surgical treatment, unless currently impotent or on transfusion program within the last two years?  Yes  
 No
- ◆ Any unstable (chronic or acute) condition that in the opinion of the investigator will prevent completion of the study?  Yes  
 No

Is the subject currently taking nitrate-based vasodilators (including, but not limited to nicorandil [available in the UK only] ), prostacyclin (inhaled, subcutaneous or intravenous) or endothelin antagonists?  Yes  
 No

If the subject is taking calcium channel blockers, have they been on a stable dose for less than 3 months?  Yes  
 No

Does the subject have a left ventricular ejection fraction of < 40% or clinically significant ischemic, valvular, or constrictive heart disease: LVEF < 40% or SF < 22%?  Yes  
 No

Is the subject involved in other research studies with investigational drugs with the exception of hydroxyurea?  Yes  
 No

Does the subject have acute or chronic impairment (other than dyspnea), limiting the ability to comply with study requirements (in particular the 6MWT), e.g., angina, pectoris, intermittent claudication, symptomatic hip osteonecrosis?  Yes  
 No

---

Done

Has the subject had a tonsillectomy for sleep apnea within the last three months?  Yes  
 No

Is the subject undergoing active therapy for pulmonary hypertension, including prostacyclin analog, endothelin-1 antagonists, or PDE-5 inhibitor?  Yes  
 No

Is the subject currently undergoing protease inhibitor therapy for the treatment of HIV?  Yes  
 No

Is the subject taking potent CYP3A4 inhibitors, including erythromycin, clarithromycin, saquinovir, or nefazodone?  Yes  
 No

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---

Done

### 3.7.3 Practicing Subject Enrollment Verification

walk-PHaSST - Mozilla Firefox

File Edit View History Bookmarks Tools Help

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Getting Started Latest Headlines

walk-PHaSST

# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

You are about to practice entering enrollment verification information for a subject.

Subject ID:

[Return to Main Menu](#)

# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

Please enter the recorded subject data below. The second walk distance measurement on this page is optional unless the first measurement and the previously recorded measurement (in Enrollment Eligibility) differ.

TRV measurement #2 (m/s):

Date of TRV measurement #2: MM:  DD:  YYYY:

Distance #2 walked (m):

Date and time of walk distance evaluation #2: MM:  DD:  YYYY:  Hr(24):  Min:

Distance #3 walked (m):

Date and time of walk distance evaluation #3: MM:  DD:  YYYY:  Hr(24):  Min:


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### 3.7.4 Practicing Subject Randomization

walk-PHaSST - Microsoft Internet Explorer


File Edit View Favorites Tools Help

Address [https://webserv1.test.rhoworld.com/rhorand\\_wkPHaSST/ivrs.jsp](https://webserv1.test.rhoworld.com/rhorand_wkPHaSST/ivrs.jsp)

 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

You are about to randomize a subject.

Subject ID:

 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

Has the subject's Right Heart Catheterization procedure been completed? If not, please select 'No' - the patient's data entered up to this point will be saved and randomization can be completed for the subject by returning to the Enrollment and Randomization function once the procedure has been performed.  Yes  No

If you have answered 'Yes' above, please fill in the following fields:

Date of Right Heart Catheterization procedure (leave blank if you wish to go back): MM:  DD:  YYYY:

Wedge pressure as obtained by the Right Heart Catheterization procedure (mmHg):


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### 3.7.5 Practicing Register a Subject Visit

walk-PHaSST - Microsoft Internet Explorer

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Address [https://webserv1.dev.rhoworld.com/rhorand\\_wkPHaSST/ivrs.jsp](https://webserv1.dev.rhoworld.com/rhorand_wkPHaSST/ivrs.jsp) Go

 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

You are about to practice entering visit information for a subject.


Subject ID:

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walk-PHaSST - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Address [https://webserv1.dev.rhoworld.com/rhorand\\_wkPHaSST/ivrs.jsp](https://webserv1.dev.rhoworld.com/rhorand_wkPHaSST/ivrs.jsp) Go

 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System


Since the last visit, has the subject's drug dose been down-titrated to the previously tolerated level for the remainder of the trial?

Yes  
 No

walk-PHaSST - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Address [https://webserv1.dev.rhoworld.com/rhorand\\_wkPHaSST/ivrs.jsp](https://webserv1.dev.rhoworld.com/rhorand_wkPHaSST/ivrs.jsp) Go

 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

Based on previously recorded data, the subject should receive through the next visit a dose of: **40mg TID**

Is the dosage information above correct?

Yes  No



### 3.7.6 Practicing Enter Enrollment Failure Data


walk-PHaSST - Mozilla Firefox

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Getting Started Latest Headlines

walk-PHaSST

 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

You are about to practice entering screen fail data for a subject into the walk-PHaSST study.

Subject ID:

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walk-PHaSST - Mozilla Firefox

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Getting Started Latest Headlines

walk-PHaSST

 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

Date of the start of enrollment screening: MM:  DD:  YYYY:

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https://www.rhoworld.com/rhorand\_wkPhaSST/lvrs.jsp

Getting Started Latest Headlines

walk-PHaSST



# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

You are about to enter screen failure data.

Please indicate the failed criteria by checking the appropriate box(es). When all failed criteria are selected, press the submit button.

- Inclusion #1: Below 12 years of age
- Inclusion #2: Female of childbearing potential and not on a reliable method of birth control
- Inclusion #3: No electrophoretic documentation of a diagnosis of sickle cell disease
- Inclusion #4: TRV < 2.7 m/s by echocardiogram
- Inclusion #5: Six minute walk distance of < 150 or > 500 m
- Inclusion #6: In the opinion of the investigator, inability to complete the protocol scheduled assessments during the 16 week, double-blind phase
- Inclusion #7: Failure to provide informed consent/assent
- Exclusion #1: Currently pregnant or lactating
- Exclusion #2.1: Stroke within the last six weeks
- Exclusion #2.2: New diagnosis of pulmonary embolism within the last three months
- Exclusion #2.3: History of retinal detachment or retinal hemorrhage in the last six months
- Exclusion #2.4: Non-arteritic anterior ischemic optic neuropathy (NAION) in one or both eyes
- Exclusion #2.5: History of sustained priapism requiring medical or surgical treatment, unless currently impotent or on transfusion program within the last two years
- Exclusion #2.6: Any unstable (chronic or acute) condition that in the opinion of the investigator will prevent completion of the study
- Exclusion #3.1: Subject is currently taking nitrate-based vasodilators (including, but not limited to nicorandil [available in the UK only]), prostacyclin (inhaled, subcutaneous or intravenous) or endothelin antagonists
- Exclusion #3.2: Subject is taking calcium channel blockers on a stable dose for less than 3 months
- Exclusion #4: Left ventricular ejection fraction < 40% or clinically significant ischemic, valvular, or constrictive heart disease: LVEF < 40% or SF < 22%
- Exclusion #5: Participation in other research studies with investigational drugs other than hydroxyurea
- Exclusion #6: Acute or chronic impairment (other than dyspnea), limiting the ability to comply with study requirements (in particular the 6MWT), e.g., angina, pectoris, intermittent claudication, symptomatic hip osteoarthritis
- Exclusion #7: Tonsillectomy for sleep apnea within the previous 3 months
- Exclusion #8: Active therapy for pulmonary hypertension, including prostacyclin analog, endothelin-1 antagonists, or PDE-5 inhibitor
- Exclusion #9: Protease inhibitor therapy for treatment of HIV
- Exclusion #10: Subject taking potent CYP3A4 inhibitors, including erythromycin, clarithromycin, saquinovir, or nefazodone
- Randomization Criteria #1: Second six minute walk distance of < 150 or > 500 m, or not within 15% of the screening six minute walk distance
- Randomization Criteria #2: Second TRV < 2.7 m/s by second echocardiogram
- Randomization Criteria #3: Right heart catheterization with pulmonary capillary wedge pressure > 24 mmHg
- Another reason not listed above

Done

### 3.7.7 Practicing Subject Discontinuation

walk-PHaSST - Mozilla Firefox


File Edit View History Bookmarks Tools Help

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https://www.rhoworld.com/rhorand\_wkPHaSST/ivrs.jsp

Getting Started Latest Headlines

walk-PHaSST

 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

You are about to practice discontinuing a test subject.

Subject ID:

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Getting Started Latest Headlines

walk-PHaSST

 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

Date of Discontinuation: MM:  DD:  YYYY:

Reason for Discontinuation:

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## **4 ECHOCARDIOGRAM PROTOCOL**

### **4.1 General Guidelines for Screening and Treatment Echocardiograms**

- All echos should be performed during steady state. In cases of vaso-occlusive crisis, acute chest syndrome event, or acute transfusion, administer echo after event resolution (i.e., approximately 2 weeks).
- Screening and treatment echos will follow the same protocol (Section 4.4).
- If echo follows the 6-minute walk test, there should be at least a one hour delay before the echocardiogram is performed.
- When possible, studies from each individual institution should be performed by the same sonographer using the same echo machine.
- For patients enrolled in the Main Interventional Trial, echos should be performed 1-2 hours after taking the morning dose of the study drug.
- Careful attention should be paid to obtaining optimal Doppler signals for both tricuspid and pulmonary regurgitation. The tricuspid regurgitation (TR) signal by continuous-wave (CW) Doppler is recorded initially from the low parasternal right ventricular inflow view, and it should be optimized in multiple other views including parasternal short-axis and apical views. Apical views should be optimized by moving the transducer medially towards the sternum in order to improve alignment with the TR jet.

### **4.2 Guidelines to follow when the TRV between Screening and Baseline are Different**

There will be instances when the TRV from Screening is • 2.7 m/s and when the Baseline echocardiogram is done the TRV is either < 2.7 m/s or is now • 3.0 m/s. The TRV can vary for several reasons, including the patient's blood pressure, medications, volume status, cardiac output and other hemodynamics.

- If the TRV is between 2.7 and 2.9 m/s at Screening, and increases to • 3.0 m/s at Baseline, a tie-breaker echocardiogram should be completed to determine which strata the patient is randomized to begin treatment initiation. If the “tie-breaker” is < 3.0 m/s, the RHC does not need to be done and the patient can be randomized. If the tie-breaker TRV is • 3.0 m/s, the RHC must be done before the patient can be randomized.
- If the TRV is • 3.0 m/s at Screening and falls to between 2.7 and 2.9 m/s during the Baseline of the MIT, the RHC is not required and the patient can be randomized to the lower strata.
- If the TRV is • 2.7 m/s during Screening and decreases to < 2.7 m/s at Baseline, you may request a protocol waiver to conduct a tie-breaker echocardiogram. If the tiebreaker TRV is < 2.7 m/s, the patient should be discontinued from the study. Please note that a protocol amendment, which would include this tiebreaker, is

being considered. Once a relevant protocol amendment is issued and approved, a waiver request will no longer be necessary.

Note: If a tie-breaker echo is required at the baseline visit, the 3D imaging component must also be completed (refer to MOO Chapter 4.0).

### 4.3 Performance and Interpretation of Echocardiograms

Local interpretation will be performed at each site and clinical alerts will be followed up per individual lab procedures. It is imperative that the local echocardiogram and the demographic case report forms are entered by the local site in the RhoEDC Ssystem **as soon as results are available** so that Vandana Sachdev can complete the central review of each study echocardiogram. The central review of the echocardiograms will be completely masked for all sites (with the exception of NHLBI Intramural because Vandana Sachdev works there). All images will be labeled with a unique specimen label; all other identifying information will be removed before it is shipped to Dr. Sachdev for review.

Transfer of images will be coordinated through the Data Coordinating Center, Rho, Inc. See Section 4.7.2 for shipping instructions. FedEx will be used to transfer 2D and 3D studies on CD (with the exception of Hammersmith Hospital which will use an on-line transfer via the Rho website).

Each site may send a practice echo for analysis and feedback before the study begins. **The first 20 studies and reports at each site will be sent to the core lab (Vandana Sachdev) for analysis within 48 hours of study completion.** The core lab will verify the analysis completed locally (with special attention to TR velocities, LV function and valvular disease) and will provide feedback within 48 hours regarding any exclusion criteria (LVEF < 40% or significant valvular disease defined as moderate or more aortic or mitral regurgitation) and missing or inadequate data.

The remaining studies will be batched and sent to the core lab **weekly** for interpretation.

Studies will be analyzed for right heart pressures, left ventricular structure and systolic function, LV diastolic function, right heart pressures, and right ventricular function. Specific measurements and calculations are described in Table 4-1.

A specific template for Walk-PHaSST will be developed and utilized by the core lab for echo measurements. Data will be exported from the analysis workstations directly into excel spreadsheets.

### 4.4 Data Acquisition for 2D Echocardiograms

Digital acquisition of echo data should be performed with simultaneous ECG tracings. Record 3-5 beats for two-dimensional images using harmonic imaging. Doppler should be performed at 100mm/second sweep speed with low filter. All Doppler parameters should be recorded at end-expiration and at least 3-5 sequential complexes should be included. Standard echocardiographic views as listed below should be performed with special attention to acquisition of specific measurements described.

1. Record height, weight, HR and blood pressure at time of echo.
2. Parasternal long axis view
  - Zoom on LVOT for measurement of LVOT diameter
  - Color on valves
3. Parasternal RV inflow view
  - Assess TR with CW
4. Parasternal short axis view
  - Aortic valve level—color on pulmonic valve; include PW of pulmonary outflow, CW of PA with baseline in middle of screen to capture complete pulmonary regurgitation signal; assess TR in this view
  - Obtain rounded short axis view of LV at chordal level, PM level, and apex for measurement of eccentricity index
5. Apical 4 chamber view
  - Increase depth to include all of left atrium and right atrium
  - PW of pulmonary vein
  - Decrease depth and optimize view of LV for Simpson's EF
  - PW of mitral inflow at tips of mitral leaflets
  - Tissue Doppler of septal and lateral mitral annulus
  - Take separate 2D acquisition of right ventricle including all of RV free wall
  - Assess TR in this view by CW
  - PW of tricuspid inflow velocity at tips of TV leaflets
  - Tissue Doppler of tricuspid annulus at RV free wall
  - TAPSE: place M-mode at tricuspid annulus free wall location and acquire
6. Apical 5 chamber view
  - PW of LVOT
  - PW of isovolumic relaxation time (include mitral inflow and LVOT flow in Doppler tracing)
7. Apical 2 chamber view
  - Increase depth to include all of left atrium
  - Decrease depth to optimize view of LV for Simpson's EF
8. Apical 3 chamber view
9. Subcostal views

- Acquire view of IVC as it enters right atrium
- Ask patient to sniff and repeat acquisition with M-mode
- PW of hepatic vein

#### **4.5 Three-Dimensional Echocardiography**

3D echo will be performed at the discretion of the enrolling institution.

3D echo will be performed on patients enrolled into the MIT. Patients should have a 3D echo at the time of their repeat 2D echo at baseline. 3D echo should then be repeated at the time of the 16 week study assessment or whenever the final 2D echo is performed.

A suggested 3D echo protocol is detailed below:

Use matrix array transducer—Adult Echo preset.  
Optimize ECG tracing to increase R wave peaks.

##### **Left ventricle**

1. Using the 2D imaging, find the best apical window to image the entire left ventricle. (Use ISCAN)
2. Scan with 3D live; decrease TGC at apex, increase gains.
3. Go to “Full Volume”—evaluate whether ventricle fits within sector; readjust transducer position if necessary to include apex . Use low scan density to maximize sector width.
4. Observe image relative to patient’s respiration to determine optimal time to acquire.
5. Instruct patient to hold breathing at optimal time and acquire.
6. Countdown as machine acquires and instruct patient to continue breath-hold while acquiring image: “Hold your breath....25...50...keep holding.....75.....BREATHE NORMALLY”
7. Select “Autocrop” and inspect for artifact

##### **Right ventricle**

- Use the best window available in a modified apical transducer location to center the RV. RV free wall must be visible within sector. (Use ISCAN)
- Follow steps 2-7 above.

Repeat acquisitions if artifacts are seen.

Store 1 best full volume acquisition of the LV and 1 best acquisition of the RV on CD/DVD.

## **4.6 Quality Control for Echocardiograms**

Local reading of echos, specifically for the TR jet velocity, will determine eligibility for enrollment into interventional trial.

Local reading of ejection fraction and valvular disease will determine if patients meet exclusion criteria for protocol.

The core lab will confirm local readings and analyze additional measurements described in section VII.

Significant discrepancies between core lab and local readings will be adjudicated by the QC committee and then sent to the Executive Committee for review.



**Table 4-1 Table of Echocardiographic Measurements**

<u>Category</u>	<u>Measurement</u>	<u>Units</u>
DEMOGRAPHICS	STUDY #	
DEMOGRAPHICS	PATIENT NAME	
DEMOGRAPHICS	AGE	
DEMOGRAPHICS	SEX	
DEMOGRAPHICS	DATE	
DEMOGRAPHICS	Height (in)	
DEMOGRAPHICS	Weight (lb)	
DEMOGRAPHICS	Systolic blood pressure (mmHg)	
DEMOGRAPHICS	Diastolic blood pressure (mmHg)	
DEMOGRAPHICS	Body surface area	
LV STRUCTURE AND SYST FXN	Septal thickness-diastole	mm
LV STRUCTURE AND SYST FXN	Posterior wall thickness-diastole	mm
LV STRUCTURE AND SYST FXN	LV diameter-diastole	mm
LV STRUCTURE AND SYST FXN	LV diameter-systole	mm
LV STRUCTURE AND SYST FXN	LV mass	gm
LV STRUCTURE AND SYST FXN	LV mass index	gm/m <sup>2</sup>
LV STRUCTURE AND SYST FXN	Left atrial diameter	mm
LV STRUCTURE AND SYST FXN	Aortic root	mm
LV STRUCTURE AND SYST FXN	LVOT diameter	mm
	Pericardial effusion (present/absent)	
LV STRUCTURE AND SYST FXN	Doppler aortic outflow VTI	cm
LV STRUCTURE AND SYST FXN	Heart rate during aortic Doppler	beats per minute
LV STRUCTURE AND SYST FXN	Stroke volume	mL
LV STRUCTURE AND SYST FXN	Cardiac output	L/min
LV STRUCTURE AND SYST FXN	Ejection fraction (Simpson's)	%
LV STRUCTURE AND SYST FXN	Ejection fraction (visual)	%
RIGHT HEART PRESSURES	Right atrial area	cm <sup>2</sup>
RIGHT HEART PRESSURES	Peak TR velocity	m/s
RIGHT HEART PRESSURES	IVC diameter	mm
RIGHT HEART PRESSURES	Collapsibility <50% (yes/no)	
RIGHT HEART PRESSURES	Right atrial pressure from IVC sniff	mmHg
RIGHT HEART PRESSURES	Estimated RVSP	mmHg
RIGHT HEART PRESSURES	RVOT PW acceleration time	msec
RIGHT HEART PRESSURES	RV ejection time	msec
RIGHT HEART PRESSURES	PR Doppler for PA diastolic press	m/s
RIGHT HEART PRESSURES	PA diastolic pressure	mmHg
LV DIASTOLIC FUNCTION	Peak E wave	cm/s
LV DIASTOLIC FUNCTION	Peak A wave	cm/s
LV DIASTOLIC FUNCTION	E/A ratio	
LV DIASTOLIC FUNCTION	Deceleration time	msec
LV DIASTOLIC FUNCTION	Isovolumic relaxation time	msec

<u>Category</u>	<u>Measurement</u>	<u>Units</u>
LV DIASTOLIC FUNCTION	LA area by planimetry-4C	cm <sup>2</sup>
LV DIASTOLIC FUNCTION	LA length-4C	mm
LV DIASTOLIC FUNCTION	LA area by planimetry-2C	cm <sup>2</sup>
LV DIASTOLIC FUNCTION	LA length-2C	mm
LV DIASTOLIC FUNCTION	Maximum LA volume	mL
LV DIASTOLIC FUNCTION	LA volume/BSA	mL/m <sup>2</sup>
LV DIASTOLIC FUNCTION	Pulm vein peak Systolic velocity	cm/s
LV DIASTOLIC FUNCTION	Pulm vein peak Diastolic velocity	cm/s
LV DIASTOLIC FUNCTION	PV S/D ratio	
LV DIASTOLIC FUNCTION	PV atrial flow reversal duration	msec
LV DIASTOLIC FXN--Septal TDI	Septal Peak Sa	cm/s
LV DIASTOLIC FXN--Septal TDI	Septal Peak Ea	cm/s
LV DIASTOLIC FXN--Septal TDI	Septal Peak Aa	cm/s
LV DIASTOLIC FXN--Septal TDI	Septal Ea/Aa	
LV DIASTOLIC FXN--Septal TDI	Septal E/ Ea	
LV DIASTOLIC FXN--Lateral TDI	Lateral Peak Sa	cm/s
LV DIASTOLIC FXN--Lateral TDI	Lateral Peak Ea	cm/s
LV DIASTOLIC FXN--Lateral TDI	Lateral Peak Aa	cm/s
LV DIASTOLIC FXN--Lateral TDI	Lateral Ea/Aa	
LV DIASTOLIC FXN--Lateral TDI	Lateral E/ Ea	
RIGHT HEART-RV TDI	Tricuspid Sa	cm/s
RIGHT HEART-RV TDI	Tricuspid Ea	cm/s
RIGHT HEART-RV TDI	Tricuspid Aa	cm/s
	TAPSE-M-mode of tricuspid annulus	mm
RIGHT HEART FUNCTION	Doppler tricuspid inflow A velocity	cm/s
RIGHT HEART FUNCTION	Doppler tricuspid inflow E velocity	cm/s
RIGHT HEART FUNCTION	Doppler RV TEI index	
RIGHT HEART FUNCTION	RV end-diastolic area	cm <sup>2</sup>
RIGHT HEART FUNCTION	RV end-systolic area	cm <sup>2</sup>
RIGHT HEART FUNCTION	%RV fractional area change	%
RIGHT HEART FUNCTION	LV end-diastolic area	cm <sup>2</sup>
RIGHT HEART FUNCTION	RV/LV ratio	
RIGHT HEART FUNCTION	Diast D2: LV parallel to septum	mm
RIGHT HEART FUNCTION	Diast D1: LV perpendic to septum	mm
RIGHT HEART FUNCTION	Diastolic Eccentricity index D2/D1	
RIGHT HEART FUNCTION	Syst D2: LV parallel to septum	mm
RIGHT HEART FUNCTION	Syst D1: LV perpendic to septum	mm
RIGHT HEART FUNCTION	Systolic Eccentricity index D2/D1	
CARDIAC VALVES	Tricuspid Regurgitation	
CARDIAC VALVES	Mitral regurgitation	
CARDIAC VALVES	Aortic regurgitation	

## 4.7 Labeling and Shipping Echocardiograms

### 4.7.1 Labeling Echocardiograms

The DCC will provide labels with unique specimen labels to affix to each echo CD and to each CD case. These labels will be included in the packet containing ALL study specimen labels that each site received prior to beginning enrollment (see Figure 4-1 to view a template of the echocardiogram specimen labels). The labels will have three identical specimen numbers in each row; each row is followed by another set of identical specimen numbers. The first label should go on the CD on which the image of the echocardiogram is saved. The second label should on the case that holds the CD. The third should go on the source document and placed in the subjects study binder. The 6-

walk-PHaSST Study Echocardiogram 123456	walk-PHaSST Study Echocardiogram 123456	walk-PHaSST Study Echocardiogram 123456
walk-PHaSST Study Echocardiogram 558746	walk-PHaSST Study Echocardiogram 558746	walk-PHaSST Study Echocardiogram 558746
walk-PHaSST Study Echocardiogram 254789	walk-PHaSST Study Echocardiogram 254789	walk-PHaSST Study Echocardiogram 254789

One copy of the each label (with the 6-digit specimen number) will be placed:

- 1) On the CD with the echo
- 2) On the case holding the CD
- 3) On the source document

All three labels will be identical across the row.

Each row of labels is immediately followed by a new, unique row of labels.

#### **4.7.2            *Shipping Echocardiograms***

Echocardiograms must be shipped using the RhoLAB system so that they can be properly tracked between the sites and the core lab. Before shipping the echo, the echo specimen must be entered into RhoLAB, and a shipment to the Echo Central Lab must be created. Echocardiograms are sent to the core lab at Screening and Visits 1, 2, and 4 of the MIT (each echocardiogram should be associated with the correct visit in RhoLAB). A barcode scanner can be used to enter this number into the proper field; otherwise the numbers must be manually entered.

For further instructions on adding specimens and creating shipments, refer to the RhoLAB training module on the walk-PHaSST website. Once a shipment is created, the RhoLAB system will generate a packing slip that lists all of the specimens contained in the shipping container or FedEx box and also identifies the FedEx tracking number entered into the RhoLAB system. The printed packing slip should be enclosed in the shipping container.

Echocardiograms should be shipped by FedEx for 2 DAY delivery directly to:

NHLBI Echo Core Lab  
c/o Cyndy Brenneman  
10 Center Drive  
CRC 5NE-Room 1436  
Bethesda, MD 20892  
Phone: 301-451-3799, 301-435-8886  
Fax: 301-435-8886  
Email: [brennemoc@nhlbi.nih.gov](mailto:brennemoc@nhlbi.nih.gov)

## **5 6-MINUTE WALK (6MW) TEST**

### **5.2.1 Introduction**

The six minute walk (6MW) is a widely employed assessment of the submaximal level of exercise capacity in cardiopulmonary disease and has been the standard primary outcome measure in clinical trials of pulmonary arterial hypertension (PAH) therapy. It is the primary outcome measure of this trial and thus, special attention to the proper conduct of this procedure is critical.

### **5.2.2 Inclusion Criteria for Main Interventional Trial (MIT)**

Prior to completing a Screening 6MW, all study participants must complete a practice walk. If a patient has a documented 6MW that was performed within the past 3 months, this can serve as the practice walk. Once the practice walk has been completed, participants who enroll into the screening study must walk between 150 and 500 meters to be eligible for the MIT. Documentation of the practice 6MW should be recorded in the patient walk-PHaSST study binder (at a minimum it should include the date, time, and the distance walked). If other inclusion criteria are met (see protocol Sections 5.3.1 and 5.3.2) and the patient enrolls into the MIT, the participant will undergo a second six minute walk. The second walk distance must be within 15% of the screening walk distance to qualify for enrollment onto the MIT. If the second walk is outside the 15% difference a third walk can be performed no sooner than 2 hours after second walk. The third walk distance must be within 15% of the second walk distance, if not, the subject will be excluded. All 6MWs that are conducted must be done at least 2 hours apart, including the practice walk.

Tests #1 and #3 cannot be compared, only consecutive tests. This is calculated by the following equation:

$$\frac{(\text{Test \#1 result} - \text{Test \#2 result})}{\text{Test \#1 result}} \times 100 = \%$$

$$\frac{(\text{Test \#2 result} - \text{Test \#3 result})}{\text{Test \#2 result}} \times 100 = \%$$

### **5.2.3 Personnel Performing Walk Testing**

Testing will be performed by medical professionals with appropriate training and certification. Every effort should be made to have a single individual perform all tests at a particular site. If this is not feasible, the same tester should conduct the procedure for an individual participant.

Requirements for certification include all of the following:

- Reviewing the protocol and the pertinent MOO sections
- Watching the training DVD available on the walk-PHaSST study website (and distributed to each of the sites)
- Being a medical professional with certification in cardiopulmonary resuscitation with a minimum of Basic Life Support by an American Heart Association-approved cardiopulmonary resuscitation course
- Completing a training session at NIH or by an individual who completed such training.
- Administering a six minute walk test and CRF completion for one individual for practice; these individuals need not be eligible for walk-PHaSST and may be colleagues, but patients similar to those to be enrolled in the clinical trial will provide more relevant experience.

#### **5.2.4 Required Equipment**

Equipment:

1. Stopwatch and lap counter
2. Two (2) small cones or masking tape to mark turnaround points
3. Measuring tape
4. A chair that can be walked along the corridor
5. Worksheets (i.e. outpatient progress note, approved medical record form) on a clipboard (Borg Scale, worksheet for coordinator)
6. A source of oxygen
7. Pulse oximeter
8. Sphygmomanometer
9. Telephone

Important Note: Access to an emergency defibrillator is required.

#### **5.2.5 Corridor Preparation**

The test must be conducted along a long-flat corridor with a hard surface. The corridor must be as quiet as possible while the test is underway to minimize interference. The distance that the participant must walk before changing directions must be at least 30 meters (approximately 100 feet) in length. The length of the corridor should be marked every 3 meters (or approximately every 10 feet) and turnaround points should be marked with cones or brightly colored tape. A starting line and a line every 60 meters (or

approximately every 200 feet) should be marked with brightly colored tape. The hallway should be 6-10 feet wide and the temperature should be set at a comfortable level. The walk course should preferably be located indoors, however walks can be done outdoors if the conditions can be duplicated.

### **5.2.6 Procedure and Measurements**

1. Instruct the participant prior to the walk test to wear comfortable footwear and loosely fitting clothing on the testing day.
2. Repeat testing should be performed about the same time of day to minimize intraday variability
3. Do not perform the 6 minute walk test before the echocardiogram unless there is adequate time for the participant to rest prior to the echo
4. A warm-up period before the test should not be performed.
5. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time perform the following:
  - a. Check for contraindications (If the baseline heart rate is  $> 120$  beats per minute or the  $SpO_2$  is  $< 90\%$ , the walk technician should call the Investigator to evaluate the subject before performing the test. The Investigator will determine the safety of proceeding with testing)
  - b. Measure pulse and blood pressure. Measure oxygen saturation ( $spO_2$ ) following manufacturer's instructions to maximize the signal and to minimize motion artifact. Make sure the readings are stable before recording.
  - c. If a patient is receiving chronic oxygen therapy, attempt to walk without oxygen. If poorly tolerated oxygen should be given at the standard rate normally used during exercise. The patient should carry or wheel his/her own oxygen during the test, if used. The oxygen flow rate used during the test must be recorded. Repeat walks must be performed at the same flow rate, with the same delivery system (i.e. continuous vs. pulsed), and the same carrying device must be used.
6. Have the participant stand and rate their baseline dyspnea using the Borg scale (see below, Table 1).
7. Set the lap counter to zero and the timer to 6 minutes. Assemble all supplies such as stopwatch, clipboard, Borg scale, worksheet and go to the starting position.
8. Instruct the participant as follows:

“The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You

are permitted to slow down, to stop and to rest as necessary. You may lean against the wall while resting but resume walking as soon as you are able.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

(Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.)

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

Start now or whenever you are ready."

9. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.
10. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.
  - a. When the timer shows 4 minutes remaining, tell the participant the following. "You have completed 2 minutes."
  - b. When the time shows 2 minutes remaining, tell the participant the following: "You have completed 4 minutes."
  - c. Do not use other words of encouragement (or body language to speed up).
11. If the participant stops walking during the test and needs a rest, say this:
  - a. "You can lean against the wall if you would like: then continue walking whenever you feel able."
  - b. **DO NOT STOP THE STOPWATCH.** If the participant stops before the 6 minutes are complete and refuses to continue (or you decide that they should not continue), wheel the chair over for the participant to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped and the reason for stopping prematurely.
12. When the stopwatch is 15 seconds from completion, say this:
  - a. "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."
13. When the timing of the 6-minute period is complete, the participant should be instructed to stop walking, the stopwatch will be stopped, and the time recorded. The participant must not move from the final location until the person conducting



the test marks that location. The technician should consider taking the chair if the participant looks exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

14. **Post-Test:** The walk technician should remind the patient of the Borg dyspnea score given before the test and ask the patient to grade his/her breathing level again by asking:
  - a. "Please grade your level of the greatest degree of shortness of breath you experienced at any time during the 6 minute walk test using this scale."
  - b. Show the patient the Borg scale (Sec. 4.2.8)
  - c. The technician should record the postwalk Borg dyspnea level
  - d. Measure heart rate, SpO<sub>2</sub>m and blood pressure
  - e. Record the number of lengths from the lap counter
  - f. Record the additional distance covered (the number of meters in the final partial lap) using the tape measure.
  - g. Calculate the total distance walked, rounding to the nearest meter and record it on the worksheet
  - h. Congratulate the patient on a good effort and offer a drink of water.
  
15. After each test, the worksheet should be filled out by the walk technician and given to the Research Coordinator for entry into Rho EDC. The six minute walk technician should retain a copy of the worksheet for his/her own records to ensure the same oxygen supplementation is used at each visit.

### 5.2.7 Stopping the Test Prematurely

Reasons for immediately stopping the test include the following: chest pain, leg cramps, intolerable dyspnea, staggering, diaphoresis, pale or ashen appearance.

If the test is stopped, the participant should sit or lie supine as appropriate. The following should be performed based on severity of the event and the coordinator's judgment: blood pressure, pulse rate, oxygen saturation. Oxygen should be administered as appropriate.

### 5.2.8 Borg Dyspnea Scoring

The Borg Dyspnea grade will be obtained prior to and immediately following the test using the visual analog scale below:

SCALE	SEVERITY	SCALE	SEVERITY
0	None at all	5	Severe

0.5	Very Very Slight (just noticeable)	6	
1	Very slight	7	Very Severe
2	Slight	8	
3	Moderate	9	Very Very Severe
4	Somewhat Severe	10	Maximum

This Borg scale should be printed on heavy paper (and perhaps laminated) in 20-point type size.

At the beginning of the 6-minute exercise, show the scale to the participant and ask the participant this: "Please grade your level of shortness of breath using this scale."

At the end of the exercise, show the scale to the participant and say: "Please grade your level of the greatest degree of shortness of breath you experienced at any time during the 6 minute walk test using this scale."

### **5.2.9 Distance Walked**

Record the final location or distance walked. Measure the distance from the starting point to the ending point and calculate the total meters walked as follow:

*Distance walked = (number of laps completed x length of laps) + distance of any partial laps completed.*

### **5.2.10 Data Collection and Reports**

Data to be recorded are:

1. Start time and end time
2. Distance walked rounded to nearest meter
3. Supplemental oxygen used and flow rate
4. Heart rate, blood pressure, and pulse oximetry at beginning and end of test
5. Borg dyspnea score prior to and immediately following the test
6. New York Heart/WHO Classification (done by physician).
7. Record the second or confirmatory six minute walk into RhoEDC

### 5.2.11 Modified New York Heart/WHO Functional Classification

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<b>Class I</b>	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
<b>Class II</b>	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
<b>Class III</b>	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
<b>Class IV</b>	Patients with pulmonary hypertension resulting in the inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present at rest, and discomfort is increased by any physical activity.

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Determine and record the patient's NYHA class:

*Ex. (Patient's name), on a normal day to day basis do you find that you become short of breath when you are.....*

- *Watching TV or talking on the phone?  
If Yes, ask "Is this normal for you?", If yes again, the patient is class IV. Move on to the next step.*
- *Taking a shower or getting dressed?  
If Yes, ask "Is this normal for you?", If yes again, the patient is class III. Move on to the next step.*
- *Doing housework (dishes, laundry, vacuuming, etc.) or moving around the house?  
If Yes, ask "Is this normal for you?", If yes again, the patient is class II. Move on to the next step.*
- *Walking briskly to the end of the block or playing sports?  
If Yes, ask "Is this normal for you?", If yes again, the patient is class I. Move on to the next step.*

### 5.2.12 References:

Adapted from Enright, Paul. MD "Respiratory Care" August 2003 Vol. 48 No. 8 and American Thoracic Society Statement: Guidelines for the Six Minute Walk Test, Am J Respir Crit Care Med Vol 166, pp 111-117, 2002.

## **6 BLOOD SAMPLE COLLECTION, LABELING, STORAGE, AND SHIPPING**

Blood samples will be collected for the walk-PHaSST participants at their Screening Visit and all four of the Main Interventional Trial (MIT) visits. At screening, participants will be asked to provide their consent to allow their blood samples, genetic material, serum, and plasma to be drawn and stored in a central repository BNP analysis, and future genetic testing. Participants should be assured that confidentiality will be maintained at all times and that all identifying information will be removed from laboratory specimens.

Walk-PHaSST site personnel are responsible for the collection, preparation and storage of laboratory samples. Phlebotomy must be performed by a certified phlebotomist, an RN, LPN, DO or MD as provided for in local and/or state health department regulations and procedures.

### **6.1 Assembly, Equipment and Supplies**

Routine venipuncture supplies will be required by specific site standard operating procedures. In addition, the sites must ensure that all walk-PHaSST study specific supplies have been ordered prior to any participant visits (beginning with Screening). Supplies will be ordered from Thomas Scientific and the NHLBI Repository contractor. Specific ordering information for supplies (tubes, cryovials, and blood spot cards) is described in Section 6.7.2.

The supplies from Thomas Scientific include:

- 1) 10-mL EDTA (lavender-top) vacutainer tube
- 2) 15-mL Falcon conical tube
- 3) 10-mL Sodium heparin (green-top) vacutainer tube
- 4) 4.5-mL Citrated plasma (light blue-top) vacutainer tube
- 5) 10-mL Serum (red-top) vacutainer tube
- 6) 2-mL cryovials(s) amber and clear.
- 7) Centrifuge (may be non-refrigerated)
- 8) 2 cardboard boxes (2") to hold up to 81 of the 2-mL cryovials (one box labeled "Repository Samples (SeraCare-Repository)" and one box labeled BNP Sample (NHLBI Central Lab)").
- 9) 1 cardboard box (3" labeled "Repository Sample (SeraCare-Repository)") to hold 15-20 of the 15-mL Falcon 2070 tubes
- 10) DNA blood spot cards (Whatman FTA cards) and the pouches with the dessicant packets
- 11) Storage and shipping supplies for the 2-mL cryovials being shipped to the NHLBI Repository

The storage and shipping supplies for the specimens sent to the NHLBI repository are provided to the domestic walk-PHaSST sites by SeraCare (the NHLBI contractor) and include:

- 1) Storage boxes for the 2-mL cryovials
- 2) Storage boxes for the 15-mL Falcon tubes
- 3) Styrofoam shipping boxes
- 4) Cardboard shipping boxes
- 5) Labels for the outside of the cardboard shipping box
- 6) Storage and shipping box instructions

Note: Dry ice is NOT provided by SeraCare or Thomas Scientific. Each site is responsible for obtaining dry ice for each walk-PHaSST shipment sent to the NHLBI central lab (Laurel Mendelsohn) or the Repository.

## **6.2 Blood Collection and Processing for Screening**

- 1) **FIRST**, fill the serum (red-top) 10-mL tube as full as possible. Invert the tube several times to ensure that the preservative is evenly distributed throughout the blood. Set aside while you collect the other 3 collection tubes.
- 2) Fill the Sodium heparin (green), EDTA (lavender), and citrated (light blue) tubes until they are as full as possible. Invert the tubes to mix the blood with the anticoagulant and then place on ice until they are processed.
- 3) **Process within 1 hour of the draw.**

### **6.2.1 Processing of the EDTA (purple top) collection tube:**

**Ideal processing time is within minutes of collection and no more than 1 hour following blood draw.**

- 1) Place a specimen label marked “EDTA Whole Blood” on the 15-mL Falcon tube. Place a duplicate copy of the label on the source document. Repeat for the DNA Blood collection card using the “DNA Bloodspot Card” label.
- 2) Invert the collection tube 3 times to distribute the preservative evenly throughout the blood. Remove 125 microliters of the whole blood with a Pipetman® and slowly drop the blood in a concentric circular motion within the confines of the printed circle on the card. Repeat to fill all 4 circles on card. **Air-dry for at least one hour.**
- 3) Once dry, store the card in a pouch (Whatman WB100037) that contains a few packets of desiccant (Whatman WB100003). Store up to 10 cards in each pouch and store at room temperature until shipped with the frozen conical tubes of whole blood.
- 4) DNA bloodspot cards are stored at room temperature until ready to ship.

- 5) Pour remainder of the whole blood into the pre-labeled 15-mL Falcon tube. Place, **standing up** in a -80 freezer, until it is completely frozen. Once frozen, place the tube in the 3" cardboard box labeled "Repository Samples (NHLBI-Repository)" and keep stored in the freezer at -80°C.

### 6.2.2 **Processing of the Sodium Heparin (green top) collection tube:**

**Ideal processing time is no more than 1hour after blood draw.**

- 1) Spin at 3,000-5,000 RPMs (approximately 1380 X g) for 10 minutes at 4°C (room temperature acceptable if centrifuge does not allow refrigerated processing).
- 2) Remove 1 mL plasma (clear supernatant) from the top of the vacutainer using a pipette tip, (take care not to disturb the pellet) and put into a **CLEAR** 2-mL cryovial labeled "BNP Plasma Sample". Place a duplicate copy of the label on the source document for the patient's medical record. Put the 2-mL cryovial into the 2" cardboard freezer box labeled "BNP Sample, NHLBI Central Lab." Store in the -80°C freezer immediately.
- 3) To avoid contamination of plasma with red blood cells, leave a small layer of plasma in the tube when separating. Aliquot 500 microliters of the rest of the plasma into 4 **CLEAR** cryovials pre-labeled "Heparin Plasma Sample." Place a duplicate copy of each label on the source document. Place into the 2" box labeled "Repository Samples (SeraCare-Repository)" and store in the -80°C freezer immediately.
  - If you do not have enough heparin plasma for 4 tubes, aliquot 3 tubes and indicate the reason why all 4 tubes were not collected on the source document.
- 4) Remove and discard the remaining plasma. To clean the RBC pellet of any remaining plasma, also remove a small portion of the top layer of the pellet.
- 5) Aliquot 200 microliters of the RBC pellet into 5 **CLEAR** cryovials pre-labeled "Heparin Pellet". Place a duplicate copy of the label on the participant's source document. Place into the 2" box labeled "Repository Samples (SeraCare-Repository)" and place in the -80°C freezer immediately. You may use a colored top to distinguish these samples from the plasma samples.

**\*\*Note:** In Version 1.0 of the MOO, amber cryovials were used to collect the heparin pellet sample. This is no longer required, clear or amber cryovials may be used. However, it is recommended to use a different color top for the heparin pellet to distinguish between the plasma and the pellet samples processed from the green vacutainer.

### **6.2.3            *Processing of the Sodium citrate (light blue top) collection tube***

**Ideal processing time is no more than 1 hour after blood draw.**

- 1) Spin the 4.5 mL tube at 3,000-5,000 RPMs (approximately 1380g) for 10 minutes at 4°C (room temperature acceptable).
- 2) Aliquot 500 microliters of the plasma (supernatant), with care not to contaminate the plasma with red cells, into 5 **CLEAR** cryovials pre-labeled “Citratated Plasma Sample”. Place a duplicate copy of each label on the participant’s source document. Discard the pellet. Place into the 2" box labeled “Repository Samples (SeraCare-Repository)” and store in the -80°C freezer immediately.
  - If you do not have enough plasma for all 5 cryovials, fill as many cryovials with 500 microliters as possible and indicate on the source document the reason why 5 samples were not collected.

### **6.2.4            *Processing of the Serum (red top) collection tube***

**Delay processing for at least 20 minutes to allow for coagulation. Processing should occur within 1 hour of collection of blood.**

- 1) Spin the tube at 3,000-5,000 RPMs (approximately 1380g) for 10 minutes at 4°C (room temperature acceptable).
- 2) Aliquot 500 microliters of the serum (supernatant) into 5 **CLEAR** cryovials pre-labeled “Serum Sample” and place a duplicate copy of each label on the participant’s source document. Place into the 2" box labeled “Repository Samples (SeraCare-Repository)” and store in the -80°C freezer immediately.
  - If you do not have enough serum for all 5 cryovials, fill as many cryovials with 500 microliters as possible and indicate on the source document the reason why 5 samples were not collected.

## **6.3                *Blood Collection and Processing for the Main Interventional Trial***

Please note that the 10-mL EDTA (lavender-top) tubes and the DNA Bloodspot Cards **are not collected** during the MIT for any of the 132 participants enrolled. However, the 4.5-mL citrated plasma (light-blue top), the 10-mL serum (red-top), and the 10-mL heparin (green-top) tubes are collected at each of the four visits for each participant and processed the same way as outlined in the screening processing.

- 1) Fill the serum (red-top) 10-mL tube first, as full as possible. Invert the tube several times to ensure that the preservative is evenly distributed throughout the blood. Put to the side while you collect the other 2 tubes.

- 2) Fill the sodium heparin (green), and citrated (light blue) tubes until they are as full as possible. Invert the tubes and **place on ice** until they are processed.
- 3) Delay processing of the serum red top tube for at least 20 minutes to allow for coagulation. **Ideal processing time is no more than 1 hour after blood draw.**

### **6.3.1 Processing of the Heparin (green top) collection tube:**

**Ideal processing time is no more than 1 hour following the blood draw.**

- 1) Spin at 3,000-5,000 RPMs (approximately 1380g) for 10 minutes at 4° C (room temperature acceptable).
- 2) Remove 1-mL of plasma (clear supernatant) from the top of the collection tube using a pipette tip, (take care not to disturb the pellet) and distribute to a **CLEAR** 2-mL cryovial labeled “BNP Sample.” Place a duplicate copy of the label on the participant’s source document. Place the 2-mL cryovial into the 2” cardboard freezer box labeled for “BNP Sample (NHLBI Central Lab).” Put into the -80°C freezer immediately.
- 3) To avoid contamination of plasma with red blood cells, leave a small layer of plasma in the tube when separating. Aliquot 500 microliters aliquots of the plasma into 4 CLEAR cryovials pre-labeled “Heparin Plasma Sample.” Place a duplicate copy of each label on the participant’s source document. Place into the 2” box labeled “Repository Samples (SeraCare-Repository)” and put into the – 80°C freezer immediately.
  - If you do not have enough plasma for all 4 cryovials, fill as many cryovials with 500 microliters as possible and indicate on the source document the reason why not all 4 plasma samples were not collected.
- 4) Remove and discard the remaining plasma layer. To clean the RBC pellet of any remaining plasma, also remove a small portion of the top layer of the RBC pellet.
- 5) Evenly aliquot the RBC pellet into 5 **CLEAR** cryovials pre-labeled “Heparin Pellet.” Place a duplicate copy of the label on the participant’s source document. Place into the 2” box labeled “Repository Samples (SeraCare-Repository)” and put into the freezer (-80°C) immediately. A colored top may be used to distinguish the difference from the plasma samples.
  - If you do not have enough pellets for all 5 cryovials, fill as many cryovials as possible and indicate on the source document the reason why 5 samples were not collected.

### **6.3.2 Processing of the Sodium citrate (Light blue top) container tube**

**Ideal processing time is no more than 1 hour after blood draw.**

- 1) Spin the tube at 3,000-5,000 RPMs (Approx. 1380g) for 10 minutes at 4° C (room temperature acceptable).



- 2) Aliquot 500 microliters of the plasma (supernatant), with care not to contaminate the plasma with red cells, into 5 **CLEAR** cryovials pre-labeled "Citrate Plasma Sample." Place a duplicate copy of each label on the participant's source document. Discard the pellet. Place the sample into the 2" box labeled "Plasma samples" and put into the -80°C freezer immediately.
  - If you do not have enough plasma for all 5 cryovials, fill as many cryovials with 500 microliters as possible and indicate on the source document the reason why 5 plasma samples were not collected.

### **6.3.3 Processing of the Serum (red top) container tube**

**Do not process for at least 20 minutes to allow for coagulation. Complete processing within 1 hour.**

- 1) Spin the tube at 3,000-5,000 RPMs (approximately 1380g) for 10 minutes at 4° C (room temperature acceptable).
- 2) Aliquot 500 microliters of the serum (supernatant) into 5 CLEAR cryovials pre-labeled "serum sample" and place a duplicate copy of each label on the participant's source document.
- 3) If you do not have enough serum for all 5 cryovials, fill as many cryovials with 500 microliters as possible and indicate on the source document the reason why 5 serum samples were not collected.

### **6.4 Storage of Blood Samples (2-mL Cryovials and 15-mL conical with whole blood EDTA) and DNA Blood Collection Cards**

Serum and plasma samples (2-mL cryovials clear), 15-mL conical with whole blood EDTA, and the 1-ml plasma Heparin BNP samples are stored in the 2" and 3" boxes in the -80°C freezer. The labels for each of the specimens and the labels for the storage boxes will be provided by Rho (Data Coordinating Center).

The DNA blood collection cards are stored at room temperature in the pouches with the desiccant packets.

### **6.5 Shipping Blood Samples (2-mL Cryovials and 15-mL conical with whole blood EDTA) and DNA Blood Collection Cards**

After each visit with blood collection and processing the study coordinator or lab technician should) scan or enter each of the collected into the RhoLAB tracking system.

After 6 months, or when one shipping box is full, the specimens should be shipped to the NHLBI Repository or the NHLBI Intramural laboratory. Shipments may only be sent

Monday-Wednesday, overnight, on dry ice, for next day delivery. There may be additional shipping restrictions due to upcoming holidays.

All shipments must be logged into RhoLAB immediately after each visit and the rescanned prior to sending the samples via FedEx to the central labs (see Section 6.6 for details).

**IMPORTANT NOTE:** As of January 15, 2009 (memorandum #017), shipping of specimens to the NHLBI Repository is ON HOLD. When the hold has been removed, a new version of this chapter will be issued. The version may include additional guidance for shipping. Instructions about shipping to the NHLBI Repository should not be followed until that HOLD is lifted.

## **6.6 Logging Specimens and Shipments into RhoLAB**

### **6.6.1 Logging Specimens in RhoLAB**

Once **three of the cardboard cryovial/falcon tube storage boxes are full**, the clinical site is required to ship the samples to the NHLBI Repository.

- 1) After each study visit involving blood collection and processing, log into the RhoLAB system via the walk-PHaSST study website
- 2) If the participant has not been “enrolled” into RhoLAB, select “Enroll Subject” and enter the 6 digit subject ID number that was generated by the RhoRAND system upon successful completion of Subject Registration (see MOO Section 3.2).
- 3) Once the participant is enrolled into RhoLAB, select “add specimens” on the left side toolbar.
  - a. The system will ask you to specify the participant, visit, and type of specimens you are entering.
  - b. Options for visit type include Screening Phase, Visit 1 MIT, Visit 2 MIT, Visit 3 MIT, Visit 4 MIT, and Early Termination.
  - c. Options for specimen types include Heparin Pellet Sample, Heparin Plasma Sample, EDTA whole blood, Serum Sample, Citrated Plasma Sample, BNP Sample, and DNA Bloodspot Card.
  - d. Each type of sample will be collected for Screening. The DNA Blood Spot Card and the EDTA whole blood will only be collected only at Screening Visits (for each of the 1000 screened patients).
- 4) Collect the “EDTA whole blood” 15-mL Falcon tube and scan or enter the specimen number into the RhoLAB system (for Screening Phase only).
- 5) Place the 15-mL Falcon tube (after it has been frozen standing upright) on its side in the 3” cardboard storage box labeled “Repository Samples (SeraCare-Repository)” before placing the box back into the freezer.

- 6) Collect the four “Heparin Plasma Sample” clear cryovials and scan or enter each specimen into the RhoLAB system.
- 7) As each specimen is entered, place the scanned specimen into the cryovial 2” cardboard storage box labeled “Repository Samples (SeraCare-Repository)”.
- 8) Collect the five “Heparin Pellet Sample” (clear with brown top) cryovials and scan or enter specimen into the RhoLAB system.
- 9) As each specimen is entered, place the scanned specimen into the 9x9 2-mL cryovial 2” cardboard storage box labeled “Repository Samples (SeraCare-Repository)”.
- 10) Collect all five “Serum Sample” clear cryovials and scan or enter each specimen into the RhoLAB system.
- 11) As each specimen number is entered, place the scanned specimen into the 2” cryovial cardboard storage box labeled “Repository Samples (SeraCare-Repository)”.
- 12) Collect all five “Citratated Plasma Sample” clear cryovials and scan or enter each specimen into the RhoLAB system.
- 13) As each specimen number is entered, place the scanned specimen into the 2” cryovial cardboard storage box labeled “Repository Samples (SeraCare-Repository)”.
- 14) Take the one “BNP Sample” clear 2-mL cryovial and scan or enter the specimen into the RhoLAB system.
- 15) Place the scanned specimen into a 9x9 2-mL cryovial cardboard freezer box labeled for “BNP Sample (NHLBI Central Lab)”.
- 16) DNA blood collection cards (FTA cards) should be stored in re-sealable pouches with packets of desiccant, at room temperature. Scan or enter each of the FTACards into the RhoLAB system.
- 17) Store the cryovial 2” and 3” cardboard boxes in the appropriate place until the 3 cryovial boxes are full or until the samples have been in storage for 6 months.

### **6.6.2            *Creating Shipments in RhoLAB***

All shipments must be documented in RhoLAB.

- 1) Take each box out of the freezer that you are shipping to NHLBI Central Lab (BNP samples) or the NHLBI Repository. Place all of the samples on dry ice near the computer that is being used to create the shipment in RhoLAB.
- 2) Log into RhoLAB via the secure walk-PHaSST study website.
- 3) Select “Create Shipments” in the toolbar on the left hand side.
- 4) Select the Lab that you are shipping samples to as the next step (i.e., NHLBI Central Lab or SeraCare Repository).

**Create Shipment**

From: Rho, Inc. Demo Study Site

Ship To: SeraCare-Repository

Ship Method: FedEx Priority Overnight

Track Ref:

Notes:

Specimen:

Include	Specimen ID	Subject ID	Type	Visit	When Collected	Collected By	Default Ship To
<input type="checkbox"/>	010010	000033	2mL Heparin Pellet Sample	Screening Phase	29May2008	JR	SeraCare-Repository
<input type="checkbox"/>	010021	000033	2mL Heparin Pellet Sample	Screening Phase	29May2008	JR	SeraCare-Repository
<input type="checkbox"/>	010032	000033	2mL Heparin Pellet Sample	Screening Phase	29May2008	JR	SeraCare-Repository
<input type="checkbox"/>	010043	000033	2mL Heparin Pellet Sample	Screening Phase	29May2008	JR	SeraCare-Repository
<input type="checkbox"/>	010059	000033	2mL Heparin Pellet Sample	Screening Phase	29May2008	JR	SeraCare-Repository
<input type="checkbox"/>	021619	030200	2mL Heparin Pellet Sample	Screening Phase	06Mar2009	JS	SeraCare-Repository
<input type="checkbox"/>	021625	030200	2mL Heparin Pellet Sample	Screening Phase	06Mar2009	JS	SeraCare-Repository
<input type="checkbox"/>	021636	030200	2mL Heparin Pellet Sample	Screening Phase	06Mar2009	JS	SeraCare-Repository
<input type="checkbox"/>	021647	030200	2mL Heparin Pellet Sample	Screening Phase	06Mar2009	JS	SeraCare-Repository
<input type="checkbox"/>	021650	030200	2mL Heparin Pellet Sample	Screening Phase	06Mar2009	JS	SeraCare-Repository
<input type="checkbox"/>	021661	030200	2mL Heparin Plasma Sample	Screening Phase	06Mar2009	JS	SeraCare-Repository
<input type="checkbox"/>	021672	030200	2mL Heparin Plasma Sample	Screening Phase	06Mar2009	JS	SeraCare-Repository
<input type="checkbox"/>	021683	030200	2mL Heparin Plasma Sample	Screening Phase	06Mar2009	JS	SeraCare-Repository
<input type="checkbox"/>	021694	030200	2mL Heparin Plasma Sample	Screening Phase	06Mar2009	JS	SeraCare-Repository
<input type="checkbox"/>	021709	030200	2mL Citrated Plasma Sample	Screening Phase	06Mar2009	JS	SeraCare-Repository

- 5) Rescan EACH of the previously entered samples in order to create the packing slip that documents what samples are being shipped to NHLBI Central Lab or the NHLBI Repository. The specimen number will be “found” and highlighted in green, as well as checked off in the list of available specimens to ship in RhoLAB.

**Create Shipment**

From: Rho, Inc. Demo Study Site

Ship To: SeraCare-Repository

Ship Method: FedEx Priority Overnight

Track Ref:

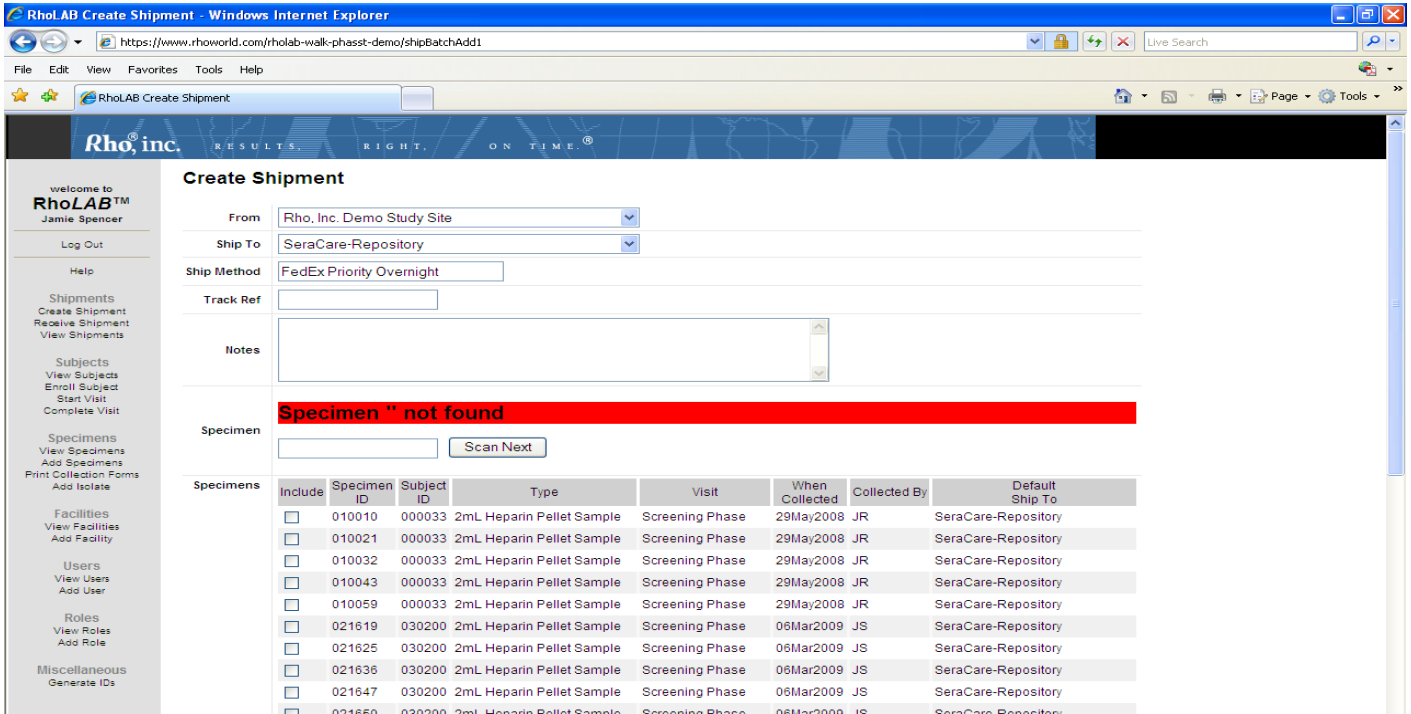
Notes:

**Specimen 010010 is found**

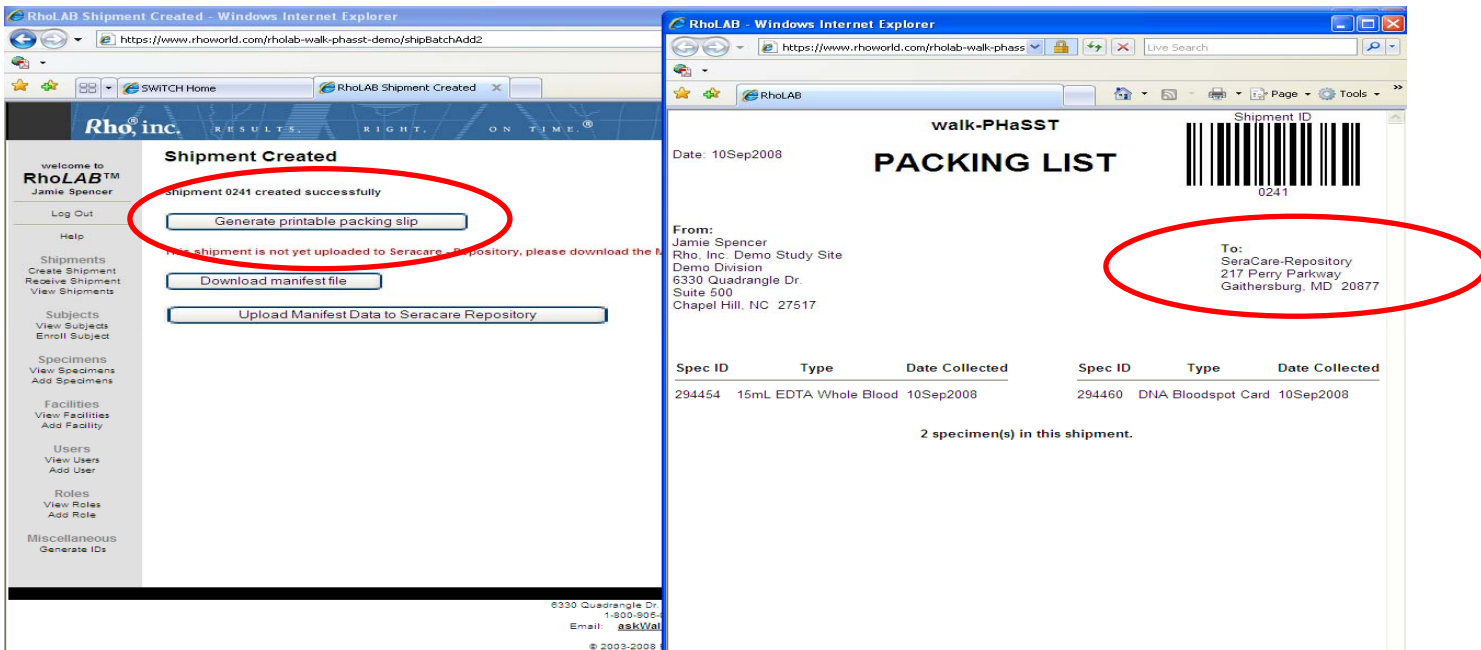
Specimen:

Include	Specimen ID	Subject ID	Type	Visit	When Collected	Collected By	Default Ship To
<input checked="" type="checkbox"/>	010010	000033	2mL Heparin Pellet Sample	Screening Phase	29May2008	JR	SeraCare-Repository
<input type="checkbox"/>	010021	000033	2mL Heparin Pellet Sample	Screening Phase	29May2008	JR	SeraCare-Repository
<input type="checkbox"/>	010032	000033	2mL Heparin Pellet Sample	Screening Phase	29May2008	JR	SeraCare-Repository
<input type="checkbox"/>	010043	000033	2mL Heparin Pellet Sample	Screening Phase	29May2008	JR	SeraCare-Repository
<input type="checkbox"/>	010059	000033	2mL Heparin Pellet Sample	Screening Phase	29May2008	JR	SeraCare-Repository
<input type="checkbox"/>	021619	030200	2mL Heparin Pellet Sample	Screening Phase	06Mar2009	JS	SeraCare-Repository
<input checked="" type="checkbox"/>	021625	030200	2mL Heparin Pellet Sample	Screening Phase	06Mar2009	JS	SeraCare-Repository
<input checked="" type="checkbox"/>	021636	030200	2mL Heparin Pellet Sample	Screening Phase	06Mar2009	JS	SeraCare-Repository
<input checked="" type="checkbox"/>	021647	030200	2mL Heparin Pellet Sample	Screening Phase	06Mar2009	JS	SeraCare-Repository
<input checked="" type="checkbox"/>	021650	030200	2mL Heparin Pellet Sample	Screening Phase	06Mar2009	JS	SeraCare-Repository
<input checked="" type="checkbox"/>	021661	030200	2mL Heparin Plasma Sample	Screening Phase	06Mar2009	JS	SeraCare-Repository
<input checked="" type="checkbox"/>	021672	030200	2mL Heparin Plasma Sample	Screening Phase	06Mar2009	JS	SeraCare-Repository

- 6) If a specimen is scanned that has **NOT** been previously entered into RhoLAB, the specimen number will be highlighted in red, indicating that the specimen is “not found”. The specimen must then be added to RhoLAB before it can be shipped using the “Add Specimen” function discussed in Section 6.5.



7) Print the packing slip and put it on top of the appropriate box prior to taping the shipment closed and sending it priority overnight via Fedex.com.



8) Once a shipment has been committed to the NHLBI Repository, the following alert will be generated by the RhoLAB System: “This shipment is not yet uploaded to SeraCare - Repository, please download the Manifest. Then Upload this manifest file manually to SeraCare - Repository.” Please ignore this message, you have completed

the shipping process in RhoLAB once you generate, print, and add the packing slip to each shipment.



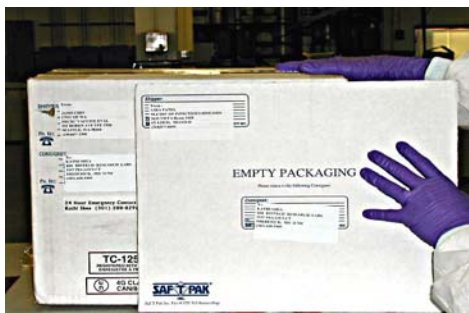
### 6.6.3 ***Shipping Instructions (see Section 6.7 for contact information for any shipping questions)***

#### ***Shipping of Frozen Samples to the NHLBI Repository***

**Schedule: Shipments may be sent Monday through Wednesday only**

#### **Using the Saf-T-Pak STP 310**

1. Remove Empty Packaging Flap from front of box. A cardboard flap with the words "empty packaging" has been taped to the front of the box to cover the shipping labels when we ship the supplies to you. This flap can easily be cut from the box and removed. Once removed all shipping labels should be present.



- i. Once "empty packaging" flap is removed the box should contain the following labels
- ii. To Label (To Linda Brunson.)
- iii. From Label (From your site)



- iv. 24 Hour Emergency Contact Label
- v. Responsible Person Label
- vi. Class 9 Diamond Label
- vii. UN3373 Biological Substance Category B Label
- viii. Dry Ice Un 1845 Label with space to add weight

(If any of the labels are missing please contact us for a replacement)

2. Place dry ice around the small inner brown box (between brown box and Styrofoam container).



3. Place a rubber band (at least 1/4" thick) around Freezer Box.
4. Place the white absorbent strip around box.
5. Place the cryovial box in the clear Biohazard bag and seal according to instructions on the bag.



6. Place the bag into the white Biohazard bag and seal according to the instructions on the bag.



7. Place the white Biohazard bag into the inner brown box (the shipping container can hold 3-2" Freezer boxes or 2-3" freezer Boxes) and tape the inner brown box shut.





8. Add additional dry ice to bring total amount to the same level as the top of the brown inner box. Note that the total amount of dry ice will be ~16lbs or 9 Kgs
9. Place the styrofoam lid on top the container (do not tape the Styrofoam lid), and place the “empty” packaging flap on top of the styrofoam lid, and seal the cardboard box.



10. Complete FedEx Airbill with your shipping address and the total amount of dry ice placed in box:
  - a. Section 2 – The” Internal Billing Reference Section” must have the following information “138, Biological Substance Category B”
  - b. Section 4a - Check the “FedEx Priority Overnight” box
  - c. Section 5 - Check the “other” box
  - d. Section 6 - Check the box that says, “Yes Shipper’s Declaration not required”. Check the “Dry Ice box” and write “1” in the first blank line and the “kg” of dry ice used on the second line; i.e., 1 x 9 kg
  - e. Section 7 - Check Recipient. The account number is 4065-3844-3
11. Fill in the Dry Ice Label on box with the total amount of dry ice used.
12. **Prior to shipment**, send an e-mail to Chem-Tel, (the 24-hour emergency response service for the NHLBI Repository), at [BBIBIOTECH@chemtelinc.com](mailto:BBIBIOTECH@chemtelinc.com). Please cc SeraCare BioServices on the Chem-Tel e-mail at [nhlbi@seracare.com](mailto:nhlbi@seracare.com). Include the following information in your e-mail.
  - a. Subject Line of E-mail should read: The study associated with shipment, FedEx, “insert tracking number”, “insert date of shipment”:
  - b. Shipper’s Name:
  - c. Shipper’s Address:
  - d. Shipper’s Phone:
  - e. Shipment Date:
  - f. Courier: FedEx
  - g. Tracking Number (no spaces):

- h. Package Weight and Unit of Measure (i.e. 20 kg):
- i. Total Volume: (approximate volume is allowed)
- j. Sample Identifier/Number of vials (Approximate number for Frozen vials is allowed).
- k. Shipment Temperature: Dry Ice, UN1845, \_\_\_ kg (insert weight of Dry Ice)
- l. Dangerous Goods Classification: Biological Substance Category B, Dry Ice
- m. Shipping Manifest Information. A paper copy of the manifest must be included in the shipment.** A manifest should include the specimen ID, participant ID, draw date, material type, volume and any other identifiers requested by the principal investigator of your study for each sample sent. **An electronic manifest must be sent with shipment notification.**
- n. Recipient: Linda Brunson
- o. Recipient Address: 217 Perry Parkway, Gaithersburg, MD, 20877
- p. Recipient Phone: 240-306-4100

Faxes may only be sent to Chem-Tel in an emergency situation when the e-mail system is not functioning at (813) 248-0582.

If you should have any questions regarding these instructions please contact SeraCare BioServices using the contact information above.

#### **6.6.4 Tips for Successful Shipments to the NHLBI Repository**

- 1) Prepare a shipment as soon as one shipping box is full (this will be after approximately 12 participant visits).
- 2) Keep all of the NHLBI Repository storage boxes on the same shelf in the laboratory freezer.
- 3) Label all NHLBI Repository boxes with the label provided by Rho “Repository Samples (NHLBI Repository)”.
- 4) Count the total number of specimens that are in the shipment at the bottom of the packing slip. This number divided by 81 should equal the number of boxes that are being shipped.

### **6.7 Contact Information**

#### **6.7.1 Data Coordinating Center (Rho, Inc)**

Jamie Spencer (Study Coordinator)  
Rho, Inc.  
6330 Quadrangle Drive, Suite 500  
Chapel Hill, NC 27517  
Phone: 919-595-6450  
Email: Jamie\_Spencer@rhoworld.com  
Fax: 919-287-0128

Christopher Woods (Research Associate)  
Rho, Inc.  
6330 Quadrangle Drive, Suite 500  
Chapel Hill, NC 27517  
Phone: 919-595-6266  
Email:  
Christopher\_Woods@rhoworld.com

### **6.7.2 SeraCare Life Sciences (Repository)**

Linda Brunson

SeraCare Bio Services

217 Perry Parkway

Gaithersburg, MD 20877

Email: [NHLBI@seracare.com](mailto:NHLBI@seracare.com)

Phone: (240) 306-4143

Fax: 301-208-8829

### **6.7.3 NHLBI Central Lab (BNP Evaluation)**

Laurel Mendelsohn (Lab Manager)

NIH/NHLBI

9000 Rockville Pike

Building 10CRC, 5E5222

Bethesda, MD, 20892

Phone: 301-451-0208

Email: [mendelsohnl@cc.nih.gov](mailto:mendelsohnl@cc.nih.gov)

Fax: 301-451-7091

## **6.8 Ordering Blood Collection Supplies**

Sites are individually responsible for ordering from Thomas Scientific the supplies listed below (in addition to the standard blood collection tools such as needles, gauze, etc). If additional assistance is needed when ordering supplies, contact Jamie Spencer.

### **6.8.1 Guidance for the Quantity Needed for Each Patient**

Please note that for **each participant in Screening**, the following supplies will be required:

- 1 10-mL EDTA (lavender top) vacutainer
- 1 15-mL conical tubes Falcon 2070
- 1 10-mL heparin (green top) vacutainer
- 1 10-mL serum SST (red top) vacutainer

- 1 4.5-mL citrate (light blue top) vacutainer
- 20 2-mL cryovials (15 clear + 5 amber)
- FTA/DNA bloodspot cards

Please note that for **each participant in the MIT**, the following supplies will be needed:

- 4 10-mL heparin green top vacutainers
- 4 10-mL serum red top vacutainers
- 4 10-mL citrated serum light blue top vacutainers
- 45 **clear** 2-mL cryovials (45 clear +15 amber)
- 15 **amber** 2-mL cryovials (can also use clear cryovials for the heparin pellet)

## **6.8.2 Contact Information and Order Information**

Supplies will be obtained from three different sources during the walk-PHaSST Trial. Order forms for categories 2 and 3 below are available on the walk -PHaSST website (under Forms).

- 1) The labels will be shipped to the sites from Rho, Inc, the Data Coordinating Center. These labels will include the type of specimen the label should go on, as well as a unique specimen number with the corresponding barcode. Rho will also provide labels for each of the storage boxes (2 for the Repository, 1 for the BNP sample) in order to help sites keep the different samples separate while in the freezer.
- 2) The shipping supplies for the Repository (SeraCare) specimens are ordered directly from Jamie Spencer at the DCC who will work with SeraCare to provide the supplies to the sites. A pre-addressed FedEx airbill will be included with these supplies.
- 3) All blood collection supplies (tubes, cryovials, blood spot cards, etc) should be purchased through Thomas Scientific to ensure consistency between sites.

### **6.8.2.1 Example Label (Labels sent to each site when activated)**

An example of the walk-PHaSST specimen labels is below.

Each specimen that is shipped via RhoLAB will have its own set of labels, which will include the name of the study, the name of the specimen, and a unique number that can either be manually entered into RhoLAB or entered by scanning the barcode. All specimen numbers are 6-digits long. Each row has three identical labels – one for the specimen, one for the source document, and one extra as a “just in case.”

walk-PHaSST DNA Bloodspot Card         123456	walk-PHaSST DNA Bloodspot Card         123456	walk-PHaSST DNA Bloodspot Card         123456
walk-PHaSST DNA Bloodspot Card         258639	walk-PHaSST DNA Bloodspot Card         258639	walk-PHaSST DNA Bloodspot Card         258639
walk-PHaSST DNA Bloodspot Card         687459	walk-PHaSST DNA Bloodspot Card         687459	walk-PHaSST DNA Bloodspot Card         687459

→ All specimen numbers are always 6 digits long (with the last digit being a “check-digit”)

Each row of labels is immediately followed by a new, unique row of labels.

**6.8.2.2 Sample order form for the NHLBI Repository (available on the website)**

## SeraCare BioServices SUPPLY ORDER FORM

Please fax form to SeraCare at (301) 208-8829 or e-mail to [nhlbi@seracare.com](mailto:nhlbi@seracare.com)  
ATTN: NHLBI Repository Manager

Site Number: \_\_\_\_\_ Study \_\_\_\_\_

Site Name: \_\_\_\_\_

Contact Name: \_\_\_\_\_

Contact Address: \_\_\_\_\_

\_\_\_\_\_

Phone #: \_\_\_\_\_ Fax #: \_\_\_\_\_

E-Mail: \_\_\_\_\_

Date of Request: \_\_\_\_\_ Date Supplies are Needed: \_\_\_\_\_

Please allow one business week to process orders.

Item Description	Quantity of Each Item Requested
Pre-Labelled Shipping Container (STP 310)- holds up to three 2" freezer boxes or two 3" freezer boxes	
Fed Ex Airbills - Domestic	
Fed Ex Airbills - International	
2" Freezer Boxes	
3" Freezer Boxes	
Absorbent Strips	
Clear Biohazard Bags for 2" Freezer Boxes	
White Biohazard Bags for 2" Freezer Boxes	
Clear Biohazard Bags for 3" Freezer Boxes	
White Biohazard Bags for 3" Freezer Boxes	

**6.8.2.3 Sample order form for Thomas Scientific (complete form and submit to Karen Rosenberg via email)**



**Blood Collection Supply Request Form**

<i>Supplier:</i> Thomas Scientific Karen Rosenberg (Cust Serv) 800-345-2100x4655 <b>karenr@thomasci.com</b> P.O. Box 99 Swedesboro, NJ 08085
--

<i>Rho Project Manager:</i>
Name: Jamie Spencer
E-mail: jspencer@rhoworld.com
Phone: (919) 595-6450
Fax: (919) 287-0128

Bill To: AECOM/walk PHaSST
Site Address:
Phone:

Sponsor: NHLBI
Protocol Name: walk-PHaSST

Date Order Placed:	Enter Date
Date Needed at Site:	Enter Date

Ship To:	Site ID: NHLBI
Study Coordinator Name	
Phone:	

Shipping Method:	
FedEx	
Freight:	Bill to Enter Here
Reference:	Enter Here

Items that you order ONE time and have no expiration date so will last the duration of the study:

ITEM #	ITEM DESCRIPTION	QTY	LOT NO.	EXPIRATION	Cost/Unit
WB120206	Whatman FTA Blood collection cards WB120206 18mo shelf life	1			336.43
1231E73	Multibarrier Pouches for storage of FTA cards (1000/pk)	1			68.53
1231E74	FTA Storage Desiccant Packets for the pouches (1000/pk)	1			170.79
2610L46	15-mL Falcon Centrifuge tube (500/cs)	1			96.72
SPECIAL-NHP	Amber Microtubes Sarstedt 72-694-034 for pellet (5,000/cs)**	1			319.50
SPECIAL-NHP	UN3373 Diagnostic Specimen label HAZ-401 1000/cs Shamrock Sci.	1			122.55
5150C22	Clear Cryovials 2.0mL (25/pack)**	140			10.00

\*\*For each Screening patients, sites will need 15 CLEAR cryovials. For each patient enrolled into the MIT, an additional 60 CLEAR cryovials will be needed. Each site is "Screening" around 100 patients and enrolling around 15 MIT patients = approximately 3500 will be needed for the duration of the study (and so that a re-order will not be needed).

Items that will need to be ordered on an as needed basis because they will expire:

ITEM #	ITEM DESCRIPTION	QTY	LOT NO.	EXPIRATION	Cost/Unit
1233Y06	10 ml EDTA Vacutainer Lavender (100/pack)	1			27.05
9668K58	10 ml Heparin Vacutainer Green (100/pack)	1			30.00
1230Z23	4.5ml Citrate vacutainer Light Blue (100/pack)	1			18.25
1230Z24	10 ml Serum Separator Vacutainer Red (100/pack)	1			41.50

Items that are required for storing and shipping supplies; will need to be ordered on an as needed basis (based on storage space):

ITEM #	ITEM DESCRIPTION	QTY	LOT NO.	EXPIRATION	Cost/Unit
5151X55	81 place Cryostore box for Shipping (6/cs)	1			26.90
0785B36	Dry Ice Shipper for shipping 5151X55 (6/cs)	1			72.42



## **7 CARDIAC CATHETERIZATION PROCEDURES QUALITY CONTROL**

### **7.5.1 Introduction**

Cardiac catheterization in patients with pulmonary arterial hypertension is a standard procedure at all participating centers. The purpose of quality control is to ensure that measurements are made under standardized conditions in the Cardiac Catheterization Laboratory and the results are interpreted in a uniform manner. Cardiac catheterization results are not used to include patients in any part of the study although a pulmonary capillary wedge pressure  $\geq 24$  mm Hg excludes patients from receipt of study medication.

Up to 132 cardiac catheterizations will be performed in up to 66 patients in 10 centers. It is proposed that for the purposes of quality control the pulmonary capillary wedge pressure data obtained from the first 5 catheterizations at each center will be scrutinized by the QC committee.

### **7.6 Measurements to be made at cardiac catheterization**

#### **7.6.1 Pressure Measurements:**

Systemic arterial pressure (systolic, diastolic and mean)

Pulmonary arterial pressure (systolic, diastolic and mean)

Pulmonary capillary wedge pressure (a wave, v wave and mean)

Right ventricular pressure (systolic and enddiastolic pressure)

Right atrial pressure (a Wave, v wave and mean).

Note:

All right heart measurements should be made at functional residual capacity: the patient should hold their breath out at the end of a normal breath, not forced expiration.

These measurements should be recorded on paper or digitally so they can be reviewed at a later date. Each measurement should show the waveform of at least three beats and the electrical mean.

Recordings should be made of pressure transducer calibrations at the start of the procedure.

The pulmonary capillary wedge pressure in sinus rhythm must demonstrate a and v waves as well as showing clear x and y decent.

To demonstrate the validity of the pulmonary capillary wedge pressure a wedge to pulmonary artery withdrawal should be recorded.

Left ventricular end-diastolic pressure should be measured if a satisfactory pulmonary capillary wedge pressure tracing cannot be obtained.

Sedation is up to the Investigator, however it is preferred that the subject be conscious during the procedure. If sedation is used for the first cauterization, it must also be used for the second.

### **7.6.2            *Measurement of cardiac output and oxygen saturations:***

Cardiac output will be measured by either thermodilution or the Fick principle (the latter only when oxygen consumption can be measured). Thermodilution cardiac output measurements should be made in triplicate and the results of the measurements should be within 15% of each other. The same method for estimating cardiac output should be used for each study in the same patient.

Mixed venous oxygen saturation and systemic arterial oxygen saturation should be measured on at least at two samples and have values which are within 3% of each other.

### **7.6.3            *Data to be recorded for review by QC committee.***

*Pressure recordings* from each site in the circulation listed above should be submitted to the QC committee. The recordings should be of pulmonary capillary wedge pressure recorded at functional residual capacity and include a withdrawal from the wedge position to pulmonary artery. In addition the recording should:

- Be provided on paper.
- Indicate the paper speed at which the recording was made.
- Indicate the pressure measurement scale
- Be supplied in a sufficiently large format that enables accurate interpretation of data (normally this will be one pressure recording per page of letter sized paper in landscape format)
- Provide a recording of the zero calibration of transducers used as well as calibration of gain appropriately annotated.
- Include the electrocardiogram on each recording
- Provide the Investigator's report of the pulmonary capillary wedge pressure (a wave, v wave and mean in mm Hg)
- Provide a recording of left ventricular end-diastolic pressure on an appropriately large scale, if an adequate pulmonary capillary wedge pressure cannot be recorded.

## **7.6.4 Procedure for Submission of Cardiac Catheterization Data**

The wedge pressure traces of the first five cardiac catheterizations done at any site must be centrally reviewed by the QC committee by uploading them to the walk-PHaSST website. The differences between the investigators' interpretation and the QC committee's interpretation of the catheterization data will be reviewed by the whole committee. The results of this comparison will be sent to the Steering Committee.

### **7.6.4.1 Submitting the Cardiac Catheterization**

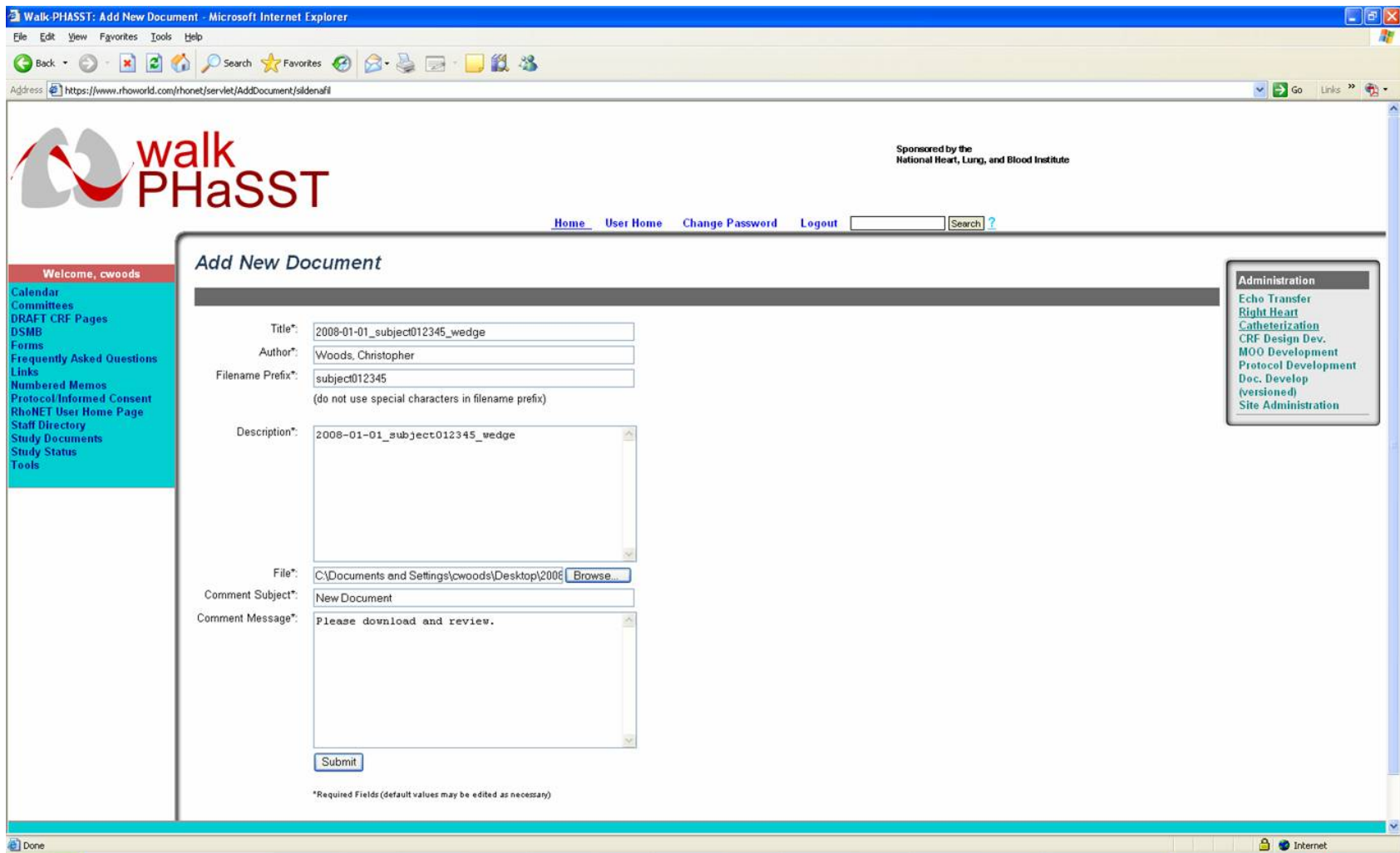
Each site is required to submit the pressure recording as described above from the first five catheterizations performed. This requires submission of a JPEG file plus the investigator's report. A full page print out of the wedge pressure trace should be scanned at 300 dpi and saved at 100% image size in a JPEG format at high resolution in black and white; the Investigator's report should be scanned as a PDF. There should be no subject identifiers on the image or in the Investigator's report, except the specimen ID.

The file name should include the date in YYYY-MM-DD format, the specimen ID, and the type of file (e.g. 2008-01-01\_Subject01234567\_Wedge.JPG and 2008-01-01\_Specimen01234567\_InvestigatorReport.PDF).

Cardiac catheterizations will be uploaded using the Document Development Category. To navigate to this category, access the website and click on the Right Heart Catheterization link in the Administration box on the right side of the page.

To add a file, click on the Add New Document button. On the next screen you will be instructed to enter a Title, Filename Prefix, and Description. In the Title field, enter the name of the file minus the file extension (e.g., 2008-01-01\_specimen01234567\_wedge). In the Filename Prefix field, enter the specimen id (e.g., specimen012345). In the Description field, enter name of the file again the same way as in the Title field. Using the Browse button, select the file from your hard drive and hit Submit. Figure 7-1 is a screen shot of the Add New Document screen.

Figure 7-1 Submitting the Cardiac Catheterization Files



## 8 PULMONARY FUNCTION STUDIES

**Pulmonary Function Tests (PFT) are not being collected as part of the study assessments anymore. However, if it is clinically required, all sites should complete the tests in order to follow good clinical practice.**

*Pulmonary function tests (PFT) are an integral component of the diagnostic evaluation of pulmonary hypertension. Once the presence of pulmonary hypertension is suspected based on echocardiography, consensus clinical practice guidelines recommend the obtainment of complete pulmonary functions studies to assess for underlying respiratory abnormalities as a potential basis for the pulmonary hypertension.*

*In this protocol, PFT will be obtained, at the discretion of the treating clinician, when the screening Doppler-echocardiogram (and confirmed by baseline Doppler-echocardiogram) demonstrates a peak tricuspid regurgitant velocity (TRV) of  $\geq 2.7$  m/s. Such testing should be obtained during a clinical steady-state period with no acute intervening illness (including vasocclusive crises, acute chest syndrome or respiratory tract infection) in the preceding 4 weeks. The purpose of PFT is to identify the presence of and quantitate the degree of ventilatory and/or diffusion impairments in the context of a comprehensive, standard-of-care, clinical cardiopulmonary assessment. Results of PFT's will be recorded for this protocol for observational purposes only. No PFT criteria are included in the inclusion/exclusion criteria for enrollment and do not constitute a study endpoint. Complete PFT include: spirometry, lung volumes, and diffusing capacity of the lung for carbon monoxide (DLCO).*

### 8.6.1 General Considerations

*Testing shall be performed in accordance with standards established and updated in 2005 by the American Thoracic Society/European Respiratory Society Task Force on Standardization of Lung Function Testing. Laboratory equipment and personnel shall meet the minimum requirements recommended.*

*At screening, record the subject's age, height, weight, and race. Note the use of inhaled or oral medications that may affect lung function and last dose and obtain smoking history.*

*At the time of scheduling the PFTs, instruct patients to*

- 1) refrain from smoking for at least one hour before testing*
- 2) refrain from alcohol consumption for at least 4 hours before testing*
- 3) avoid vigorous exercise for at least 30 minutes prior to testing*
- 4) avoid eating a large meal within 2 hours of testing*
- 5) wear clothes that will not restrict full chest and abdominal expansion.*

*All testing will be performed in a seated position.*

### 8.6.2 Spirometry

*Spirometry involves the performance of a forced vital capacity (FVC) maneuver. The latter is the maximal volume of air exhaled with maximally forced effort from a maximal*

inspiration, expressed in liters at body temperature and ambient pressure saturated with water vapor (BTPS). The primary signal may be either flow or volume. The lips must make an adequate seal around the mouthpiece and a nose clip is attached. The subject should inhale to total lung capacity (TLC) from functional residual capacity (FRC), following immediately (pause of < 1 sec) by a maximal “blast” of exhalation continuing until no more air can be expelled (residual volume; RV). A time-volume curve should be displayed to ensure acceptable start of test and end of test criteria.

The forced expiratory volume exhaled in the first second ( $FEV_1$ ) is determined from the time-volume curve. A minimum of 3 acceptable FVC maneuvers are obtained. The two largest FVC and  $FEV_1$  values must be within 150 ml of each other. If not, repeated maneuvers are obtained until these criteria are met or the subject has performed 8 tests or cannot continue. The largest FVC and  $FEV_1$  are recorded. The test with largest sum of FVC +  $FEV_1$  is used to derive a flow-volume loop and other spirometric indices.

#### **8.6.2.1.1 Reversibility Testing**

When the baseline spirometry demonstrates airflow limitation, acute reversibility after bronchodilator administration should be performed. Albuterol is inhaled at a dose of 100 µg, followed by repeat spirometry 10 – 15 minutes later.

### **8.6.3 Lung Volumes**

FRC can be measured by either body plethysmography or gas dilution techniques based on the routinely employed method at the site’s pulmonary function laboratory. The specific technique employed should be specified. Once an acceptable FRC measurement is obtained, spirometric time-volume tracings are performed to measure the expiratory reserve volume (ERV) and inspiratory vital capacity (IVC). Residual volume is calculated as FRC – ERV and total lung capacity is calculated as FRC + IVC.

### **8.6.4 Carbon Monoxide Diffusing Capacity of the Lung (DLCO)**

The single breath method for determination of DLCO will be employed. If possible, the subject should use supplemental oxygen for 10 minutes prior to the test. After a slow exhalation to residual volume, the subject rapidly inhales to TLC a gas mixture containing 0.3% CO and an inert tracer (helium or methane). The inspired volume (VI) should be within 85% of the measured vital capacity. The subject then holds his/her breath for  $10 \pm 2$  sec, followed by an unforced exhalation. The first 0.75 – 1.0 L of exhaled gas are discarded as dead space and the remainder is analyzed as the alveolar gas sample for calculation of DLCO, expressed as ml CO/min/mmHg STPD (standard temperature, pressure and dry). At least two acceptable tests within 3 ml/min/mmHg of each other or within 10% are required. Absolute DLCO and DLCO corrected for alveolar volume (DLVA) will be reported.

#### **8.6.4.1.1 Correction for Anemia**

DLCO values will be recorded unadjusted and adjusted for the most recent hemoglobin (Hb) value as follows:

$DLCO \text{ adjusted for Hb} = DLCO \text{ unadjusted} \times (1.7Hb / (10.22 + Hb))$

*Similar adjustment will be made for DL/VA.*

### **8.6.5 Predicted Values**

*All pulmonary function variables will be reported as absolute values and as percent predicted. Since pulmonary function laboratories employ different reference equations, it will be important to apply the same equation to derive percent predicted values in this study. Age, gender and height are used to derive predicted values in most reference equations. It is also well recognized that race affects lung volumes. Equations derived from Caucasian populations have been shown to overestimate TLC, FVC and FEV1 by ~ 12% and FRC and RV by ~ 7% in Blacks. Absolute values will be recorded in a database, along with anthropometric and ethnic characteristics of the subject. A consensus among investigators regarding the appropriate reference equation to employ and adjustment for race will be obtained to derive percent predicted values.*

## **9 CHEST RADIOGRAPH STUDY**

Standard chest radiography will be obtained on all study participants as part of the baseline assessment for the MIT after meeting screening criteria. The purpose of the chest radiograph is to assess for presence of acute or chronic cardiopulmonary abnormalities, particularly as they may relate to pulmonary hypertension and lung disease.

### **9.7.1 *Technique***

Standard posterior-anterior and lateral digital chest radiographic images will be obtained. The electronic images will be stored at each site.

### **9.7.2 *Interpretation***

The images will be interpreted by a chest radiologist at the clinical site and the report forwarded to the central data center. In addition, the electronic image will be uploaded on to the Rho site and interpreted by the Study's radiology panel, which will score and analyze the radiographs for many variables.

### **9.7.3 *Submitting the Chest Radiograph***

The chest radiographs will be uploaded for review via the secure walk-PHaSST website. Radiographs should be saved as JPEG files. There should be no subject identifiers on the image or in the Investigator's report, except the subject ID.

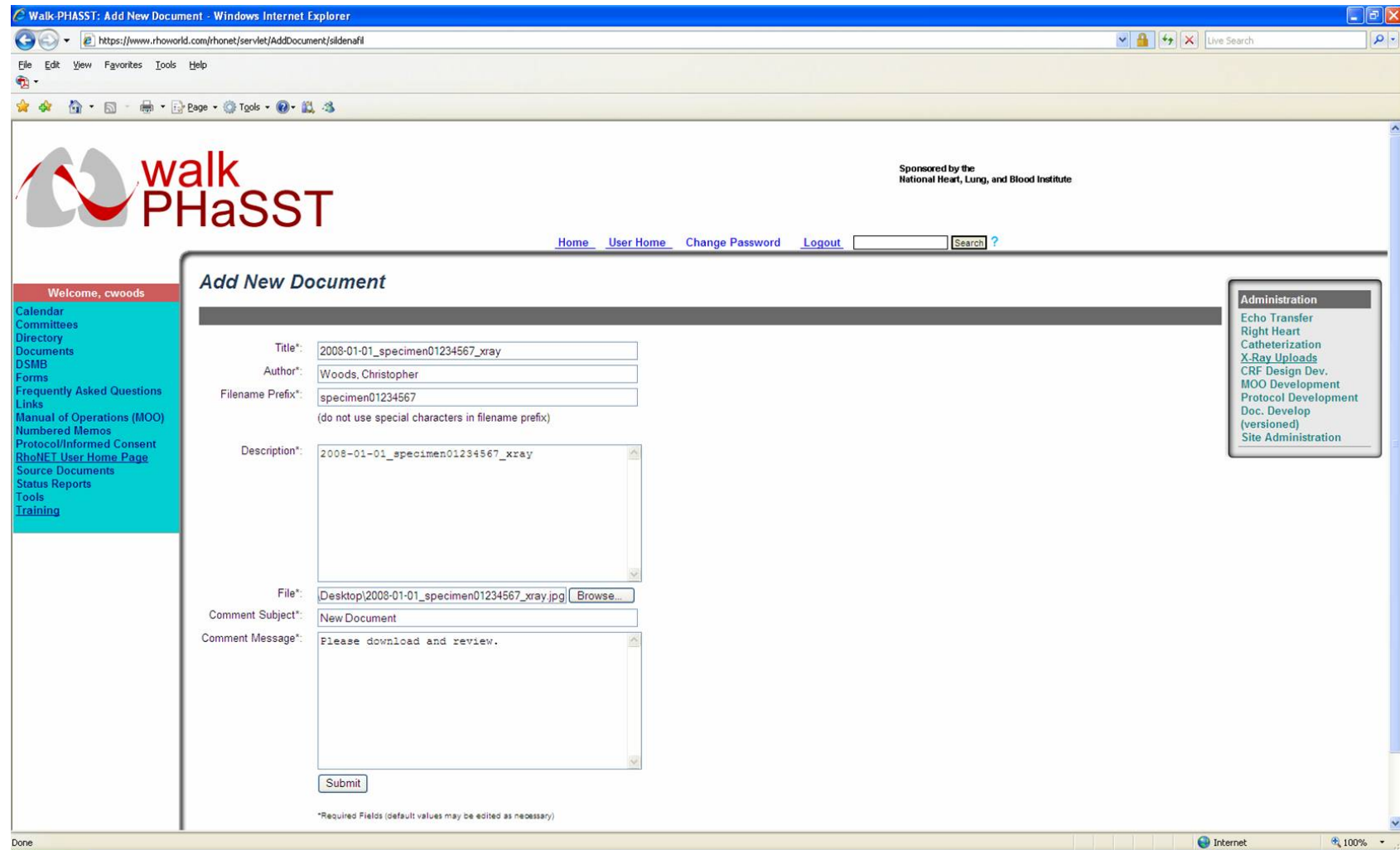
The file name should include the date in YYYY-MM-DD format, the specimen ID, and the type of file (e.g. 2008-01-01\_Subject01234567\_PA xray).

Chest radiographs will be uploaded using the Document Development Category. To navigate to this category, access the website and click on the X-Ray Uploads link in the Administration box on the right side of the page.

To add a file, click on the Add New Document button. On the next screen you will be instructed to enter a Title, Filename Prefix, and Description. In the Title field, enter the name of the file minus the file extension (e.g., 2008-01-01\_specimen01234567\_xray). In the Filename Prefix field, enter the specimen id (e.g., specimen012345). In the Description field, enter name of the file again the same way as in the Title field. Using the Browse button, select the file from your hard drive and hit Submit. Figure 9-1 is a screen shot of the Add New Document screen.



Figure 9-1 Submitting the Chest Radiograph



## **10 PRIAPISM MANAGEMENT PLAN**

### **10.8.1 MANAGEMENT CONSIDERATIONS FOR PRIAPISM**

Adapted from:

Rogers, Z: Priapism in Sickle Cell Disease, *Hematology/Oncology Clinics of North America* 19:5, 917-928, 2005

Erectile Dysfunction Guideline Update Panel. The management of priapism. Baltimore (MD): American Urological Association, Inc.; 2003 ([www.guideline.gov](http://www.guideline.gov), NGC 002967)

**It is recommended that a priapism management protocol be established at each site. This protocol should delineate the site's preferred approach, including medication dosing, and identification of pulmonary, hematology and urology consultants who will assist with management.**

#### **Definition of Priapism-Related Terms:**

Priapism: For purposes of this protocol, priapism is defined as a sustained, painful erection lasting more than 3 hours or intermittent painful unwanted erections lasting less than 3 hours.

Low Flow Priapism: Usually painful, clinically absent cavernous blood flow, after four hours can be considered a compartment syndrome. This results in fibrosis if untreated. In sickle cell disease there may be blood flow at presentation; the definition of priapism is based upon the pH, oxygenation, and arterial blood flow that could lead to ischemia. This is considered to be a medical emergency requiring immediate intervention.

Detumescence: Resolution of priapism with 50 to 75% reduction in pain and rigidity, or complete resolution.

Penile Shunt: There are various medical procedures to increase the cavernous blood flow using vessels or creating an arterial-venous shunt surgically to relieve low flow priapism.

### **10.8.2 Initial Evaluation**

1. Obtain brief history, with attention to:
  - a. Time since onset of priapism
  - b. Potential precipitating events, including:
    - More recent dose and timing of study drug
    - Intracavernosal injection of impotence (aprostadil, papaverine, prostaglandin E1, phentolamine)
3. Perineal or pelvic trauma

4. Psychoactive medications:
  - a. antihypertensives (prazosin)
  - b. antidepressants (bupropion, trazadone, fluoxetine, sertraline, lithium)
  - c. antipsychotics (clozapine)
  - d. tranquilizers (mesoridazine, perphenazine, chlorpromazine)
- c. Prior episodes of priapism and outcome
- d. Maneuvers taken to end this episode
2. Physical exam to confirm fully rigid painful penis
3. Stat Urology Consultation

### **10.8.3      *Intervention – in consultation with urologist, pulmonary hypertension provider and hematologist***

1. Intravenous hydration
2. Supplemental oxygen for documented hypoxia
3. Pain relief with parenteral opioids
4. Keep patient NPO until episode resolved in the event conscious sedation is needed for additional intervention
5. Consider intracorporeal injection of a vasoactive agent (e.g. phenylephrine<sup>1,2</sup>)
6. Consider an oral dose of a vasoactive agent, if cardiovascular status permits and in consultation with the pulmonologist:
  - a. terbutaline (5-10 mg)<sup>3,4,5</sup>
  - b. etilefrine, if available (0.25 mg/kg-50 mg)<sup>6,7</sup>
7. Consider aspiration and irrigation if intracorporeal injection does not result in detumescence
8. Consider penile shunt for refractory episodes

### **10.8.4      *Transfusion Therapy***

There has been no demonstrated benefit to acute transfusion therapy for priapism and there are rare reports of potential delayed neurological events after exchange transfusion for priapism (ASPEN Syndrome)<sup>8</sup>. However, transfusion therapy (usually exchange transfusion) may be considered at local site, in consultation with the sickle cell physician, if this is a routine part of local practice.

### **10.8.5        REFERENCES**

1. Dittrich A, Albrecht K, Bar-Moshe O, et al. Treatment of pharmacologic priapism with phenylephrine. *Journal of Urology* 146:323-4, 1991.
2. Muruve N, Hosking DH. Intracorporeal phenylephrine in the treatment of priapism. *Journal of Urology* 155:141-3, 1994.
3. Lowe FC, Jarow JP. Placebo-controlled study of oral terbutaline and pseudoephedrine in the management of prostaglandin E1-induced prolonged erections. *Urology* 42:51-3, 1993.
4. Gavier FE, Jonsson E, Kramer-Levien D. Oral terbutaline for the treatment of priapism. *Journal of Urology* 151:878-9, 1994.
5. Priyadarshi S. Oral terbutaline in the management of pharmacologically induced prolonged erection. *International Journal of Impotency Research* 16:424-6, 2004.
6. Bachir D, Virag R, Lee K, et al. Prevention and treatment of erectile disorders in sickle cell disease. *Rev Med Interne* 18(Suppl 1):46s-51s, 1997.
7. Gbadoe AD, Atakouma Y, Kusiaku K, et al. Management of sickle cell priapism with etilefrine. *Arch Dis Child* 85:52-3, 2001.
8. Siegel JF, Rich MA, Brock WA. Association of sickle cell disease, priapism, exchange transfusion and neurological events: ASPEN syndrome. *Journal of Urology* 150:1480-2, 1993.

## **11 QUALITY OF LIFE ASSESSMENTS**

Quality of life (QOL) will be assessed by either the SF-36 or the PedsQL at baseline (before randomization) and at end of study (16 weeks or early termination) during the MIT. Both scales are suitable for self-administration or administration by a trained interviewer. Sites will not be responsible for scoring these assessments; this will be done by the DCC based on the data entered into the EDC system.

Copyrights have been obtained for the use of both of these instruments in this study, and the source documents are located on the Source Documents page of the walk-PHaSST website.

### **11.1 SF-36**

The SF-36, version 2, will be used for subjects who are • 14 years of age.

The SF-36 is a self administered test and assesses the following 8 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)
- 8) General health perceptions

### **11.2 Peds Quality of Life (PedsQL)**

The PedsQL will be self-administered with minimal assistance from the Study Coordinator or designee. The parent/child will complete only the PedsQL Generic Core Scales. There is no sickle cell disease-specific PedsQL module. Administrative guidelines provided by the developers include the following recommendations:

- Parents and children (ages 12-13) may self-administer the PedsQL after introductory instructions from the administrator. If the administrator determines that the child or teenager is unable to self-administer the PedsQL (e.g., due to illness, fatigue, reading difficulties), the PedsQL should be read aloud to the child or teen.
- The parent and child must complete the questionnaires independently of each other. Discourage the parent, child or other family members from consulting with one another during the completion of the questionnaire. Let them know that they can feel to discuss their answers following completion of the questionnaires, but that it is important to get both the parent's and the child's individual

- perspectives. If you are administering the questionnaire to the child, the child should be facing away from the parent.
- If the child or parent has a question about what an item means or how they should answer it, do not interpret the question for them. Repeat the item to them verbatim. Ask them to answer the item according to what they think the question means. If they have trouble deciding on an answer, ask them to choose the response that comes closest to how they feel. The child and/or parent has the option of not answering a question if they truly do not understand the question.
  - If a parent/child asks for an interpretation of the responses, the Study Coordinator or other designee should tell him/her that they are not trained to interpret or provide a score for the answers given.

### **11.2.1        *Administering the PedsQL***

Provide the respondent with a pen or pencil and a solid writing surface. If a table is not available, the participant should be provided with an item such as a clipboard. Remain nearby should questions or concerns arise.

When the parent/child returns the PedsQL, look it over and check to see that all answers have been completed. Verify that no item has more than one response. If any responses are incomplete, illegible, or there are multiple responses for an item, please ask the parent or child to indicate their responses.

The following scripts have been developed as a guide to introduce the PedsQL to the child and his/her parent(s). Modify the language to a style that is most appropriate for you and the respondent.

#### **11.2.1.1        For the Child:**

The PedsQL asks you the questions about how you feel and what you think about your health. It is not a test, and there are no right and wrong answers. It takes about 5 minutes to complete. If you have any questions, please let me know.

#### **11.2.1.2        For the Parent:**

The PedsQL is a questionnaire that assesses health-related quality of life in children and adolescents. It contains questions about your child's physical, emotional, social, and school functioning in the past one month.

The PedsQL is a brief and typically takes less than 5 minutes to complete. It is not a test, and there are not right and wrong answers. Please be sure to read the instructions carefully and choose the response that is the closest to how you truly feel. Please do not compare your answers with your child's responses. We are interested in your and your child's individual perspectives. However, feel free to discuss the questionnaire with your child after you have both completed it and returned it to me. If you have any questions, please let me know.

## **12 BRIEF PAIN INVENTORY (BPI)**

### **12.1 Introduction**

The Brief Pain Inventory (BPI) is a comprehensive, multidimensional pain assessment tool that measures both the intensity of pain (sensory dimension) and interference of pain in a patient's life (reactive dimension)(1). It also queries the patient about pain relief, pain quality, and patient perception of the cause of pain. The BPI was developed as a balance between the need to assess as much as possible of the multidimensional components of pain and the need to limit respondent burden. The BPI contains four questions about pain intensity, seven questions about pain-related interference, and a numeric scale to rate overall pain intensity and pain interference. It also asks the patient to diagram his or her pain.

It is a powerful tool and, having demonstrated both reliability and validity across cultures and languages, is being adopted in many countries for clinical as well as epidemiological studies involving cancer pain as well as non-cancer pain(2). Pain score as assessed by the BPI is a secondary efficacy endpoint in this study. BPI assessments will occur for one week periods at baseline and during the Randomized, Double-blind Phase at 6±1 wk, 10±1 wk, 16± wk /early term.

Study coordinators will receive printed copies of this BPI coupled with a study drug diary. Each printed copy will have enough space to complete the BPI and the study drug diary for one week. Study coordinators will be responsible for filling in the dates on each page for which the patients should complete the diary, and should also call and remind their patients the day before completion should begin. An electronic copy of the BPI and study drug diary is available on the study website under “Forms”.

#### **12.1.1 Baseline Evaluation**

After the MIT consent has been signed and **prior** to Randomization, subjects will be asked to complete a one-week pain diary composed of daily assessment using the Brief Pain Inventory and to bring the diary with them for the baseline visit. This should happen BEFORE the patients completes their right heart catheterizations if their TRVs ≥ 3.0 m/s.

#### **12.1.2 Randomized, Double-blind Phase**

Subjects will maintain a diary for 1 week between each study visit. The diary will capture study drug compliance and self-reported pain assessments. Daily pain assessments will be carried out by the subject using the BPI for one week between each follow-up visit. Subjects will be asked to bring the pain diary during study visits at 6±1 wk, 10±1 wk, 16± wk /early term.

### **12.1.3        *References***

1.        Cleeland, C.S., and Ryan, K.M. 1994. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 23:129-138.
2.        Keller, S., Bann, C.M., Dodd, S.L., Schein, J., Mendoza, T.R., and Cleeland, C.S. 2004. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain* 20:309-318.

### **12.1.4        *SAMPLE Brief Pain Inventory Short Form***

The study has received approval from the BPI author to administer the form to all subjects in the trial. Approval is based on an agreement that the form will be used without modification.



STUDY ID #: \_\_\_\_\_

DO NOT WRITE ABOVE THIS LINE

HOSPITAL #: \_\_\_\_\_

### Brief Pain Inventory (Short Form)

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

Time: \_\_\_\_\_

Name: \_\_\_\_\_

Last

First

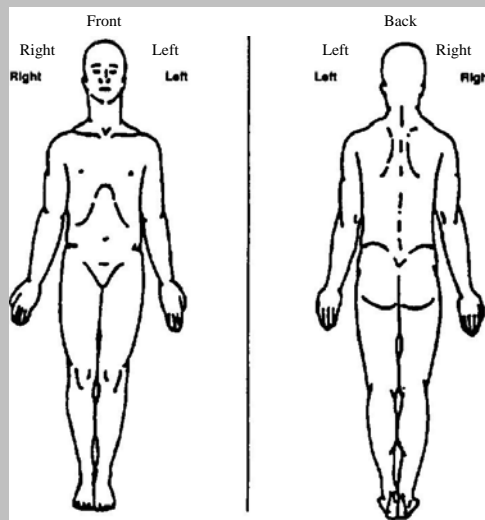
Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every day kinds of pain today?

1. Yes

2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its **worst** in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No										Pain as bad as
Pain										you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its **least** in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No										Pain as bad as
Pain										you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the **average**.

0	1	2	3	4	5	6	7	8	9	10
No										Pain as bad as
Pain										you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have **right now**.

0	1	2	3	4	5	6	7	8	9	10
No										Pain as bad as
Pain										you can imagine

STUDY ID #: \_\_\_\_\_

DO NOT WRITE ABOVE THIS LINE

HOSPITAL #: \_\_\_\_\_

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

Time: \_\_\_\_\_

Name: \_\_\_\_\_

Last

First

Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

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## 13 STUDY DRUG ADMINISTRATION AND ALTERNATIVE THERAPIES GUIDELINES

The **Main Interventional Trial** is the randomized, double-blind, placebo controlled phase of Walk-PHaSST. It is designed to determine the effects of 16 weeks of sildenafil therapy on exercise endurance, cardiopulmonary hemodynamic parameters and symptoms in this patient population. In addition, in patients undergoing right heart catheterization we will test the acute hemodynamic effects of oral sildenafil.

The **Open-label Follow-up Phase** is designed to provide up to 1 additional year of sildenafil therapy to subjects who completed the randomized, double-blind phase.

This chapter will describe practical issues about study drug administration and the use of alternative therapies.

### 13.1 Sildenafil

#### 13.1.1 Description of Study Drug and Dosing Regimen

Sildenafil is an oral therapy for erectile dysfunction and is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). It is available in tablet form (Pfizer). Pfizer will provide the drug and matching placebo for this study free of charge through an Independent Research Grant Agreement.

#### 13.1.2 Acute Hemodynamic Effects of Sildenafil

In subjects undergoing right heart catheterization the acute hemodynamic effects of inhaled NO and oral sildenafil will be assessed at rest. During the baseline catheterizations sildenafil (active drug) will be administered according to the following guidelines:

	<b>Intervention</b>	<b>Duration</b>	<b>Assessment</b>
Step 1	Baseline		Resting hemodynamics
Step 2	Inhaled NO 40 ppm	10 minutes	Resting hemodynamics <sup>1</sup>
Step 3	None	10 minutes	Resting hemodynamics
Step 4	Sildenafil 60 mg orally	30 minutes post oral dose	Resting hemodynamics
Step 5		60 minutes post oral dose	Resting hemodynamics

<sup>1</sup> Resting hemodynamics assessed at the end of the 10 minute period of inhaled NO, while the subject is still inhaling the NO.

Right heart catheterization will be repeated at the end of the double-blind phase. This hemodynamic assessment will follow the guidelines below:

- Subjects will take their nighttime dose of study medication, but will not take their morning dose prior to right heart catheterization.
- Subjects will bring study medication to visit.

- Study medication is administered with direct observation by study coordinator
- Right heart catheterization will be performed approximately 4 hours after study medication is administered
- Baseline hemodynamic measurements will be performed as outlined in Table 2 (steps 1 and 2).
- Blinded study medication will be administered and hemodynamic measurements will be performed at 30 and 60 minutes post dosing as outlined in steps 4 and 5 of Table 2.

If during right heart catheterization, it is not possible to obtain an adequate reading of the pulmonary capillary wedge pressure, a left heart catheterization will be performed for the measurement of left ventricular end-diastolic pressure.

(Text duplicated from: Protocol, version 4.0, 27Nov2008, Section 4.4.2.2)

### **13.2 Main Intervention Trial**

During the randomized, double-blind phase, the initial dose of study drug (20 mg every 8H PO) is given for a total of 6 weeks, followed by 4 weeks of 40 mg TID, and finally 80 mg TID for 6 weeks. All study drug should be given by mouth.

The dosing regimen was designed to achieve the following 2 objectives:

1. Minimize sildenafil related adverse effects such as headache and facial/periorbital edema through gradual dose escalation
2. Provide the ability to evaluate the relative efficacy of different sildenafil doses on functional capacity and pulmonary artery pressures as evaluated by echocardiogram

### **13.3 Open-label Follow-up Phase**

The open label sildenafil will be available in 20 mg strength and may also be available in 25 mg strength. At the beginning of the Open Label Phase, all eligible subjects will be down titrated from 80 mg TID of sildenafil or placebo to 20 or 25 mg of sildenafil TID. The doses will then be titrated upwards as tolerated. Doses will increase by 20-25 mg TID every 2 weeks. The maximum dose will either be 75 mg or 80 mg TID, depending on 20 mg or 25 mg tablet availability.

If patients choose to not receive active drug in the open label follow up phase it is strongly recommended that the study medication be tapered down. The duration of the taper will be a maximum of 7 days and blinded study medication will be provided in a number sufficient to complete that taper. Tapering will not be required for patients requiring discontinuation of the drug due to AEs.

We suggest the following regimen for patients taking EOS dose of 80 mg TID:

Day 1 40 mg TID

Day 2 40 mg TID

Day 3 40 mg BID

Day 4 40 mg QD

### **13.4 Potential Adverse Effects of Sildenafil**

A detailed description of AEs associated with sildenafil is available in the study protocol. Some of the potential AEs include hypotension, headache, flushing, dyspepsia, nasal congestion, urinary tract infection, abnormal vision, diarrhea, dizziness, rash, myalgia, epistaxis, insomnia, parasthesia, pyrexia, and decreased or loss of hearing.

#### **13.4.1 *Sildenafil and Sickle Cell Disease: Specific Potential Adverse Effects***

At the NIH, we have treated 22 patients with SCD and PH with sildenafil. The drug was well tolerated and only 2 patients required drug discontinuation due to headaches. We have also observed the presence of eyelid edema in three sickle cell patients at either sildenafil initiation or dose escalation. This phenomenon was not reported in the literature, is transient in nature even with continuation of the drug and was not associated with any impairment in visual function.

Up to 45 % of male patients with sickle cell disease (HbSS) will develop one episode of priapism as a consequence of the disease. As such, patients SCD are advised to use sildenafil with caution. No cases of priapism were reported in clinical trials of sildenafil. Interestingly, there are no case reports of sildenafil-induced priapism with SCD. There was one report of an individual with sickle cell trait (HbAS) presenting with priapism after a 50 mg dose of sildenafil. In contrast to that report, Bialecki and Bridges describe resolution of recalcitrant priapism with acute administration of sildenafil in three patients with sickle cell disease. Interestingly in the two patients who were offered outpatient therapy, the use of sildenafil at the onset of priapism resulted in resolution of the episode.

We have treated seven males with SCD and PH with sildenafil on a chronic basis. Three were at low risk for the development of priapism (due the chronic exchange transfusion and erectile dysfunction) and 4 were at risk. One of the 4 subjects at risk developed an episode of mild priapism that spontaneously resolved in two hours without any clinical sequelae.

(Text duplicated from protocol version 4.0, 27Nov2007, Section 12.3.2.4)

### **13.5 Dose Modification or Discontinuation Due to Expected Adverse Events: Headache or Facial/skin Edema**

Dose adjustment instructions for symptomatic/dose limiting headache or facial/skin edema sufficient to warrant discontinuation of the drug (only for symptoms that are severe enough as described by subject or physician to warrant holding the drug) are provided herein.

1. If present during initial dose (20 mg) hold for one day and rechallenge, if symptoms occur upon rechallenge discontinue drug. Data collection should continue for such subjects to the extent possible.
2. If present during dose escalation (40 or 80 mg) hold drug for one day and restart at previously tolerated dose for one week. If symptoms recur, discontinue drug but continue to follow subject for collection of safety and other data. If tolerated for one week increase dose to desired level as dictated by protocol. If symptoms recur upon second increase hold drug for one day and drop dose to previously tolerated dose for the duration of the trial.

(Text duplicated from protocol version 4.0, 27Nov2007, Section 7.2)

### **13.6 Monitoring for Priapism**

Priapism is defined in this study as a sustained, painful erection lasting more than 3 hours or intermittent painful unwanted erections lasting less than 3 hours. Males will be monitored for priapism for 6 hours after sildenafil therapy in the catheterization laboratory (for subjects with TRV • 3.0 m/s) and in the clinic after the first dose of study drug during the double-blind phase for subjects with TRVs between 2.7 m/s and 2.9 m/s.

In addition, all male patients will be monitored in the clinic for priapism after their first dose of sildenafil during the open label follow-up phase.

Males will be specifically monitored for incidence of priapism during their study visit interviews. Additionally, they will be instructed to contact a member of the study team at the onset of any degree of priapism and will be admitted for immediate evaluation and treatment. Each site will have a priapism management plan in place. For further information consult MOO Chapter 4.7, which provides possible therapeutic interventions that will be individualized as clinically appropriate for each episode of priapism.

(Reference protocol version 4.0, 27Nov2007, Section 4.4.2.3)

### **13.7 CRITERIA FOR STUDY DRUG DISCONTINUATION AND WITHDRAWAL OF SUBJECTS**

Therapy will be discontinued for the following reasons:

1. Major bleeding complication including intracerebral hemorrhage or stroke, GI hemorrhage, need for major surgery.

2. One episode of severe priapism defined as priapism lasting for more than 4 hours or requiring transfusion or surgical therapy (see Chapter 10 for further details of priapism monitoring)
3. Positive quantitative blood HCG or pregnancy
4. New retinal detachment, hemorrhage or clinically significant visual change
5. Serious adverse events considered to be related to the study drug
6. Introduction of specific treatments for pulmonary hypertension (excluding acute administration during a catheterization procedure to test vascular reactivity)
7. Initiation of chronic transfusion therapy (in this instance, EOS assessments should occur either immediately prior to initiation of transfusions or between 2-3 weeks after the transfusion)
8. Protease inhibitor treatment for HIV
9. If an emergency clinical unblinding of treatment assignment is required
10. Initiation of potent CYP3A4 inhibitor therapy (e.g., itraconazole, ritonavir, ketoconazole)

Sickle cell related clinical deterioration, other than those requiring initiation of chronic transfusion therapy, does not require withdrawal of study medication. Likewise, clinical deterioration of PH does not necessarily require discontinuation of study medication, unless the Investigator feels it is necessary to introduce another PH medication. In any situation where subject discontinuation is not required, the Investigator may always choose to discontinue the subject based on his or her clinical judgment.

Any premature discontinuation of study drug precludes participation in the Open-Label Follow-up Phase of the MIT. At the time of study drug discontinuation all EOS visit assessments should be obtained to the extent possible. Such subjects should continue to be followed for adverse events and collection of other study data to the extent possible. Assessment of study endpoints should be made blinded to subjects' study treatment as much as possible.

(Text duplicated from protocol version 4.0, 27Nov2007, Section 7.1)

## **13.8 Alternative Therapies during the Double-blind Phase**

### **13.8.1 Permitted regimens**

- Hydroxyurea therapy, if stable for at least 1 month preceding randomization and throughout the trial (no change in dose, except decrease for safety reasons)

- Long-term oxygen therapy, if stable for a least 2 weeks prior to randomization
- Chronic blood transfusions, if started within at least 1 month preceding randomization and continued throughout the trial. Chronic blood transfusions must be given at least 1 week before or at least 1 week after each efficacy assessment visit.
- Anticoagulants should be continued during the whole study period, if ongoing at time of entry into MIT
- ACE inhibitors, beta blockers, vasodilators (not including nitrate-based), diuretics provided they have been stable on the medication at least one month prior to enrollment in the study

Both the initiation of hydroxyurea therapy to those naïve to that treatment and tonsillectomy surgery should be delayed until conclusion of the double-blind phase of the MIT, unless deemed clinically necessary in the opinion of the investigator. Those subjects requiring either therapy during the MIT may, however, remain on study.

(Text duplicated from protocol version 4.0, 27Nov2007, Section 4.4.3)

### **13.8.2      *Forbidden regimens***

- Specific treatments for pulmonary hypertension (excluding acute administration during a catheterization procedure to test vascular reactivity)
- Protease inhibitor treatment for HIV
- Initiation of potent CYP3A4 inhibitor therapy (e.g., itraconazole, ritonavir, ketoconazole)
- Initiation of Chronic elective transfusion therapy during the double-blind phase of the MIT

(Text duplicated from protocol version 4.0, 27Nov2007, Section 4.4.3)



## **14 DATA COLLECTION (RHOEDC™)**

### **14.1 Introduction**

The clinical data from this trial will be entered by trained staff at each participating site into the clinical database via Rho's proprietary electronic data capture software. Web-based RhoEDC is a secure and fully validated system.

Study data will be stored in a relational database employing Oracle Database 10g software. Rho will produce SAS datasets from the Oracle data for the purposes of reporting and analysis.

It is anticipated that some data requirements will be addressed outside RhoEDC using SAS software.

This section of the Manual of Operations describes the data collection and validation process established for this study.

### **14.2 Responsibilities**

#### **14.2.1 *Clinical Site Responsibilities***

- Practice EDC prior to using the production EDC
- Complete, accurate, and timely entry of clinical data into the RhoEDC application
- Maintain source documentation
- Resolve queries promptly
- Electronically sign-off by the Clinical Investigator on all information entered into EDC when required

#### **14.2.2 *Clinical Research Associate Responsibilities***

- Verify EDC data against source documents

#### **14.2.3 *Clinical Data Management Responsibilities***

- Create e-CRFs for data entry
- Set-up the clinical database
- Review practice-data entered by each site user, certify users for production EDC
- Preparation of a data management plan
- Validate study data via programmed and manual checks as defined in the study Data Management Plan

- Track query resolution
- Ensure that all forms have been completed and queries have been resolved prior to database lock
- Archive study data after study closeout

## **14.3 Case Report Form and Source Documents**

### **14.3.1 Case Report Form**

The web-based electronic forms presented by the RhoEDC system constitute the Case Report Form (e-CRF) for this study. Sites should complete the e-CRF from the source documents used to capture study information. The data entered in the EDC system must be verifiable against the source document.

### **14.3.2 Source Documents**

Each site is responsible for ensuring that it has appropriate source documentation of all data collected in “real-time” and required for entry into the e-CRF. To assist the sites with source documents, Rho will provide templates based on the e-CRF (available on the study website).

The templates should be used only when other source documentation is unavailable or for non-standard data such as medical history, patient reports, etc. All assessments that have results documented in the subject’s medical record – such as echocardiogram, chest x-ray, and chemistry/hematology panels – should be completed in the EDC system from the medical record. All original patient questionnaire data should be filed in the subject’s folder as source documentation and should be used for entering data in the EDC system (such as the BPI, study drug diary, quality of life assessments).

Sites may print the blank templates as provided and use them as source documents for a portion of subject data. The source document templates have sections shaded in gray. These shaded areas are information that “should” be obtained directly from the patient’s medical record. Alternatively, sites may choose to create their own source documents. Sites are **not** required to use the source document templates provided by Rho.

The complete set of source documents (as pdfs) is available on the Source Document Template page of the walk-PHaSST website.

## **14.4 Timing of Data Submission**

### **14.4.1 e-CRF Data**

Clinical sites should enter all clinical data (study assessments) into RhoEDC as soon as possible and **no more than one week** from the data collection date. Medical History

forms in the Screening EDC system can be submitted two weeks after the patient has completed his/her first Screening assessment.

However, data associated with Serious Adverse Events must be entered in RhoEDC on an expedited basis. **After learning that a subject has experienced any Serious Adverse Event, the site must complete the Adverse Events form, including the corresponding Serious Adverse Events form, before the end of the next business day.**

#### **14.4.2            *Query Data***

All queries should be resolved as soon as possible and **no more than one week** from the date the query was issued, provided the information required to resolve the query is available. If the site is waiting for information (for example, a lab result or the outcome of an ongoing adverse event), the query should be answered as soon as that information becomes available.

#### **14.4.3            *Patients Consented to Screening who are Lost to Follow-up***

Patients who consent to the Screening/Observational Follow-up Study and never return for the Screening assessments still need to be added to the Screening EDC System. At a minimum, the following fields need to be entered into the Demographics CRF:

- 1) Birth Date
- 2) Gender
- 3) Race
- 4) Ethnicity

#### **14.4.4            *Patients who do not Complete all Screening Assessments***

Patients who consent to Screening/Observational Follow-up Study and only complete some of the assessments should have all available data entered into the EDC. If a patient does not complete the 6MW, the echocardiogram, the physical exam, or the biomarkers collection, a protocol deviation should be filed as a missed assessment. The Subject Disposition CRF should be completed in the Screening EDC and the Enrollment Failure function should be completed in RhoRAND in order for the patient to be considered “discontinued” from Screening.

### **14.5                *RhoEDC™ Training***

RhoEDC training and resource materials will be provided via face-to-face training and documentation available on the walk-PHaSST website.

Prior to being authorized to record data in the production EDC, users must complete a study-specific training by entering a pre-specified set of mock data in the demo RhoEDC. After a user has successfully completed the practice session, he/she will be authorized to

enter data in the live production system. For further details on EDC training, refer MOO Chapter 13.5 - RhoEDCTraining Module.

## **14.6 RhoEDC**

### **14.6.1 Access to RhoEDC**

RhoEDC operates in a secure environment that is accessible only to users who are authenticated and authorized to use it. Contact the RhoNET Help Desk at 1-800-905-0460 if you have any problem accessing the site.

To access RhoEDC:

1. Open your web browser to [www.rhoworld.com](http://www.rhoworld.com).
2. Log in to RhoNET using your assigned RhoNET user ID and password (If you do not have a RhoNET account or if you do not remember them, contact the RhoNET Help Desk at 1-800-905-0460).
2. Navigate to the study RhoNET web site or page.
3. Click the study RhoEDC link.
4. RhoEDC will prompt you to enter your RhoEDC user ID and password.

(Note: You may make your RhoEDC™ and your RhoNet password the same; however, RhoEDC™ still requires that it be entered so the system can authenticate you as a user.)

Exiting the RhoEDC™ System

1. Click the Logout link on the gray navigation menu on the left side of the screen.
2. Log out of RhoNET.
3. Close your web browser.

**IMPORTANT:** When you exit RhoEDC, you must log out and close your browser window to completely exit the application.

### **14.6.2 Disabling Your Pop-Up Blocker**

RhoEDC uses pop-up windows to display error messages on forms. If your browser is set to block pop-up messages, these error messages will not function for you. You must **turn off your browser's pop-up blocker** before you use RhoEDC™.

The method for disabling pop-up blocking varies depending on the browser you are using. Click on the EDC HELP link on the gray navigation menu on the left hand screen for details on how to disable pop-up blocking for the browser you are using. If you need further help or assistance, contact the RhoNET Help Desk at 1-800-905-0460.

### 14.6.3 ***Navigating RhoEDC***

The RhoEDC main screen consists of two main sections:

1. **Navigation Menu:** The gray Navigation Menu on the left displays your username and the current date, and provides links to the various levels (sections) of the menu system.

The 'Log Out' and 'EDC Help' links are also located here.

2. **Display Area:** The right portion of the screen displays the menu of links associated with the currently selected section. The name of the section currently displayed – the study, site, or subject ID number – always appears above the links. A secondary navigation bar at the top of the display area provides direct links to other sections of the menu system.

Note: RhoEDC will display to a user only the studies, sites, subjects, and forms the user is authorized to view. If you find that you do not have access to the correct site, studies, forms, or features to which you believe you should have access, contact the RhoNet Help Desk at 1-800-905-0460.

#### 14.6.3.1 **The Menu System**

RhoEDC™ uses a branching menu system. When you open the application, the basic menu is shown in the Display Area. When you click an option on the menu, RhoEDC will display the options at the next menu level, and so on. If you do not have more than one option available on a particular level, RhoEDC automatically advances you to the next level of options.

Here is a list of menu levels available for the study:

1. **Site List:** Displays a list of sites for the study, if you have access to more than one site. If you have access to only one site, RhoEDC will advance you to the next level.

welcome to  
**RhoEDC™**  
nyovetic  
01 Feb 2008  
**PRODUCTION SYSTEM**  
v4.05.04

LOG OUT  
EDC HELP

Data Collection

Studies  
1. Screening  
1. Screening  
Sites

**Studies > 1. Screening > 1. Screening > Sites**

### Sites

Select:  or Find:

- Albert Einstein College of Medicine (S)
- Children's Hospital of Oakland (S)
- Children's Hospital of Pittsburgh (S)
- Hammersmith Hospital (S)
- Howard University (S)
- Johns Hopkins University (S)
- NHLBI Intramural (S,!)
- Rho Federal Systems Division, Inc. (!)
- University of Colorado (S)
- University of Illinois, Chicago (S)

Sites Count: 10

6330 Quadrangle Dr. Suite 500 • Chapel Hill, NC 27517  
1-800-905-0460 8am-6pm EST M-F

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**RhoEDC™**  
nyovetic  
01 Feb 2008  
**PRODUCTION SYSTEM**  
v4.05.04

LOG OUT  
EDC HELP

Data Collection

Studies  
1. Screening  
1. Screening  
Sites  
NHLBI Intramural  
Subjects

**Studies > 1. Screening > 1. Screening > Sites > NHLBI Intramural > Subjects**

### Subjects

Select:  or Find:

- 080016 (S,!)
- 080027 (!)
- 080053 (!)

Subjects Count: 3

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3. All Visits: Displays a list of study events – such as visits – for the selected subject.

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v4.05.04

LOG OUT  
EDC HELP

Data Collection

Studies  
1. Screening  
1. Screening  
Sites  
NHLBI Intramural  
Subjects  
080016

Studies > 1. Screening > 1. Screening > Sites > NHLBI Intramural > Subjects > 080016

080016 View

Forms

Screening  
As Needed

The following actions are required before this set of forms is complete: Sign

Rho, inc. RESULTS. RIGHT. ON TIME.®

welcome to  
**RhoEDC™**  
nyovetic  
01 Feb 2008  
**PRODUCTION SYSTEM**  
v4.05.04

LOG OUT  
EDC HELP

Data Collection

Studies  
1. Screening  
1. Screening  
Sites  
NHLBI Intramural  
Subjects  
080016

Screening  
As Needed

Studies > 1. Screening > 1. Screening > Sites > NHLBI Intramural > Subjects > 080016 > Screening

Screening

Forms

- ✓ Demographics
- ✓ Medical History, Part 1
- Medical History, Part 2
- ✓ Medical History, Part 3
- ✓ Physical Examination
- ✓ Chemistry
- ✓ Hematology
- Urinalysis
- ✓ HIV Test
- ✓ Pregnancy Test
- Echocardiogram (Local)
- ✓ 6-Minute Walk Test
- Biomarker/Genotype Sample Collection
- ✓ Subject Disposition

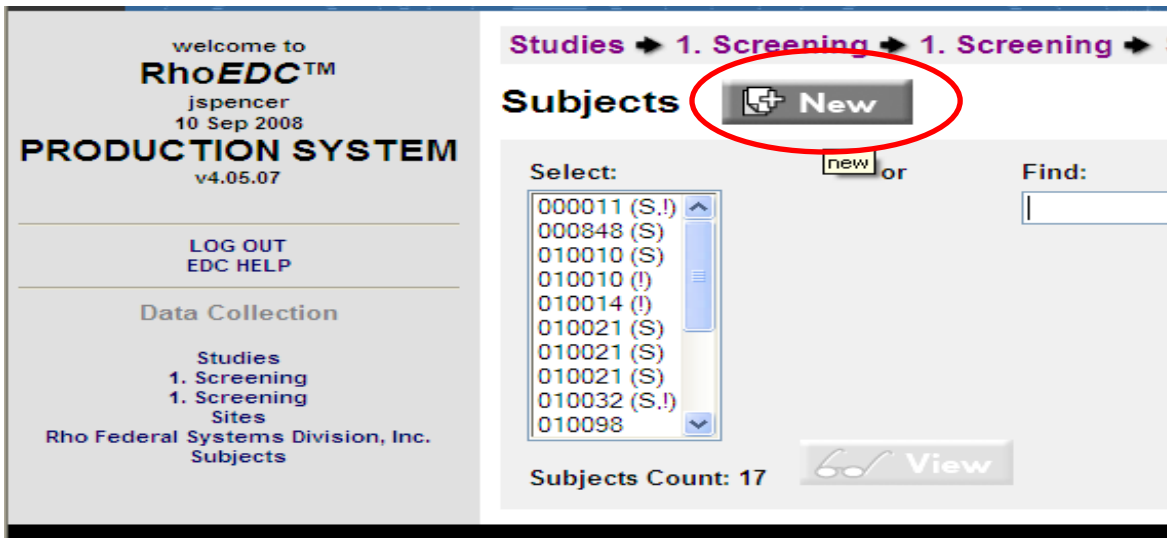
The following actions are required before this set of forms is complete: DM Review

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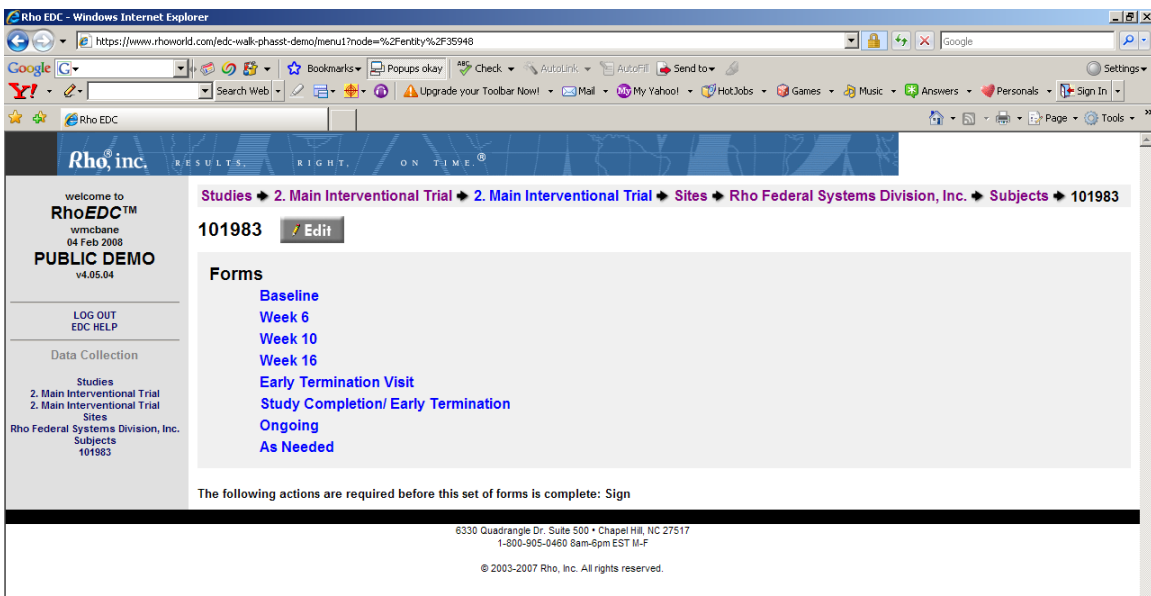
As you navigate through the menu system, the Navigation Menu updates to display links for each menu level you visit. You can jump directly to any higher menu level by clicking its link. The navigation bar at the top of the Display Area also provides links to higher menu levels in this manner. (See the illustrations.)

### 14.6.4 Creating a New Subject Record

When you are ready to enter data for a newly enrolled subject (Registered in Screening),



The system will create an e-CRF for the subject and will display a list of visits and forms that are expected to be completed for the new subject.





### 14.6.5 *Importing Subjects from Screening to MIT, Observational Follow-up Study or the Open-label Follow-up Study*

When a subject has completed Screening, he/she will be enrolled into the MIT (if

The screenshot shows the RhoEDC interface. On the left is a sidebar with the text: "welcome to RhoEDC™ jspencer 10 Sep 2008 PRODUCTION SYSTEM v4.05.07", "LOG OUT EDC HELP", and "Data Collection" with a list of "Studies" including "2. Main Interventional Trial". The main content area has a breadcrumb trail: "Studies > 2. Main Interventional Trial > 2. Main Interventional Trial". Below this is a "Subjects" header with two buttons: "New" (crossed out with a red X) and "Import" (circled in red). There is a "Select:" list box containing: "000011 (S,!)", "000848 (S)", "010014", "010032 (S,!)", "010098", "123123 (S,!)", and "123123 (S,!)". To the right is a "Find:" search box. At the bottom, it says "Subjects Count: 7" and a "View" button.

The screenshot shows the RhoEDC interface. The sidebar is identical to the previous screenshot. The breadcrumb trail is "Studies > 2. Main Interventional Trial > 2. Main Interventional Trial". The "Subjects" header now has "New" and "Select" buttons. The "Select:" list box contains: "010010", "010010", "010021", "010021", "010021", "010120", "010120", "010518" (highlighted in blue), "123123", and "123123". The "Find:" search box contains "010518". At the bottom, it says "Subjects Count: 10" and the "Import" button is circled in red.

### **14.6.6 Using Forms**

The forms in RhoEDCwork much like any other forms commonly used on the Internet. There are a number of ways to enter data:

- Text Fields: Empty fields that allow you to type text and numbers
- Drop-down Menus/Lists: Menus or lists containing multiple options from which you may select one choice. To select a response from a drop-down menu, click the down-arrow to open the list, and then click the response to select it.
- Checkboxes

Multiple response checkboxes: These are used for questions that can have multiple responses, where the question might include “Check all that apply.” To select a response, click in the empty checkbox. To uncheck a response, click in the checkbox a second time.

Single response checkboxes: This variation of the checkbox is used for questions that can have only one response, such as ‘Yes’ or ‘No’. To select a response, click the checkbox. If you select another response for that question, the original response is automatically unselected.

#### **14.6.6.1 Adding a New Form**

If this is the first time you are entering data on a form for this subject, a blank version of the form will open. Navigate to the visit level of the study and click on the link for the form you wish to complete.

#### **14.6.6.2 Navigation within a Form**

- To move from the current field/control to the next one on the page, press the TAB key.
- To move from the current field/control to the previous one on the page, hold down the SHIFT key and press TAB.
- To move the cursor directly to any field/control on the page, click on that field/control.
- To replace existing data in a text field, highlight the data you want to replace, press DELETE, and type the new data. Or, you can highlight the data to be replaced and simply type the new data over it.

#### **14.6.6.3 Saving, Canceling or Submitting a Form**

The very first time that you enter information into a form, you are “creating” it. When you have completed the form or have entered a subset of the required data and want to

save what you've entered, click the **Create** button at the bottom of the form to submit the form and save the data. Please note that if you choose to save the form after you have entered only a subset of the data, it is likely that queries will be generated. That is to be expected, simply select "Submit as is" and return later to modify the empty fields.

To exit the form without saving your changes, click **Cancel**.

The screenshot shows a web browser window with the URL <https://www.rhoworld.com/edc-walk-phasst-demo/edit/entity/24487>. The form is titled "15. Extremities & Skin" and contains the following sections:

- Nails:**  Normal,  Clubbing,  Hyperpigmentation
- Lower Extremities:**
  - Edema:**  None,  +,  ++,  +++,  ++++
  - Pulses:**  Normal,  Abnormal. If **Abnormal**, describe: [text input]
  - Ulcers:**  None,  Active,  Healed. If **Active or Healed**, describe: [text input]
- Skin:**
  - Hyperpigmentation:**  Absent,  Present
  - Rashes or skin lesions:**  Absent,  Present. If **Present**, describe: [text input]
  - Comment/other findings or abnormalities:** [text input]

At the bottom of the form, there is a "Comments for page:" section with a text input field. Below the form are buttons for "Update", "Cancel", "Delete", and "Print", along with a "Form Completion Help" link and the Rho logo.

#### 14.6.6.4 Editing an Existing Form

You might want to return to a form that was previously created to change data or add additional data. Navigate to the visit level of the study and click on the link for the form you wish to update. The form will open and display the previously entered data. After you make your changes, click **Update** to save the updated data.

#### 14.6.7 **Data Validation**

Data entered via RhoEDC will be validated against a series of automatic and manual checks designed to test whether the entries 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 study's data managers periodically after the data are entered.

### 14.6.7.1 Automatic Checks

When the system detects a possible error during data entry, an automatic query box will pop up on the screen immediately after you attempt to submit a page either missing data or with data that is out of the expected range. These fields will also turn pink indicating that the system would like confirmation that the field was left blank on purpose or that the value entered is correct.

You will have three options once you select the appropriate query in the box:

**‘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 and you can come back to it later. The field with the suspect value will remain pink.

**‘Fix 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.

**‘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. Another example is if you are collecting medical history from patient report and only the year and month is known, but not the actual day. You would leave the field for the day blank, and override the query.

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.

### 14.6.7.2 Reasons for Overriding Automatic Queries

Your reason for overriding an automatic query should be brief but complete.

Here are some examples of reasons you might have for overriding an automatic query:

<b>Data Issue/Problem</b>	<b>Reason</b>
Missing Date	Date is unknown
Field left Blank	Value is unknown
	Assessment was not done
	Not applicable
	Subject refused to answer

Value outside of expected range	Confirmed per source document
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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.

To view automatic queries about data found upon completion of the form and before you submit the form, right-click on the highlighted field to view an explanation about the possible error.

### **14.6.7.3 Automatic Checks Resulting When Forms are Submitted that Contain Validation Errors**

Some possible errors will not automatically be detected by the system 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 "discrepancy" errors present, a warning box will pop up on the screen immediately after you submit the form.

This warning box will contain a list of all automatic queries appearing on the page, including both the ones generated when you submitted the form and any others flagged 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 and it will direct you to the query 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.

### **14.6.7.4 Status of Automatic Queries**

The study menu uses an icon to display the query status of each site by subject. The exclamation point indicates outstanding queries. It appears next to:

- The subject ID in the All Subjects list if one or more of the subject's forms has outstanding queries.
- Link to a specific visit in the All Visits list if one or more of the forms within that visit has outstanding queries.
- The link to an individual form if it has one or more outstanding queries.

A check mark or asterisk indicates all required data is complete and there are no outstanding queries. It appears next to:

- The subject ID in the All Subjects list if all of the subject's forms are complete and contain no outstanding queries.
- The link to a specific visit in the All Visits list if all of the visit's forms are complete and contain no outstanding queries.
- The link to an individual form if it does not have outstanding queries.

#### **14.6.7.5 Manual Checks**

Some data elements are not suited to automatic computer checks. Rho data managers will programmatically test the integrity of the data to 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 assessment time points to confirm that they occur in an appropriate sequence. For example, a Week 4 assessment should come before a Week 8 assessment.
- Confirming that all visit dates occur before the date of the investigator's signature.
- Confirming that all screening eligibility and baseline assessments occur before treatment initiation.
- Confirming that the recorded onsets of all treatment emergent adverse experiences are after treatment initiation.

Any issues detected by manual data review 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 Rho. Rho data managers will review the resolutions to verify that the data issue has been closed. All manual query trackers should be returned to the Rho data manager within one week of receipt.

Future releases of RhoEDC will include functionality that will allow manual queries to be issued, resolved, and tracked within the system.

#### **14.6.8 *CRF Completion Guidelines***

CRF completion guidelines explaining the various fields and responses found on a form are available. To access these, click the Form Completion Help link at the bottom of any form. If you have a question on how to answer a field in a form, please send all queries to the Rho data management listserv: walk-phasst\_DM@rhoworld.com.

### 14.6.9 *Printing Forms*

RhoEDC allows you to print individual form pages for your records. To print a form page:

1. Open the form you want to print.
2. On the form, click the Print button in the lower right corner of the form.
3. The standard Windows Print prompt appears. Follow the instructions on the prompt to print the page.

You can also print a form page using your browser's Print function.

Note: Some study forms are wider than others, and information might be cut off if the form is printed in standard (portrait) mode. If there is a scroll bar along the bottom edge of the form when it is displayed, print the form in wide (landscape) mode. To do so, select Landscape in the Orientation section of the Windows Print prompt. Consult your Windows documentation if you are unfamiliar with setting print options.

Also, these printed versions of the form **cannot** serve as source documentation.

### 14.6.10 *Electronic Signature*

RhoEDC allows for the use of electronic signatures. Electronic signatures allow users with the appropriate roles to “sign-off” on data entered in the system, removing the need to print out hard copies of the CRF and sign them manually. Any time a form is updated with data after an electronic signature has been done, the electronic signature will need to be repeated.

The following signatures are present in the Walk-PhaSST studies:

**Clinical Investigator:** The clinical investigator will be prompted to electronically sign in the EDC system in the following cases:

- Serious Adverse Events – The Adverse Events form for any adverse event that is recorded as being serious should be signed electronically in the EDC system by the clinical investigator. If the data about the SAE is changed in the EDC system after the clinical investigator signs, the clinical investigator will be prompted to sign electronically again to show that that he/she has reviewed the information reported about the SAE.
- Subject Data – When a subject has completed the study, the clinical investigator should sign electronically in the EDC system to show that he/she has reviewed the data reported in the e-CRF and can attest that it is complete and accurate to the best of his/her knowledge. If any subject data is changed in the EDC system after the clinical investigator signs, he/she will be prompted to sign again.

Note: The Clinical Investigator role has been updated so that they are only responsible for providing electronic signatures and not entering subject data.

**Data Manager:** The data manager(s) assigned to the study will be prompted to electronically sign in the EDC system in the following cases:

- Subject Visits – When a subject’s data for any given visit has been completed in the EDC system, the study’s data manager(s) will review the entries in the e-CRF for the visit and sign-off on the visit if no data discrepancies are found.
- Subject Data: When a subject has completed the study, the study’s data manager(s) will review the entries in the e-CRF for the subject and will sign-off on the subject if no data discrepancies are found. visit

Note: The Data Manager’s sign-off on a subject’s data is a prerequisite to the Clinical Investigator’s sign-off on a subject’s data.

#### **14.6.10.1 Applying Electronic Signatures**

To apply an electronic signature, navigate to the data level to be signed and click the “Sign” button. (Note: The “Sign” button appears only to users who have permission to sign the data.)

When the “Enter Signature” dialog displays, verify that your intent matches the signature intent description that is displayed at the top.

To sign:

- Enter the user name you used to login to the system.
- Enter the password you used to login to the system.
- Enter any optional comment you wish to attach to the signature
- Click the sign button.

The EDC system will display information related to the completed signature, including the signer’s name and user name, the type of signature applied, date and time of signature, and signer’s intent and optional comments.

#### **14.6.10.2 Changes to Signed Data**

The signatures for the walk-PHaSST study are set up so that the information under the signature is protected from inadvertent changes. This protection is called a “guard” and is represented in the EDC system with a shield icon.

Data that is guarded may be changed, but the user entering the change must acknowledge that the change is intentional. A change to guarded data will invalidate the previous signature and the EDC system will prompt the original signer to review the changed data and sign off again.



**14.6.11 E-CRFs Per Study Visit****Screening**

<b>Study Visit</b>	<b>Expected E-CRFs In RhoEDC</b>	<b>Suggested Source Document</b>
<b>Screening Visit</b>	Demographics	Medical Record
	Medical History, Part 1	Medical Record
	Medical History, Part 2	Medical Record
	Medical History, Part 3	Medical Record
	Physical Examination	Medical Record
	Chemistry	Medical Record
	Hematology	Medical Record
	Urinalysis	Medical Record
	HIV Test	Medical Record
	Pregnancy Test	Medical Record
	Echocardiogram (Local)	Medical Record/Template on website
	6-Minute Walk Test	Medical Record/Template on website
	Biomarker/Genotype Sample Collection	Template on website
	Subject Disposition	Template on website
<b>As Needed</b>	Protocol Deviation	Template on study website
	Adverse Events	Medical Record/Template on website
<b>Rescreening *</b>	Physical Examination	Medical Record
	Chemistry	Medical Record
	Hematology	Medical Record
	Urinalysis	Medical Record
	HIV Test	Medical Record
	Pregnancy Test	Medical Record
	Echocardiogram (Local)	Medical Record/Template on website
	6-Minute Walk Test	Medical Record/Template on website

	Subject Disposition	Template on study website
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\* If a subject does not meet the criteria for enrollment into the Main Interventional Trial and is rescreened at a later date, his/her demographic and medical history data must be updated on the Screening Demographics and Medical History forms at the time of rescreening. Data collected for the specific tests performed at the rescreening (i.e., echocardiogram, 6-Minute Walk Test, Chemistry, Hematology, etc) visit must be recorded on the appropriate forms under the "Rescreening" link. **A new set of forms should be completed for each subsequent rescreening.**

### ***Main Interventional Trial***

<b>Study Visit</b>	<b>Expected E-CRFs In RhoEDC</b>	<b>Suggested Source Document</b>
<b>Baseline Visit</b>	Visit Record	Template on study website
	Physical Examination	Medical Record
	Symptoms Documentation	Medical Record/Template on website
	Chemistry	Medical Record
	Hematology	Medical Record
	Hemoglobin Electrophoresis	Medical Record
	Urinalysis	Medical Record
	Pregnancy Test	Medical Record
	Echocardiogram (Local)	Medical Record
	Right Heart Catheterization	Medical Record/Template on website
	6-Minute Walk Test *	Medical Record/Template on website
	Chest X-Ray	Medical Record/Template on website
	Quality of Life ** <ul style="list-style-type: none"> <li>• SF-36 Health Survey</li> <li>• Pediatric Quality of Life Inventory Parent Report for Teens (13 Yrs Old)</li> <li>• Pediatric Quality of Life Inventory Teen Report (13 Yrs Old)</li> <li>• Pediatric Quality of Life Inventory Parent Report for Child (12 Yrs Old)</li> <li>• Pediatric Quality of Life Inventory Child Report (12 Yrs Old)</li> </ul>	Print survey from template on study website from the "Study Documents" category, (under Quality of Life Assessments), have patient complete and file in the patient's study binder/record.
	Biomarker/Genotype Sample Collection	Template on study website
	Brief Pain Inventory	Patient will be complete the BPI for one week using the diary preprinted and provided by Rho. Collect this form from your patient and file it in the patient's study binder/record.
	Randomization/Subject Disposition	Template on study website

<b>Week 6 Visit</b>	Visit Record	Template on study website
	Physical Examination	Medical Record
	Symptoms Documentation	Medical Record/Template on website
	Chemistry	Medical Record
	Hematology	Medical Record
	Urinalysis	Medical Record
	Pregnancy Test	Medical Record
	Echocardiogram (Local)	Medical Record/Template on website
	6-Minute Walk Test	Medical Record/Template on website
	Biomarker/Genotype Sample Collection	Template on study website
	Brief Pain Inventory	Patient will be complete the BPI and study drug diary for one week using the diary preprinted and provided by Rho. Collect this form from your patient and file it in the patient's study binder/record.
	Study Drug Diary	
<b>Week 10 Visit</b>	Visit Record	Template on study website
	Physical Examination	Medical Record/Template on website
	Symptoms Documentation	Medical Record
	Chemistry	Medical Record
	Hematology	Medical Record
	Urinalysis	Medical Record
	Pregnancy Test	Medical Record
	6-Minute Walk Test	Medical Record/Template on website
	Biomarker/Genotype Sample Collection	Template on study website
	Brief Pain Inventory	Patient will be complete the BPI and study drug diary for one week using the diary preprinted and provided by Rho. Collect this form from your patient and file it in the patient's study binder/record.
	Study Drug Diary	
<b>Week 16 (or Early Termination) Visit</b>	Visit Record	Template on study website

	Physical Examination	Medical Record
	Symptoms Documentation	Medical Record/Template on website
	Chemistry	Medical Record
	Hematology	Medical Record
	Urinalysis	Medical Record
	Pregnancy Test	Medical Record
	Echocardiogram (Local)	Medical Record/Template on website
	Right Heart Catheterization	Medical Record/Template on website
	6-Minute Walk Test	Medical Record/Template on website
	Quality of Life ** <ul style="list-style-type: none"> <li>• SF-36 Health Survey</li> <li>• Pediatric Quality of Life Inventory Parent Report for Teens (13 Yrs Old)</li> <li>• Pediatric Quality of Life Inventory Teen Report (13 Yrs Old)</li> <li>• Pediatric Quality of Life Inventory Parent Report for Child (12 Yrs Old)</li> <li>• Pediatric Quality of Life Inventory Child Report (12 Yrs Old)</li> </ul>	Print survey from template on study website from the "Study Documents" category, (under Quality of Life Assessments), have patient complete and file in the patient's study binder/record.
	Biomarker/Genotype Sample Collection	Template on study website
	Brief Pain Inventory	Patient will be complete the BPI and study drug diary for one week using the diary preprinted and provided by Rho. Collect this form from your patient and file it in the patient's study binder/record.
	Study Drug Diary	
<b>Study Completion/Early Termination</b>	Study Completion/ Early Termination	Template on study website
<b>Ongoing</b>	Study Drug Dosing	Template on study website
	Study Drug Accountability Log	Template on website/Copy of accountability from pharmacist record
	Concomitant Medications	Medical Record/Template on website
	Adverse Events	Medical Record/Template on study website
<b>As Needed</b>	Protocol Deviation	Template on study website
<b>Repeat Baseline ***</b>	Randomization/Subject Disposition	Template on study website
	Visit Record	Template on study website

	Physical Examination	Medical Record
	Symptoms Documentation	Medical Record/Template on website
	Chemistry	Medical Record
	Hematology	Medical Record
	Urinalysis	Medical Record
	Pregnancy Test	Medical Record
	Echocardiogram (Local)	Medical Record/Template on website
	Right Heart Catheterization	Medical Record/Template on website
	6-Minute Walk Test *	Medical Record/Template on website
	Chest X-Ray	Medical Record/Template on website
	Quality of Life ** <ul style="list-style-type: none"> <li>• SF-36 Health Survey</li> <li>• Pediatric Quality of Life Inventory Parent Report for Teens (13 Yrs Old)</li> <li>• Pediatric Quality of Life Inventory Teen Report (13 Yrs Old)</li> <li>• Pediatric Quality of Life Inventory Parent Report for Child (12 Yrs Old)</li> <li>• Pediatric Quality of Life Inventory Child Report (12 Yrs Old)</li> </ul>	Print survey from template on study website from the "Study Documents" category, (under Quality of Life Assessments), have patient complete and file in the patient's study binder/record.
	Biomarker/Genotype Sample Collection	Template on study website
	Brief Pain Inventory	Patient will be complete the BPI for one week using the diary preprinted and provided by Rho. Collect this form from your patient and file it in the patient's study binder/record.
<b>Unscheduled Visits</b>	Complete forms as needed to record data collected at any unscheduled visits. Contact coordinating center for guidance.	

\* Two copies of the 6-Minute Walk Test form should be completed if the walk test is repeated per the protocol requirement (See protocol Section 9.2.3).

\*\* Complete the Quality of Life forms appropriate for the subject's age. Use the form for the same age throughout the study, even if the subject has a birthday while on study.

\*\*\* Use the Repeat Baseline link if a subject does not meet the criteria for randomization into the Main Interventional Trial **and** is subsequently rescreened and repeats the baseline visit.

- If the subject **is randomized** in the Main Interventional Trial after the repeated baseline visit, complete all of the Repeat Baseline forms with information from the repeat baseline visit.
- If the subject **is not randomized** after the repeat baseline, complete only the Randomization/Subject Disposition form. Complete for each repeated baseline visit.

***Open-Label Follow-Up to MIT***

<b>Study Visit</b>	<b>Expected E-CRFs In RhoEDC</b>	
<b>Ongoing</b>	Adverse Events	Medical Record/Template on study website
<b>As Needed</b>	Protocol Deviation	Template on study website

***Observational Follow-Up***

<b>Study Visit</b>	<b>Expected E-CRFs In RhoEDC</b>	
<b>Every 6-12 Months for 3 Years</b>	Health/Therapy Update	Medical Record/Template on study website
<b>End of Study</b>	Study Termination	Template on study website
<b>As Needed</b>	Protocol Deviation	Template on study website

## **15 GUIDELINES AND SAMPLE FORMS FOR SERIOUS ADVERSE EVENT REPORTING**

For additional safety information, please refer to Chapter 13 of the walk-PHaSST protocol.

### **15.1 Definitions:**

#### **15.1.1 Adverse Events:**

An adverse event (AE) is defined for this study as any untoward medical occurrence in a subject or clinical investigation subject that does not necessarily have a causal relationship with the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that began or worsened during the course of clinical study participation, whether or not related to sildenafil. AE data are recorded on the CRF.

#### **15.1.2 Serious Adverse Events**

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

- Results in death;
- Is life-threatening (i.e., an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- In the opinion of the investigator, is an important medical events 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 events 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.

#### **15.1.3 Adverse Clinical Laboratory Trend**

An adverse clinical laboratory trend is a shift, in an adverse direction, in the mean (or median) change-from-baseline of a clinical laboratory parameter that is more adverse in an active treatment group than in a control group (e.g., mean ALT change-from-baseline increases significantly more in the active treatment group than in the control group). An adverse clinical laboratory trend may also be evaluated via a “shift table,” which cross-tabulates subjects’ lab results (e.g., ALT values) in three categories (below normal range,

within normal range, above normal range) at baseline, by their results in the same three categories post-baseline, separately for each treatment group. An adverse clinical laboratory trend would be demonstrated by increased frequencies of shifts in an adverse direction (e.g., above-normal ALT) in the active treatment group in comparison to the control group.

1. Screening labs should only be reported as AEs if they occur from the time the subject signs informed consent through 7 days after the last screening procedure AND only if the investigator believes the event to be possibly associated with that study procedure.
2. MIT labs are drawn at Baseline, Week 6, Week 10, Week 16, and study completion/Early Termination. 'Baseline labs' should be the starting point and at each subsequent visit sites should assess 'clinical significance' and determine if it is:
  - a. Clinically significant and a new AE: Defined as the subject has associated signs and symptoms which required intervention. The site should review the abnormal lab and determine if it was associated with a disease entity. If it could be associated with a disease, the lab itself would not be the AE term but the underlying disease that caused the abnormal lab. There are times that a correlation cannot be made thus leaving the lab itself as an AE. In these incidences, the event term should note how the lab was abnormal such as elevated/decreased. Just stating 'Abnormal hemoglobin' does not specifically note how this lab was abnormal.
  - b. Clinically significant and NOT a new AE: Defined as the lab is clinically significant but doesn't require intervention. These are usually (but not limited to) labs that are outside of normal range but normal for the subject.
  - c. Not clinically significant: Defined as no clinical significance with the lab value. These are usually (but not limited to) labs that are within normal range.
3. Open-label labs should be monitored at a frequency dictated by each sites' standard of care, but every 6 months at a minimum. The guidelines outlined in the MIT should be applied to the Open-label lab assessment.
4. In terms of establishing severity with labs that are reported as AEs, it is best to use the severity criteria as outlined in the protocol. In times where this is hard to establish, the CTCAE manual can be used as a guideline but please keep in mind that not all of these ranges are applicable for the sickle cell disease population. The CTCAE grading correlates as Grade 1=mild, Grade 2=moderate, Grade 3=severe, Grade 4=life threatening, Grade 5=death).



## **15.2 AE and SAE Reporting Timelines**

### **15.2.1 AE Reporting Timeline**

Screening Phase: AEs will be captured from the time the subject signs informed consent through 7 days after the last screening procedure AND only if the investigator believes the event to be possibly associated with that study procedure.

Main Interventional Trial (MIT): AEs will be captured from the time the subject signs MIT informed consent through either the last dose of study drug or until discontinuation from the MIT.

Open-label Follow-up Phase: AEs will be monitored at a frequency dictated by each sites' standard of care, but every 6 months at a minimum.

### **15.2.2 SAE Reporting Timeline**

Screening Phase: SAEs will be captured from the time the subject signs informed consent through 7 days after the last screening procedure AND only if the investigator believes the event to be possibly associated with that study procedure.

Main Interventional Trial (MIT): SAEs will be captured from the time the subject signs MIT informed consent until 1 month after the last dose of study drug or until discontinuation from the MIT.

Should a subject experience a SAE within the 1<sup>st</sup> month of being transitioned from MIT to Open-label Follow-up Phase, the SAE should be captured within the MIT phase. Any SAEs that occurs after 1 month should be recorded in the Open-label Follow-up Phase.

Open-label Follow-up Phase: Subject's should be seen at a frequency dictated by each sites' standard of care, but at a minimum every 6 months. At each visit, subjects and/or their parents will be queried regarding recent medical events or procedures. If any of these events meet SAE reporting criteria, they must be reported to the DCC within 24 hours of becoming aware of the event. SAEs will be captured until 1 month after the last dose of study drug or until discontinuation from the Open-label Follow-up Phase. All SAEs must be followed until resolution or until a new baseline is established.

### **15.2.3 AE/SAE Reporting for Subjects in Observational Follow-Up Study**

Subjects will be contacted every 6-12 months and asked to report on their experience in relation to a pre-designated list of clinical events only. These clinical events are noted in the protocol under the section title 'Efficacy Evaluations'.

### **15.3 Initial SAE Reporting by Clinical Investigator (CI)**

After learning that a subject has experienced any SAE, the site is responsible for entering all available information about the event into the SAE page of the EDC within 1 business day of learning of the event. SAE forms must be electronically signed by the Clinical Investigator in order to be completely processed by the DCC.

System software will evaluate the SAE database twice daily and will alert the DCC PS Scientist of newly entered SAEs. After being notified of an SAE, the PS Scientist will log into the EDC system and print the SAE report. The report will be reviewed for clarity and completeness. If there are additional questions, the PS Scientist will contact the site to gather additional information as necessary. After the report is reviewed by the PS Scientist, the information will be entered into a safety database and a narrative will be generated. This information will then be forwarded to the study specific medical monitor for review. Any follow up requests by the medical monitor will be facilitated by the PS Scientist.

The PS Scientist may call the site's study staff to gather additional information. Because of the regulatory requirements it is imperative that all such requests are responded to as soon as possible.

### **15.4 Follow-Up SAE Reporting by Clinical Investigator (CI)**

All SAEs must be followed until resolution or until a new baseline is established. Events that are ongoing at the end of trial will be followed by the CI for one additional month to determine outcome, if possible.

When follow-up information is known, the site should update the EDC system as appropriate and follow the same reporting process as outlined in the Initial SAE reporting process. Please remember that EDC will prompt the Clinical Investigator to electronically resign the SAE report if any changes are made to the information.

Medical records should not be submitted in lieu of completing the SAE form in EDC. It is the sites responsibility to review all medical records and report significant findings and tests in the appropriate sections of the SAE form. Should specific medical records be requested by the PS Scientists or Medical Monitor, the site will be notified.

The same timelines and processes will be followed for Follow-Up SAEs as for Initial SAE reporting. This process will continue until the event is deemed 'closed' by all involved parties.

### **15.5 Follow-Up Requests by the Data Coordinating Center's (DCC) Product Safety (PS) Department**

On an ongoing basis, the DCC PS Department will submit SAE Queries to sites for events that have outstanding information. If a case is deemed 'Expedited', queries should be resolved in an expedited fashion. If a case is deemed 'Non-Expedited' an urgent response is NOT required. For 'Non-Expedited' cases, please gather all the follow up

requests and updated EDC at one time. When a query is submitted to a site, the case status of 'Expedited' and 'Non-Expedited' will be noted on the query. Outstanding queries will be submitted to sites approximately every 30 days therefore every attempt should be made to resolve the outstanding issues prior to the next submission of queries.

## 15.6 Electronic Signatures for SAE Reporting

Because certain SAE reports may require expedited reporting to Regulatory Agency(ies), an Investigator signature is required to assure that the report has been reviewed and agreed upon by a Physician.

- The reporting Clinical Investigator (not the study nurse/coordinator or study monitor) must apply their electronic signature just as they would when signing the case report form.
- The SAE form must be reviewed and signed by a physician. The physician must be an investigator (principal or sub-investigator) who is officially documented to be associated with the clinical study (i.e., listed on the Form FDA 1572 and the Delegations of Responsibilities Log).

**Timeline to Submit:** Initial: Once a site is notified that a SAE has occurred at their site, the site has 24 hours to submit a SAE report in EDC.

Follow Up: Upon receipt of a query from Rho Product Safety, sites should gather the requested follow up information and enter the follow up directly into EDC. If a query is deemed expedited, Rho Product Safety will note that and request a specific deadline date for the information to be entered by.

**Initial SAE Reports:** All attempts should be made to obtain an electronic signature within the timeframe for submitting initial SAE report (24 hrs). If an electronic signature can not be obtained within 24 hours, one should be applied as soon as possible.

**Follow Up SAE Reports:** Rho Product Safety personnel will submit follow up requests to the sites after review of the initial SAE report. Sites should gather the information and provide updates within the EDC system. The following guidelines can be applied for follow up SAE report signatures.

- A) If any of the follow-up information provides an update to the following fields, a PI signature is required at the time of submission:
- Event Term
  - Causality Assessments: this includes a causality assessment to study drug, underlying disease, study procedure, or concomitant medication.

- B) If a case is deemed ‘expedited’ by Rho Product Safety, a PI signature should accompany any follow up information populated in EDC.
- C) If the follow-up information provides an update to the following fields, a CI signature is **not** required at the time of submission:
  - Additional course of events/Narrative updates
  - Additional test and associated results
  - Treatment medications
- D) Once a case is deemed closed and all follow-up requests have been entered in EDC, the CI should review the entry and provide a final CI electronic signature (if one has not already been applied).

## **15.7 Pregnancy Reporting**

Because of potential adverse effects on the fetus, pregnant subjects will be excluded from the study. Female subjects who are pubertal will be regularly assessed throughout the study. In the event of a positive pregnancy test, the subject will be immediately informed of this result and will have sildenafil treatment discontinued.

### **15.7.1 Initial Pregnancy Reporting by the Clinical Investigator**

The CI or designee must report the pregnancy via phone or email to the DCC Product Safety Scientist within 1 business day of learning of the condition. The associated form must be completed, signed by the Clinical Investigator, and faxed to DCC Product Safety within 2 weeks of learning of the subject’s pregnancy.

### **15.7.2 CI Responsibility for Following Pregnancies**

- All pregnancies must be followed until delivery or until termination of pregnancy. A follow up pregnancy notification should be completed within 7 calendar days once the outcome of the pregnancies is known.
- Product Safety will contact the CI approximately 6 to 8 weeks after the calculated delivery date to follow up on the outcome of the pregnancy.
- Pregnancy notification forms (initial and follow up) can be found on the walk-PHaSST website under walk-PHaSST “Forms” category.

### **15.7.3 Pregnancy Reporting in CRF**

- Pregnancies are not considered AEs or SAEs therefore the event of ‘pregnancy’ should not be recorded on the AE CRF or SAE Report, but rather the Pregnancy Reporting Form found on the walk-PHaSST website.

- When complications of pregnancy arise, then the episode should be evaluated for AE or SAE criterion and recorded as such.
- Spontaneous abortions, congenital anomalies and certain elective abortions\* are considered SAEs and should be reported on an SAE Report.
  - \*Certain Elective Abortions are defined as the subject electively aborting the pregnancy due to the immediate risk of the subject.
  - Abortions that are due to the immediate risk of the subject should be termed medically induced abortion.
  - Abortions that are not due to the immediate risk of the subject should be termed 'elective abortion'.

## **15.8 SAE Report Completion Guidelines**

### **15.8.1 General Rules for SAE Report Completion.**

- For initial reporting, please submit as much information as is known. As further details are known, the report can be updated accordingly.
- All SAE forms will require updated CI signature and date.
- Only submit supporting documentation when requested from the PS Scientist. It is the Clinical Investigator's responsibility to summarize supporting documentation and record on the appropriate section of the SAE report. It is not acceptable to submit supporting documentation in lieu of completing an SAE report. This includes CRF pages, diagnostic testing reports, H+P / Admission summary and Discharge summaries.
- For any supporting documentation requested from the PS Scientist, please obliterate all subject information and replace with the subject's study ID number.

### **15.8.2 Adverse Event/Description**

- The event term should be a final diagnosis rather than signs and symptoms (S/S). If only S/S are known at the time of initial reporting, list the primary symptom that caused the event to meet serious criteria. Concurrent S/S can be recorded in the narrative/comments section. If a primary symptom cannot be determined, then each symptom must be separated into separate entries.
- Once a diagnosis is known, then the event term should be updated to the final diagnosis. A comment should be made in the narrative/comments section specifically stating that S/S were updated to a final diagnosis. Example: Initial Event reported as 'shortness of breath' and follow-up reported the final diagnosis as 'pneumonia'. The adverse event/diagnosis should be updated to

Pneumonia and in the narrative/comments section a comment should be made '11Dec2007: The event shortness of breath has been updated to pneumonia'.

If an Investigator has indicated a "possible" diagnosis (e.g., "possible myocardial infarction", or "suspected pneumonia") this should be clarified or confirmed when further information becomes available.

### **15.8.3 Start Date**

- The start date should be the start date of S/S. This is not necessarily the date the serious criteria were fulfilled. (e.g., A subject is diagnosed with pneumonia following hospitalization on 07JUL2003. However, the subject reports that she developed fever, chills, productive cough with rust colored sputum on 05JUL2003. Onset date for the SAE would therefore be 05JUL2003.
- If the subject experiences an exacerbation/worsening of a pre-existing medical condition, but the initial symptoms were apparent before entry into the study, the date of onset should be the date of the exacerbation or worsening.
- The date of onset should never be a date prior to the subject's entry into the study.
- If the exact date of onset is unknown, the Investigator should do his or her best to estimate the date. Complete dates should be given whenever possible, but partial dates (e.g, JAN2003) are better than none.

### **15.8.4 Stop Date**

- Record the date of resolution, date of new baseline or stabilization or the date of death.
- If the exact date of resolution is unknown, the Investigator should do his or her best to estimate the date. Complete dates should be given whenever possible, but partial dates (e.g, JAN2003) are better than none.
- The date of cessation is not necessarily the date of discharge from the hospital. When the outcome date is after the date of discharge from the hospital, it is helpful for the date of discharge to be provided in the Narrative/Comments section of the SAE Report form.

### **15.8.5 Severity**

- Intensity is synonymous with severity. Intensity is NOT the same as serious.
- The maximum intensity occurring over the duration of the event should be documented. The intensity should be amended if it increases.
- The following scale should be used to 'grade' severity:

- 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: Adverse event is life threatening.
- DEATH: Adverse event causes death.

**15.8.6      *Related to Sickle Cell Disease and Related to Pulmonary HTN***

Please refer to the protocol Section 13, Table 11 to assess these questions.

**15.8.7      *Relationship to Study Drug***

- **THIS FIELD SHOULD NEVER BE LEFT BLANK! IT MUST BE PROVIDED AS PART OF THE INITIAL NOTIFICATION.**
- The **CI** is required to assess the relationship to study drug based on the information available. The assessment should be reviewed on receipt of any new information and amended, if necessary.
- A “reasonable possibility” is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence/arguments that may support a “reasonable possibility” include a meaningful temporal relationship, a pharmacologically predictable event, or a positive dechallenge/rechallenge.
- Confounding factors, such as concomitant medication, a concurrent illness or relevant medical history, should also be considered.
- Causality is defined by protocol as:

Unrelated	<ul style="list-style-type: none"> <li>• No temporal association to study product.</li> <li>• An alternate etiology has been established.</li> <li>• The event does not follow the known pattern of response to study product.</li> <li>• The event does not reappear or worsen with re-challenge.</li> </ul>
Probably not related / remote	<ul style="list-style-type: none"> <li>• No temporal association to study product.</li> <li>• Event could readily be produced by clinical state, environmental or other interventions.</li> <li>• The event does not follow the known pattern of response to study product.</li> <li>• The event does not reappear or worsen with re-challenge.</li> </ul>
Possibly related	<ul style="list-style-type: none"> <li>• Reasonable temporal relationship to study product.</li> <li>• The event is not readily produced by clinical state, environmental, or other interventions.</li> <li>• The event follows a known pattern of response to the study product or as yet unknown pattern of response.</li> </ul>
Probably related	<ul style="list-style-type: none"> <li>• There is a reasonable temporal association with the study product.</li> <li>• The event is not readily produced by clinical state, environmental, or other interventions.</li> <li>• The event follows a known pattern of response to the study product.</li> </ul>

	<ul style="list-style-type: none"> <li>• The event decreases with de-challenge.</li> </ul>
Definitely related	<ul style="list-style-type: none"> <li>• There is a reasonable temporal relationship to the study product.</li> <li>• The event is not readily produced by clinical state, environmental, or other interventions.</li> <li>• The event follows a known pattern of response to the study product.</li> <li>• The event decreases with de-challenge and recurs with re-challenge.</li> </ul>

### 15.8.8 **Outcome**

- Adverse events and SAEs will be followed until resolution, until the condition stabilizes or no further changes in the condition are expected (e.g. “resolved with sequelae”), until the subject is lost to follow-up, or until the Investigator and the DCC agree that further follow-up of the event is not warranted
- Only the ‘primary cause of death’ should be listed with a fatal outcome. Events that were ongoing at the time of death should be recorded as ‘Present at Death, not contributing to death’.
- “Resolved with sequelae” is intended to capture the outcome for those events which may never fully resolved and for which it would be unrealistic to follow-up forever. It provides an indication that an SAE has improved/stabilized or the subject has partially recovered. It may be used to reflect that the Investigator is comfortable with the recovery of the subject particularly if they had experienced a critical condition. It is especially useful when a condition is diagnosed and successfully treated, but a number of associated symptoms are still evident. Examples of this situation include:
  - A subject suffers a stroke. The stroke itself "resolves" but there is a lingering paralysis that may never completely disappear.
  - A subject has severe hepatitis. The subject recovers from the hepatitis with the exception of persistent elevation in just one liver function test that has not returned to baseline.
  - A subject has a severe asthma attack. The subject makes a full recovery, but has a persistent tickling cough.
- The "sequelae" are assumed to be captured as part of the overall SAE diagnosis and need not be reported as separate adverse events, however, any sequelae should be described in the subject's medical records and in the Narrative/Comments section of the SAE Report Form.

### 15.8.9 **Action Taken with Study Drug**

- This should be indicated only for the specific event(s) that were directly responsible for action taken with study drug.
  - NONE: Study drug continues even though an SAE has occurred.



- DISCONTINUED: Administration of study drug was stopped permanently and not restarted. The date that study drug was discontinued should be provided in the Study Drug section of the SAE Report form.
- INTERRUPTED/MODIFIED: Administration of study drug was stopped temporarily but then restarted or Modified due to the SAE being reported. The interruption may be the result of a brief period of hospitalization when study drug was not accessible or, the Investigator may have interrupted study drug in order to treat the SAE.
- Enter 'None' if the subject experienced the SAE during the Screening phase.
- If a subject's study drug is initially interrupted but is later permanently discontinued, the SAE report form should be updated to reflect the "worst case scenario".

#### **15.8.10      *Serious? Yes/No And Serious Criterion***

- When you answer the question, "Serious? Yes/No" the remainder of the form should be completed.
- All the reasons why the event(s) meets the definition of serious should be documented. This section should never be blank; at least one box should be checked.
- If the event reported is fatal, then complete: date of death, cause of death and clarify if an autopsy was performed.
- If an SAE Report form is completed, but it is later determined that serious criteria were not fulfilled, the event should be changed from "Serious = Yes" to "Serious = No" In the narrative section, the Investigator should document the reason that the event is no longer considered "serious" and re-submit the SAE form via the processes outlined in section 8.3 and 8.4.

#### **15.8.11      *Possible Contributing Factors to SAE Other than Study Drug***

- Indicate all possible explanations/circumstances that may have contributed to the SAE. If none are known, this section may be left blank.

#### **15.8.12      *Study Medication***

- If the subject experienced an SAE in between signing informed consent and receiving first dose of study medication, please check 'NO' for the question "Did the subject receive study medication?" and comment in narrative section. The remaining questions in this section will remain blank.
- If the subject experienced an SAE after signing informed consent for MIT, check the appropriate box if the event occurred during the 'Double Blind Phase' or during the 'Open Label Follow-Up Phase' and record corresponding attributes.
- HINT: If action taken was recorded as either 1/None or 2/Interrupted, be sure that the 'Ongoing' box is checked.

### **15.8.13 Concomitant Medications (Con Meds)**

To avoid duplication in reporting concomitant medications, EDC has been updated.

Should a SAE occur in the MIT Phase, it is no longer required to enter medications in both the SAE section and in the Concomitant section. All con meds will be reported directly on the Concomitant Medication EDC page. A question has been added to the MIT Concomitant Medication EDC page that should be completed for all medications. The question asks: ‘Associated with a Serious Adverse Event?’; the associated responses are (1) Not Related, (2) Possible Cause of SAE or (3) Medication given in response to SAE.

- If the Concomitant Medication is not related to the SAE, please choose ‘Not Related’.
- If it is felt that the Concomitant Medication is a possible cause of the SAE, please choose ‘Possible Cause of the SAE’.
- If the Concomitant Medication was used to treat the SAE, please choose ‘Medication given in response to SAE’.

Should a SAE occur in either the Screening Phase or the Open-label Follow-up Phase, relevant concomitant medications should be recording in the appropriate section of the SAE report because there is not an associated Concomitant Medications EDC page for these Phases. The following guidelines should be applied when completing this section in SAE report:

- List all relevant concomitant medications that the subject was on at the onset of the event.
  - Relevant is defined as any concomitant medication that the subject was taking at the onset of the SAE that is medically relevant to the event being reported.
  - Example: Subject is admitted with elevated blood pressure, all HTN medications the subject was taking at the time of SAE onset should be reported with the event. On the other hand, if the subject was taking multivitamins, this would not be relevant to the event being reported.
  - It is not expected that all the con meds the subject was taking at the time of onset are recorded with the SAE as this information is captured on the con med CRF. That is why the CRF requests for a medical assessment of con meds that are relevant to the event being reported.
  - The medical monitor and regulatory agencies are looking for all possible reasons for the SAE being reported. Part of this assessment is to look at the subject is relevant con meds and medical history. If a subject is admitted with elevated blood pressure, one question that an independent reviewer would ask “Does the subject have a history of HTN and are they on any HTN medications?” Remember to ask these questions when

completing this section and if there are any questions, consult with a Clinical Investigator at your site.

- If reporting more than one SAE per episode, only one con med section needs to be completed. In these incidences, tick 'Previously Reported with SAE: and list SAE term'. This can ONLY be used when reporting several events during one episode. It should not be used when reporting an SAE that occurred several months after a previous SAE.
  - Example: Subject is admitted with sickle cell crisis and acute chest pain. These are 2 independent events and need to be listed separately but they are occurring simultaneously during the same hospitalization. To avoid duplicate entry of con meds for both entries, the 'previously reported with' button can be used so that the con meds are only recorded once.
  - Example when NOT to use this button: If an SAE is reported in January 2008 for Sickle Cell crisis and is re-admitted in April 2008. Since these episodes occurred at different time periods, the 'previously reported button' should not be used due to the time elapsed between events. Con meds could have changed over 4 months therefore they need to be re-recorded when reported the 2<sup>nd</sup> event.
- Medication used to treat the SAE should NOT be reported here; list treatment medications in appropriate section.
- HINT: Any concurrent medication specified under 'Possible contribution factors to SAE other than study drug' should be reported here and the causality should be listed as 'Yes'.

#### **15.8.14      *Treatment/Procedures for SAEs***

The same guidelines should be applied to treatment medications as explained for Concomitant Medications under section 15.8.13. Please reference the guidelines in this section when adding treatment medications in response to a SAE.

- If reporting treatments for a SAE that occurred in the MIT Phase, only list procedures used to treat the SAE. Medications used to treat a SAE should be recorded on the Concomitant Medication EDC page and the response to the question 'Associated with a Serious Adverse Event?' should be answered with 'Medication given in response to SAE treatment' If the treatment was a procedure, then the procedure should be reported in this section of the SAE report. An example of this would be a cholecystectomy in response to gallstones.
- If reporting treatments for a SAE in the Screening Phase or Open-label Follow-up Phase, list all treatment medication and/or procedures used to treat the SAE.
- Supplemental documents should not be submitted in lieu of completing this section of the SAE Report form.

- If reporting more than one SAE per episode, only one treatment section needs to be completed. In these incidences, tick ‘Previously Reported with SAE: and list SAE term’. This can ONLY be used when reporting several events during one episode. It should not be used when reporting an SAE that occurred several months after a previous SAE.

### 15.8.15 **Relevant Medical History**

- Include any **relevant** previous medical conditions. Provide details of the date of onset of these conditions and clarify whether they were still present at the time of the SAE. (e.g., a subject who had an episode of hepatitis 20 years ago who reports hepatic failure as an SAE)
- Medical history information can be relevant because it eliminates other causes (e.g., a previous appendectomy in a subject reporting severe abdominal pain).
- Also include any background information that may be relevant to the SAE and may help explain the SAE. This could include any **relevant family history** (*subject’s mother had breast cancer, history of psychological problems in family*), **relevant social history** (*smoked 20 cigarettes/day for 30 years, regular and excessive alcohol use*), **relevant dietary habits or restrictions, occupational hazards** (*worked in coal mine for 20 years, subject does heavy lifting with his job*).
- HINT: Any concurrent illness specified in Section 4 as possibly contributing to the SAE should be reported here as well.
- If reporting more than one SAE per episode, only one med hx section needs to be completed. In these incidences, tick ‘Previously Reported with SAE: and list SAE term’. This can ONLY be used when reporting several events during one episode. It should not be used when reporting an SAE that occurred several months after a previous SAE.

### 15.8.16 **Relevant Laboratory/Diagnostic Tests**

- Provide details of assessments, supplementary investigations, or examinations that were conducted as part of the subject’s care and/or on the investigator’s clinical judgment. This may include but is not limited to:
  - Laboratory data. Always provide the date of the tests, the units of measurement, and the reference ranges.
  - Findings of ECG’s, x-rays, CAT scans, etc.
  - Results of other diagnostic tests or assays.
  - *Key findings* from hospital discharge or pathology reports.
- List all laboratory and/or diagnostic testing (dates and results) that support the diagnosis of the event reported.
- It may be appropriate to include negative results/findings as they can often be very useful when trying to understand or interpret an SAE. (e.g., negative cardiac

enzymes for a subject reporting “chest pain” as an SAE, normal chest x-ray for an SAE of “possible pneumonia”).

- **DO NOT ROUTINELY SEND HOSPITAL DISCHARGE SUMMARIES, PATHOLOGY REPORTS, OR ANY OTHER MEDICAL RECORDS WITH THE SAE REPORT FORM.** The investigator must provide the key points from these reports on the SAE form. Such reports may be specifically requested by DCC Product Safety, if required.

#### **15.8.17      *Weight/Height***

- List the subject’s weight and height at the time of the event. If it is not known at the time of the event, please provide the most recent height and weight prior to onset.

#### **15.8.18      *Narrative/Comments***

- Complete a brief, concise narrative detailing the course of events surrounding the episode reported.
- Each time details are reported in this section, a date is REQUIRED.
- Example:
- 30Jun2007: The subject was admitted with .....
- 05Jul2007: Test revealed that the subject was diagnosed with....
- HINT: If action taken was interrupted, be sure that interruption dates are recorded in this section.
- HINT: If event resolved w/ sequelae, be sure that the specific sequelae associated with the event is recorded in this section.
- List any relevant comments that the CI would like to report about the episode.

### **15.9            SAE Reporting to IRB**

The CI is responsible for submitting SAE reports to the governing IRB, according to their IRB’s requirements.

### **15.10          Product Safety Contact Information**

SAE Hotline #: 888-746-7231

SAE Fax #: 888-746-3293

Product Safety E-mail: [rho-productsafety@rhoworld.com](mailto:rho-productsafety@rhoworld.com)

Primary Contact

Karyn Mumma, Senior Product Safety Scientist

Phone: (919) 595-6201 / [Karyn\\_Mumma@rhoworld.com](mailto:Karyn_Mumma@rhoworld.com)

Medical Monitor:

Dr. Brian Boehlecke, Medical Monitor

Phone: (919) 595-6343 / [Brian\\_boehlecke@rhoworld.com](mailto:Brian_boehlecke@rhoworld.com)

Cell Phone: (919) 619-6582

Back Up Contacts:

Victoria Williams, Senior Product Safety Scientist

Phone: (919) 595-6237 / [Victoria\\_Williams@rhoworld.com](mailto:Victoria_Williams@rhoworld.com)

Jennifer Stasiak, Product Safety Scientist

Phone: (919) 595-6329 / [Jennifer\\_Brown@rhoworld.com](mailto:Jennifer_Brown@rhoworld.com)

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## **16 PHARMACY INSTRUCTIONS AND SAMPLE FORMS**

### **16.1 Introduction**

Perry Point will manage the distribution of the investigational product to the Clinical Center Pharmacies. Perry Point must comply with the U.S. Food and Drug Administration (FDA) regulations governing the receipt, use, and disposition of study drugs investigated in clinical trials. In order to comply with FDA regulations and standards of research involving investigational drugs, the DCC has the responsibility of assuring all investigators establish and maintain adequate accountability records of investigational study drug receipt, use, return, and disposition. This will be done during the annual visit from the DCC's Clinical Research Associate (CRA).

In order to coordinate the shipping, receipt and request for study drug, the electronic RhoRAND system (developed by the DCC) will be utilized at all site pharmacies. Site pharmacists will be required to complete practice functions within RhoRAND before receiving access to the live system, allowing him/her to receive the study drug and request additional study drug.

See Section 16.4 for more details.

### **16.2 Responsibilities of Pharmacists of Record**

Each clinical trial should provide a Pharmacist of Record to the DCC to designate the responsible contact at the clinical site. The pharmacist designated as the Pharmacist of Record is the primary person responsible for study drug management, including procedures for study drug ordering, dispensing, and accountability. The Pharmacist of Record is expected to follow the guidelines in this section of the Manual of Operations (MOO). The pharmacist should be aware of all local and federal regulations governing the practice of pharmacy.

All investigational drugs will be received, stored, inventoried monthly, and dispensed to the subject by the clinical site pharmacies directly or by way of study personnel. If study personnel obtain investigational study drugs labeled for a subject, the subject's specific supplies must be stored under appropriate conditions and in an area that is only accessible to study personnel. Appropriate conditions for storage is an area set at room temperature and in a secure area that is only accessible to authorized personnel, and only drugs, no food, should be stored in the area. If subject specific study drug is not supplied to the subject during the scheduled study visit by study personnel, the study drug must be returned to the clinical site pharmacy by the end of the same business day in which it was dispensed.

All investigational drug should be stored under appropriate conditions as specified on the label to maintain its stability. The area of storage must be accessible to only authorized personnel. Each clinical site pharmacy is responsible for monitoring the expiration date of the investigational product to ensure that expired doses are not administered. Clinical site procedures for control of all investigational drug should be sufficient to meet the requirements of the FDA and other pertinent regulatory bodies.

All documentation should be typed or printed legibly. All entries must be made in dark ink. Corrections may be made by drawing a line through the incorrect entry, then entering the correct entry and initialing/dating the correction. No “whiteouts” are permitted on any form.

Upon approval by the local Institutional Review Board (IRB) or other regulatory/review bodies, a record system (file and/or notebook) should be created and stored in the Pharmacy; the records will include:

- Copy of the current IRB(or other applicable body)-approved version of the protocol and future addenda, clarifications, or amendments
- Study drug label
- Drug accountability, transfers, and disposition records
- Study drug request, shipment receipts, and return records
- Correspondence related to investigational drugs
- Latest version of the pharmacy and study treatment sections of the MOO

In order to ensure appropriate dispensing of investigational product to subjects enrolled in the walk-PHaSST Study, the clinical site pharmacist of record is responsible for at least the following:

- Establish a communication system with other study personnel for notification of institutional, NHLBI, and DCC approval for the use of the investigational product ordered.
- Verify the randomization “kit” number assignment of each subject prior to dispensing study drug (pharmacists will be blinded to the treatment arm, along with all other site personnel).
- Ensure clinicians are authorized to prescribe investigational product for the walk-PHaSST protocol according to the 1572 and the Delegation of Responsibility (DoR) log.
- All doses of investigational product dispensed should be labeled with instructions for appropriate use per the walk-PHaSST Study and physician orders.
- The dispensing or transfer of investigational product to unauthorized physicians is prohibited.
- Monitor labeled expiration dates. Once approval is granted from the DCC, all expired investigational product should be disposed per federal, local, and institution guidelines.
- Subject returns, disposition, and transfer of investigational product should be documented on the forms provided.
- The Pharmacist of Record is also responsible for working with study personnel regarding the measurements of returns for monitoring adherence.
- Obtain and maintain an authorized, prescriber sample signature list.



## **16.3 Study Product Control**

### **16.3.1 Study Product Ordering**

An initial shipment will be sent to the clinical site pharmacies by Perry Point once a site is activated (all appropriate training has taken place and has been documented, all regulatory documents have been submitted to the DCC, and the protocol and informed consents have been approved by the local IRB or other regulatory body). The RhoRAND system will generate a notification to the site's study pharmacist alerting him/her that a shipment has been sent from Perry Point. Upon receipt and confirmation of the box contents, the pharmacist will be required to log in to RhoRAND and receive the shipment using the "Order Number".

All initial shipments will contain a total of 100 bottles, and will be broken down based on the following schema:

- **20** bottles of 20 mg **double-blind sildenafil citrate** (each bottle contains 75 pills)
- **20** bottles of 20 mg **double-blind placebo** (each bottle contains 75 pills)
- **8** bottles of 80 mg **double-blind sildenafil citrate** (each bottle contains 85 pills)
- **8** bottles of 80 mg **double blind-placebo** (each bottle contains 85 pills)
- **1** bottle of 20 mg **open-label sildenafil citrate** for baseline right heart catheterization (bottle contains 30 pills and the label has a yellow background with the 20 mg highlighted in green)
- **24** bottles of 20 mg **open-label sildenafil citrate** (each bottle contains 75 pills and the label has a yellow background with the 20 mg highlighted in black)
- **19** bottles of 80 mg **open-label sildenafil citrate** (each bottle contains 85 pills and the label has a blue background with the 80 mg highlighted in black)

All bottles of MIT study drug will be pre-packaged by Perry Point with a bottle code and a corresponding barcode in order to mask the actual study drug contents to all study staff (the Pharmacist, Clinical Investigator, Study Coordinator) and the subject. The RhoRAND system will reorder additional double-blind study drug when the quantity falls below a pre-established threshold at the site. The RhoRAND system does not monitor the distribution of Open-label study drug to individual subjects; as such, it cannot automatically reorder supply. Therefore, it is the pharmacist's responsibility to attend to the Open-label inventory and reorder study drug via RhoRAND when supplies are low.

Study drug should be ordered Monday-Wednesday for receipt that week. Orders received by Perry Point on Thursdays or Fridays will be shipped the first business day of the next week.

### **16.3.2 Study Product Accountability**

The walk-PHaSST Study Product Accountability Record or other DCC approved form with the same information must be used to document the receipt and dispensing of all study products received from Perry Point. Each dose dispensed should be signed out in the accountability records with subject identifiers, bottle number, strength of the pills (20

or 80 mg), number of pills in the bottle, and lot number. All of this information is located on each bottle's label. All investigational product must be managed by the Pharmacist of Record.

Information to be recorded on the accountability record includes:

- Study product name
- Manufacturer
- Lot number
- Expiration date
- Bottle number
- Dose
- Storage temperature
- Prescription number
- Date dispensed
- Subject's study ID number
- Subject's initials
- Quantity dispensed and returned
- Pharmacist's initials

Documentation on the accountability form is required every time a study product is received from Perry Point, dispensed to research participants, and returned by research participants. All entries require the date of the action and the initials of the pharmacist. It is required that prescriptions for the corresponding entry in the accountability record be easily retrievable for review by authorized representatives from the DCC and FDA. Site pharmacists are required to keep returned study drug on site until the walk-PHaSST CRA completes his/her first monitoring visit. After this visit, the CRA will determine whether or not a second pill count (by the CRA) will be required at the next monitoring visit. If the CRA determines that it is not necessary, the site pharmacist can destroy the returned study drug according to local processes immediately following the initial pill count done in-house after each subject visit. Identification of the dispensing pharmacist is required when there is an audit review of the study product accountability forms and prescriptions. A list of pharmacists' signatures and initials to identify each dispensing pharmacist must be available.

Study product accountability records and shipment invoices (both the RhoRAND notifications and the form that arrives with the box of each shipment) should be maintained in the clinical site pharmacy until the study is completed. Copies of accountability records will also be obtained during monitoring visits conducted by the DCC. As required in Title 21 CFR 312.62, records for completed studies must be retained for two years following the date a New Drug Application (NDA) is approved for the indication for which it is being investigated, or if the NDA is not filed or if the

application is not approved for such indication, until two years after the study produce it discontinued and the FDA is notified.

A copy of the walk-PHaSST Study Product Accountability Record form is provided in Section 16.3.3 on and on the walk-PHaSST secure website.

Site pharmacists will also be responsible for the destruction of all returned or expired study drug. This information will be collected on the “Study Drug Disposition Record of Destruction” form and will be reviewed by the DCC CRA when he/she comes to the site for the annual visit. A copy of this form is provided in Section 8.3.4 and on the walk-PHaSST secure website.

The information that will be collected on this form includes:

- Investigator Name
- Product Name
- Site ID
- Date Disposition Approved
- Study Drug Dose (20 or 80)
- Bottle Number
- Expiration Date
- Quantity Disposed
- Date Disposed
- Disposed By (Initials)
- Comments



STUDY PRODUCT ACCOUNTABILITY RECORD

INVESTIGATOR NAME: [REDACTED] PHARMACIST NAME: [REDACTED]  
SITE NAME: [REDACTED] SITE ID: [REDACTED]

Study Product Name: [REDACTED]		Dispensing Area: [REDACTED]
Manufacturer: [REDACTED]		Strength/Dosage Form: [REDACTED]
Lot Number: [REDACTED]	Expiration Date: [REDACTED]	Storage Temperature: [REDACTED]

	BOTTLE NUMBER	SUBJECT ID NUMBER	SUBJECT INITIALS	DATE DISPENSED	PRESCRIPTION NUMBER	DOSE (20/40/80)	QUANTITY DISPENSED	DATE RETURNED	QUANTITY RETURNED	PHARMACIST INITIALS
1										
2										
3										
4										
5										
6										
7										
8										
9										



**STUDY PRODUCT DISPOSITION RECORD OF DESTRUCTION**

**INVESTIGATOR NAME:** \_\_\_\_\_ **STUDY PRODUCT:** \_\_\_\_\_

**SITE NAME:** \_\_\_\_\_ **SITE ID:** [ ][ ]

NO.	DATE DISPOSITION APPROVED	STUDY DRUG DOSE (20 OR 80)	BOTTLE NUMBER	EXP. DATE	QUANTITY DISPOSED	DATE** DISPOSED	DISPOSED BY (INITIALS)	COMMENTS
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								
17								
18								
19								
20								
21								
22								

All entries must be made in ink. Corrections may be made by drawing a line through the incorrect entry, then enter the correct entry and initial the correction.

This is a standard form used for walk-PHaSST. Photocopying is authorized.

\*\*Disposition should occur as per federal, local, and institutional policies.

## **16.4 RhoRAND – Screening, Registration, Enrollment, & Randomization System**

### **16.4.1 *Quick Reference Guide for Pharmacists***

All site pharmacists will be required to use the RhoRAND system in order to complete the following:

- 1) Acknowledge Receipt of Study Drug
- 2) Request Additional Open-label Drug

The RhoRAND system provides communication between the study drug distributing company (Perry Point), the site pharmacist, and the DCC. When a study drug shipment has been registered by Perry Point, RhoRAND issues a notification to the pharmacist and DCC. Upon receipt and confirmation of shipment contents, the Pharmacist registers receipt via RhoRAND, and a notification of receipt is sent to Perry Point and the DCC. Additionally, the pharmacist will communicate to Perry Point via RhoRAND during the Open-label Follow-up Phase when more study drug is needed.

RhoRAND also provides a means of communication between the site study coordinator and the pharmacist. The study coordinator will use RhoRAND to randomize the subject, as well as to register each additional MIT subject visit. These functions will alert the pharmacist that study drug is needed and will identify which bottles should be distributed to the subject (based on the walk-PHaSST subject ID number).

On the following page is the “Quick Reference for Pharmacists” which provides a succinct clarification of the RhoRAND system as it relates to the pharmacist activities. Requirements for practicing the system, along with annotated screenshots, are included in Section 16.4.2.



## Screening Registration, Enrollment & Randomization System

Powered by RhoRAND™

### Pharmacist Quick Reference Guide

#### WEB ADDRESS

<https://www.rhoworld.com/login/>

#### MENU OPTIONS

- Acknowledge Receipt of Drug
- Request Additional Open-Label Drug
- Practice Functions (for all functions above)
- Resend Notifications

#### SYSTEM/PROCESS FLOW

- Log on to Website
  - Enter User ID
  - Enter User Password
- Acknowledge Receipt of Drug**
- Enter Shipment ID
  - Confirm Shipment Composition
  - Indicate additional kits associated with shipment, if any
  - Notifications sent
- Request Additional Open-Label Drug**
- Enter Number of Kits/Bottles
  - Notifications sent
- Resend Notifications**
- Select the Desired Notification Type to be Re-sent
  - Enter Shipment ID
  - Notifications re-sent

#### Practice Functions

Use the Practice RhoRAND Worksheets stored in the Manual of Operations to practice each system feature. You must perform both practice functions before you can receive or request drug. You will receive a notification for each completed practice function. If you do not receive a notification within 15 minutes of completing a practice function, please contact the Site Support Center.

#### Website Access

To gain access to RhoRAND, please contact your website administrator to obtain user access forms. Follow the instructions on the form and allow a few days for access to be granted.

#### Study Data Integrity

Please **do not share** your user ID or password. Also, remember to logout of the system and close your browser while away from your computer.

#### Site Support Center:

1-800-905-0460

9:00 am 6:00 pm Eastern

Monday through Friday

Email:

[walkphasst\\_rhorand@rhoworld.com](mailto:walkphasst_rhorand@rhoworld.com)

#### FAQ

- Q** What is RhoRAND™ used for?
- A** RhoRAND™ is a Internet-based software system used for subject screening, enrollment and randomization.
- Q** Can everyone working at a site use the same user ID and password?
- A** No. It is necessary for each person to use his/her individual user ID and password.
- Q** How can I get a user ID and password?
- A** Please contact your website administrator to obtain user access forms. Follow the instructions on the form and allow a few days for access to be granted.. If necessary, the RhoRAND™ Site Support Center is available from 9:00 am to 6:00 pm EST, Monday-Friday to assist you with any system-related issues. The Site Support Center may be reached at 1-800-905-0460.
- Q** Do I need a different user ID and password for each Rho website?
- A** No, you may use the same user ID and password.
- Q** What should I do if I have to terminate a session before I have entered all of the information?
- A** The system will require you to log back in and start from the beginning. When away from your computer, please log out for security purposes.
- Q** Who should I contact if my email address or fax number changes?
- A** You should notify the Site Support Center as soon as possible via email at [walkphasst\\_rhorand@rhoworld.com](mailto:walkphasst_rhorand@rhoworld.com).



WPPRG122107

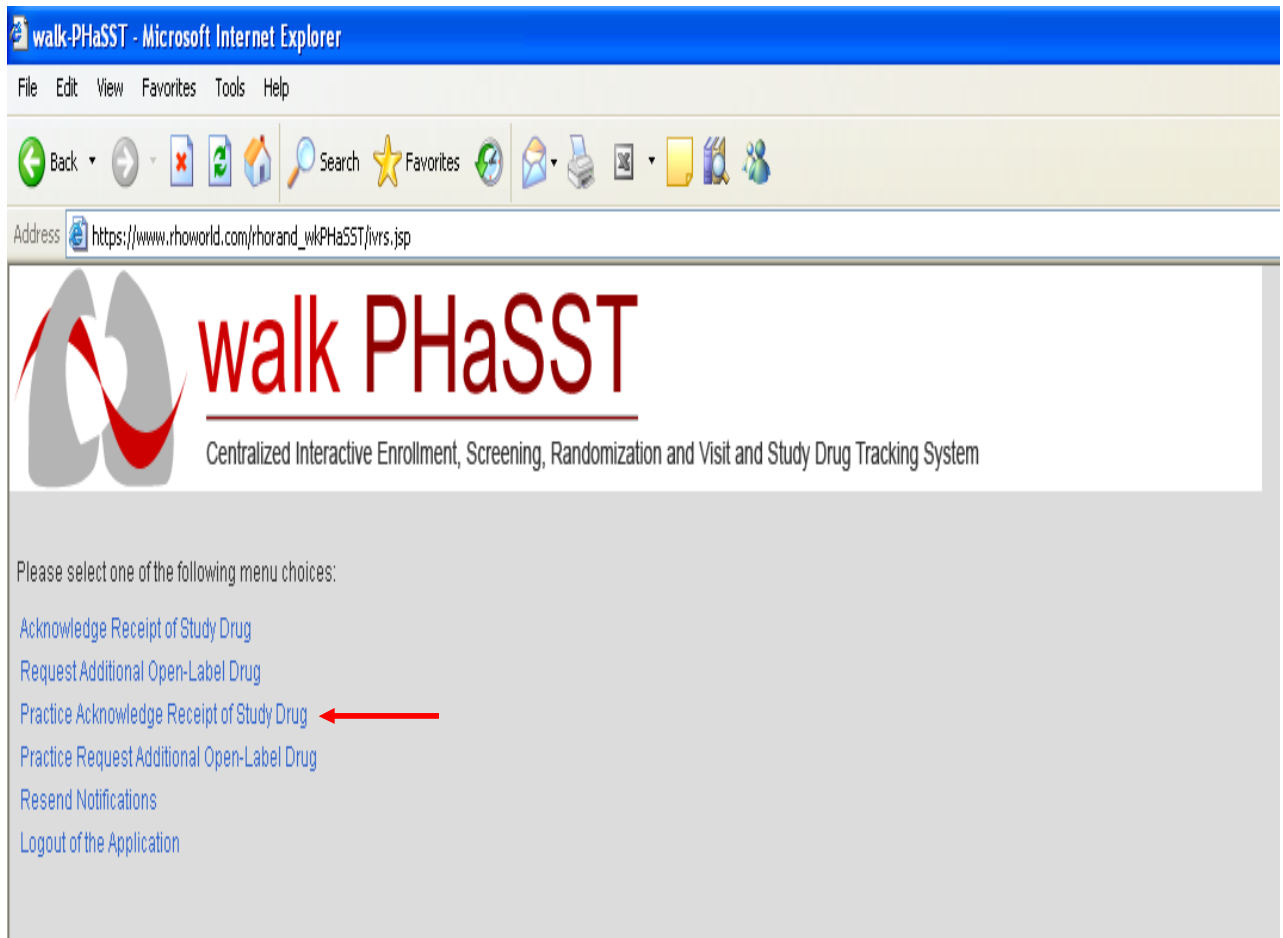
## 16.4.2 **Completing the RhoRAND Practice Functions**

Perry Point will physically ship the initial supply of study drug to the site pharmacist when the site has been activated (approved to begin enrolling patients). Prior to being activated, the site is required to have one pharmacist complete all “practice” functions in RhoRAND in order to receive access to the live RhoRAND system in which the shipment, receipt, and distribution of study drug is tracked and monitored.

Once practice functions have been completed and the site has been activated, an email notification will be sent to the pharmacist to alert them that a shipment has been prepared and is en route to the site (this makes having the most accurate and current pharmacist contact information available in the walk-PHaSST website critical). When the shipment arrives at the site’s pharmacy, the pharmacist will be responsible for logging into the RhoRAND system in order to “acknowledge” receipt of the study drug.

The following graphics depict the screens displayed in the “Practice Acknowledge Receipt of Study Drug” function. (Please note: Slight differences between these screen shots and the actual system may exist when a system update precedes a revision of the MOO.)

### **Initial RhoRAND Screen**






walk-PHaSST - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Refresh Home Search Favorites

Address [https://www.rhoworld.com/rhorand\\_wkPHaSST/ivrs.jsp](https://www.rhoworld.com/rhorand_wkPHaSST/ivrs.jsp)

 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

You are about to practice acknowledging receipt of study drug.

Order Number:

[Return to Main Menu](#)


The order number (7 digit number) will accompany the shipment from Perry Point.

walk-PHaSST - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Refresh Home Search Favorites

Address [https://www.rhoworld.com/rhorand\\_wkPHaSST/ivrs.jsp](https://www.rhoworld.com/rhorand_wkPHaSST/ivrs.jsp)

 **walk PHaSST**  
Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

You are about to verify the status of the kits associated with a received shipment.

Status of Kit ID TEST KIT :

Received  
 Damaged  
 Missing

Number of additional kits received:

If you wish, you may use the text box to the right to record any additional information about the shipment.

[Return to Main Menu](#)

Each kit (bottle) ID associated with the system will be displayed; the pharmacist will have to indicate whether it was received, damaged, or missing. If any additional (unexpected) bottles were in the shipment, this must be documented as well.

walk-PHaSST - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Refresh Home Search Favorites

Address [https://www.rhoworld.com/rhorand\\_wkPHaSST/ivrs.jsp](https://www.rhoworld.com/rhorand_wkPHaSST/ivrs.jsp)

# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

You have successfully completed the Practice Acknowledge Receipt of Study Drug function.  
Notifications have been generated and should be delivered to the appropriate study personnel shortly.

If you would like to perform additional operations, please click the menu link below. Otherwise, click the logout link or close your web browser to exit the system.

[Return to Main Menu](#)  
[Logout of the Application](#)

walk-PHaSST - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Refresh Home Search Favorites

Address [https://www.rhoworld.com/rhorand\\_wkPHaSST/ivrs.jsp](https://www.rhoworld.com/rhorand_wkPHaSST/ivrs.jsp)

# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

Please select one of the following menu choices:

- [Acknowledge Receipt of Study Drug](#)
- [Request Additional Open-Label Drug](#)
- [Practice Acknowledge Receipt of Study Drug](#)
- [Practice Request Additional Open-Label Drug](#)
- [Resend Notifications](#)
- [Logout of the Application](#)





# walk PHaSST

Centralized Interactive Enrollment, Screening, Randomization and Visit and Study Drug Tracking System

You have successfully completed the Practice Request Open-label Drug function.

Notifications have been generated and should be delivered to the appropriate study personnel shortly.

If you would like to perform additional operations, please click the menu link below. Otherwise, click the logout link or close your web browser to exit the system.

[Return to Main Menu](#)

[Logout of the Application](#)

The pharmacist will receive email notifications after each practice function has been completed successfully; a copy of the email will also be sent to the DCC (see below). Similar notifications will also be sent when the “live” system is being used (communication between the study coordinator, the site pharmacist, and the Data Coordinating Center).

Within 1 business day of the pharmacist’s successful completion of the two practice functions in RhoRAND, access to the live system will be granted. If more immediate

From: walkphasst\_rhorand@rhoworld.com  
To: Jamie Spencer  
Cc:  
Subject: Practice Shipment Received Notification

PRACTICE PRACTICE PRACTICE PRACTICE PRACTICE PRACTICE PRACTICE

walk-PHaSST

Practice Shipment Received Notification

Site ID: 99  
Site Name: Test Site  
Order Number: 1111111  
Shipment Information: Kit ID | Status  
TEST KIT | RECEIVED  
Request Date: TEST DATE  
Shipment Date: TEST DATE  
Received Date: 21 December 2007  
Notes:

A shipment of study drug containing the kits indicated above has been received at Site 99. Please store this notification in the study files.

PRACTICE PRACTICE PRACTICE PRACTICE PRACTICE PRACTICE PRACTICE

Generated 21-Dec-2007 12:56 Eastern Time

## 17 PROCESS FOR UNMASKING OF TREATMENT ASSIGNMENTS

### 17.1 Sildenafil Related Considerations

Sildenafil is a phosphodiesterase Type 5 (PDE5) inhibitor which enhances the vasodilating effect of nitric oxide (NO), a compound released from vascular endothelial cells, by reducing the degradation of a molecule (cGMP) stimulated by NO which in turn produces smooth muscle relaxation. PDE5 is found in many tissues including vascular and visceral smooth muscle, corpus cavernosum smooth muscle and platelets. The main side effects associated with sildenafil may be related to effects on these tissues and/or the lowering of systemic blood pressure due to vasodilation. Epistaxis, headache, flushing, dyspepsia and insomnia have been the most commonly reported adverse events occurring more commonly in patients taking sildenafil than in those on placebo. Sudden loss of vision due to non-arteritic anterior ischemic optic neuropathy (NAION) has been reported rarely post marketing in temporal association with use of all PDE5 inhibitors. Priapism has also been infrequently reported since sildenafil was approved for marketing.

Clinical management of most Adverse Events (AEs) and Serious Adverse Events (SAEs) which might occur during the study would likely not require unmasking (a.k.a “unblinding”). If the clinical investigator is concerned that the event may be related to the study drug and that withdrawal of the study drug would be appropriate, knowledge of the treatment assignment would not alter the clinical management of the subject. No drug-specific treatment for the effects of sildenafil is available.

The package insert states the following regarding over dosage: “In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses, but incidence rates were increased. In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins, and it is not eliminated in the urine.”

Therefore, there are few situation in which unmasking is necessary. However, if the clinical investigator feels that it is warranted, he/she should **first** contact the medical monitor, Dr. Brian Boehlecke (919) 619-6582, or a member of the Executive Committee -- Dr. Roberto Machado (301) 592-7034, Dr. Mark Gladwin (412) 692-2117, Dr. Robyn Barst (914) 582 9002, or Dr. Kathryn Hassell (303) 266-9881, -- for further discussion.

If an emergency occurs in which the clinical investigator feels that immediate knowledge of the treatment assignment is essential for clinical management and the welfare of the subject AND none of the individuals named in the previous paragraph are available for discussion, the Investigator may unmask a subject's treatment assignment via the secure RhoRAND system. For details of the RhoRAND “blind break” function, refer to Section 17.3. When an Investigator is unmasked, the RhoRAND system will notify the DCC (Administrative and Product Safety teams), NHLBI, and Clinical Investigator that the unmasking has occurred. Only the Clinical Investigator and the DCC unmasked statistician will receive a notification containing the actual treatment assignment. Please note, this unblinding/unmasking function will **ONLY** be available to Clinical

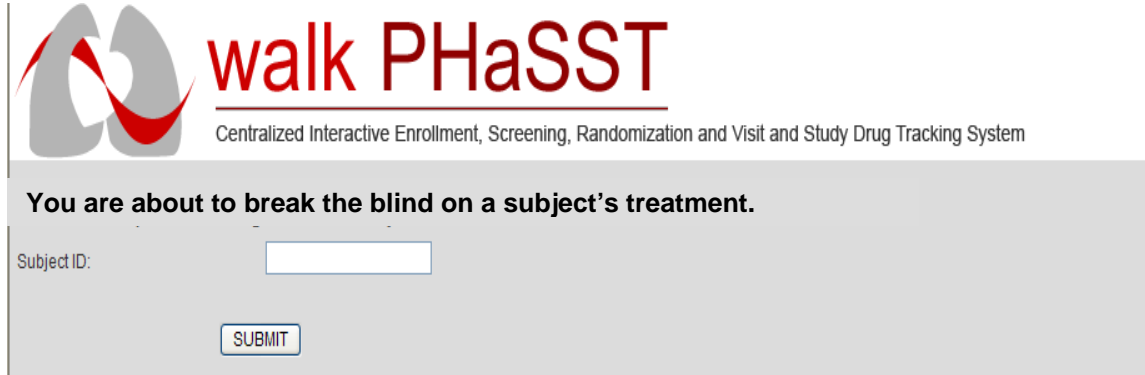
Investigators who have satisfactorily practiced this function in RhoRAND. Practice of this function is expected to take fewer than 5 minutes. However, it can take up to 1 business day to be granted access to the production system after practice has occurred. See Section 17.3 for further details.

## **17.2 Rho Product Safety**


For SAEs reported to Rho Product Safety, the staff may unmask the treatment assignment for the affected subject, if requested by a government agency (e.g., FDA) or regulatory body. Reports will be initially prepared in a masked manner and reviewers (e.g., the NHLB project officer and the PI of the DCC) will remain masked to treatment assignment. Immediately before distributing the report to the FDA or Medicines and Healthcare Products Regulatory Agency (MHRA), the subject's treatment group may be unmasked by the Product Safety Associate. When applicable, a masked copy of the regulatory report would be sent to Clinical Investigators in accordance with relevant regulations.

### 17.3 RhoRAND Blind Break Function

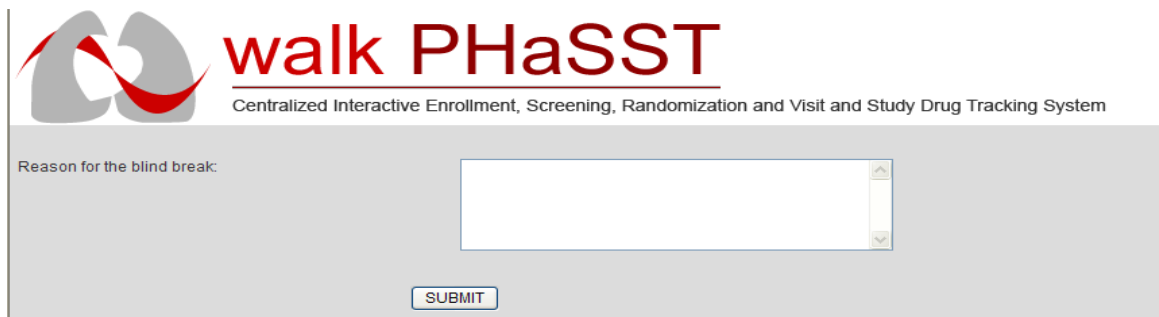
Only a clinical investigator is authorized to “Enter Blind Break Data” in RhoRAND. This option does not appear on the RhoRAND menu for study coordinators. The following 3 screen shots depict the Blind Break function in RhoRAND. A clinical investigator must have successfully practiced this function in order to be certified to use the production system to unmask a subject at the site.



The screenshot shows the top header with the walk PHaSST logo and title. Below the header, a grey box contains the instruction: "You are about to break the blind on a subject's treatment." Underneath, there is a text input field labeled "Subject ID:" and a "SUBMIT" button.



The screenshot shows the top header with the walk PHaSST logo and title. Below the header, a grey box contains the instruction: "Prior to breaking the blind, the Medical Monitor or Principal Investigator should be consulted." Below this, there is a text input field labeled "Please indicate whether you have consulted with the Medical Monitor or Principal Investigator about breaking the blind for this subject." followed by three radio button options: "Yes, the Medical Monitor or Principal Investigator has been consulted.", "No, the Medical Monitor or Principal Investigator has not yet been consulted.", and "No, there has been no consultation, but the blind must be broken for emergency reasons." A "SUBMIT" button is located at the bottom of the form.



The screenshot shows the top header with the walk PHaSST logo and title. Below the header, a grey box contains the instruction: "Reason for the blind break:" followed by a text input field. A "SUBMIT" button is located at the bottom of the form.

## **18 REGULATORY RESPONSIBILITIES**

### **18.1 Description of Investigator's Responsibilities**

The Code of Federal Regulations [21 CFR 312.3(b)] defines an Investigator as “an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug [or investigational product] is administered or dispensed to [or involving] a subject). In the event an investigation is conducted by a research team of individuals, the Investigator is the responsible leader of that team” [21 CFR 312.3(b) and 812.3(i)]. The Clinical Investigator (CI) is responsible for the scientific and technical conduct of the research protocol. Additionally, clinical research is expected to be conducted in conformance with Good Clinical Practice as described in the International Conference on Harmonisation (ICH) E6 guideline. In order to properly document any delegation of this authority, the site CI should complete and sign a Delegation of Responsibility Log and update as needed. For more specific information regarding Investigator responsibilities, refer to Chapter 14 of the MOO.

### **18.2 Site Activation Procedure**

Before any study procedure can be undertaken at a site, the DCC must notify the site that they are approved to proceed. In order to activate a site, the site is required to supply the DCC all requested essential documents. Once these documents are received and approved, the DCC will notify the site and provide the site the Investigator's Regulatory Binder, including copies of all approved regulatory documents.

The DCC holds the responsibility for obtaining all the essential research documents to qualify a site for subject enrollment. However, the site will supply the following documents in a timely manner when requested:

- FDA Form 1572
- Curriculum vitae and professional license(s)
- Financial Disclosure Form
- Human subjects protection training documentation for all investigators
- Laboratory certification(s) (CLIA at a minimum)
- Laboratory normal ranges
- Original Protocol Signature Page signed by Principal Investigator
- IRB approval documentation
- IRB compliance documentation
- IRB approved Informed Consent Forms and advertisements if applicable

For specific instructions, please refer to the Study Start-up Materials Guidelines provided by the DCC (located on the walk-PHaSST Study website).



### 18.3 Essential Documents during the Conduct and after the Termination of the Trial

The Investigator’s Regulatory Binder will be provided by the DCC. In addition to having on file the above documents, the documents listed in Table 18-1 should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available.

**Table 18-1: Essential Documents During the Clinical Conduct of the Trial<sup>1</sup>**

Title of Document	Purpose	File
Audit documentation (if applicable)	To document that audit was performed	<ul style="list-style-type: none"> <li>• Rho Central File</li> <li>• Investigator's Regulatory Binder</li> </ul>
Biological Sample/ Specimen Log	To document location and identification of retained samples if assays need to be repeated	<ul style="list-style-type: none"> <li>• Rho Central File</li> <li>• Investigator's Regulatory Binder</li> </ul>
Blank Informed Consent Form (all versions) approved by IRB	<ul style="list-style-type: none"> <li>• To document the informed consent</li> <li>• To track changes in the version number, dates of the document(s), and content</li> </ul>	<ul style="list-style-type: none"> <li>• Rho Central File</li> <li>• Investigator's Regulatory Binder</li> </ul>
Delegation of Responsibilities Log	To document signatures and initials of all persons authorized to make entries and/or corrections in EDC. Includes the following personnel: <ul style="list-style-type: none"> <li>○ Physicians</li> <li>○ Clinicians</li> <li>○ Nurse practitioner/physician</li> <li>○ Research nurse</li> <li>○ Study coordinator</li> <li>○ Pharmacists</li> <li>○ Data personnel</li> </ul>	<ul style="list-style-type: none"> <li>• Rho Central File</li> <li>• Investigator's Regulatory Binder</li> </ul>
Copy of currently approved version of protocol	<ul style="list-style-type: none"> <li>• To document investigator and sponsor agreement to the protocol and amendments</li> <li>• To document revisions of trial-related documents that take effect during the trial</li> </ul>	<ul style="list-style-type: none"> <li>• Rho Central File</li> <li>• Investigator's Regulatory Binder</li> </ul>
Documentation of investigational product and trial-related materials shipment	<ul style="list-style-type: none"> <li>• To document shipment dates, batch numbers, and method of shipment of investigational product and trial-related materials</li> <li>• To allow tracking of product batch, review of shipping conditions, and accountability</li> </ul>	<ul style="list-style-type: none"> <li>• Rho Central File</li> <li>• Investigator's Regulatory Binder</li> </ul>
In-Service Material	To provide internal training for trial personnel	<ul style="list-style-type: none"> <li>• Investigator's Regulatory Binder</li> </ul>
IND Safety Reports	Sponsor to notify investigators of safety information	<ul style="list-style-type: none"> <li>• Rho Central File</li> <li>• Investigator's Regulatory Binder</li> </ul>
IRB/IEC: approval, correspondence, and update reports	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/ favorable opinion	<ul style="list-style-type: none"> <li>• Rho Central File</li> <li>• Investigator's Regulatory Binder</li> </ul>
Interim Monitoring Visit Progress Reports	To document site visits by, and findings of, the monitor	<ul style="list-style-type: none"> <li>• Rho Central File</li> <li>• Investigator's Regulatory Binder</li> </ul>
Investigational Product Accountability Log	To document that investigational product(s) have been used according to the protocol	<ul style="list-style-type: none"> <li>• Rho Central File</li> <li>• Investigator's Regulatory Binder</li> </ul>
Master Subject Log	<ul style="list-style-type: none"> <li>• To document that investigator/institution keeps a confidential list of names and contact information of all subjects enrolled in the trial</li> </ul>	As per requirements of institution (separate from Regulatory)

<sup>1</sup> “Essential Documents for the Conduct of a Clinical Trial.” International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (E6).

Title of Document	Purpose	File
	<ul style="list-style-type: none"> <li>To allow investigator/institution to contact the subject</li> </ul>	Binder)
Monitoring Log	To document site visits by the monitor	<ul style="list-style-type: none"> <li>Investigator's Regulatory Binder</li> </ul>
SAE documentation (copies of reports, submission to IRB/IEC)	Sponsor and/or investigator to notify regulatory authority(ies) and IRB(s)/IEC(s) of unexpected SAEs and of other safety information	<ul style="list-style-type: none"> <li>Rho Central File</li> <li>Investigator's Regulatory Binder</li> </ul>
Signed Protocol Signature Pages	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	<ul style="list-style-type: none"> <li>Rho Central File</li> <li>Investigator's Regulatory Binder</li> </ul>
Signed Informed Consent Forms for all subjects	See Section 12.7.	<ul style="list-style-type: none"> <li>As per requirements of institution</li> </ul>
Study communication	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	<ul style="list-style-type: none"> <li>Investigator's Regulatory Binder</li> </ul>
Subject Identification List	<ul style="list-style-type: none"> <li>To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial</li> <li>To allow investigator/institution to reveal identity of any subject</li> </ul>	<ul style="list-style-type: none"> <li>As per requirements of institution (separate from Regulatory Binder)</li> </ul>
Subject Screening Log	To document identification of subjects who entered pretrial screening	<ul style="list-style-type: none"> <li>Investigator's Regulatory Binder</li> </ul>

After completion or termination of the trial, all the documents identified above should be in the file together with the documents listed Table 18-2.

### 18.3.1 ***Procedures to Follow if IRB Approval Expires During the Trial***

If a site's IRB approval expires during the course of the walk-PHaSST trial, the site should immediately contact the DCC alerting them of the expiration.

A memo to file from the Sponsor's project officer (or representative) will be generated and sent to the site via email to be filed in the regulatory binder. The memo to file will document the official decision to put the clinical site on temporary enrollment hold until IRB approval is re-attained. The memo will also request that the Clinical Investigator contact the IRB Chairman to request that any patients who are currently on treatment in the MIT be allowed to proceed with study assessments in order to prevent potential risk to the patient.

Once IRB approval has been re-attained, another memo to file will be generated from the Sponsor's project officer (or representative) notifying the site that enrollment can resume. This memo to file should also be filed in the site's regulatory binder. The study's CRA will confirm that both memos are filed in the regulatory binder and the no study activities were conducted without approval from the site's local IRB.

**Table 18-2: Essential Documents After Completion or Termination of the Trial<sup>2</sup>**

Title of Document	Purpose	File
Audit certificate (if required)	To document that audit was performed	<ul style="list-style-type: none"> <li>• Rho Central File</li> <li>• Investigator's Regulatory Binder</li> </ul>
Clinical study report	To document results and interpretation of trial	<ul style="list-style-type: none"> <li>• Rho Central File</li> <li>• Investigator's Regulatory Binder</li> </ul>
Close-out Visit Progress Report	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files	<ul style="list-style-type: none"> <li>• Rho Central File</li> <li>• Investigator's Regulatory Binder</li> </ul>
Completed subject identification code list	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	<ul style="list-style-type: none"> <li>• Investigator's Regulatory Binder</li> </ul>
Documentation of investigational product destruction or shipment	<ul style="list-style-type: none"> <li>• To document destruction of unused investigational product by sponsor or at site</li> <li>• To document return of investigational product to sponsor</li> </ul>	<ul style="list-style-type: none"> <li>• Rho Central File</li> <li>• Investigator's Regulatory Binder</li> </ul>
Final report by investigator/ institution to IRB/IEC	To document completion of the trial	Investigator's Regulatory Binder
Treatment allocation and decoding documentation	Returned to sponsor to document any decoding that may have occurred	<ul style="list-style-type: none"> <li>• Rho Central File</li> </ul>

## 18.4 Package Insert

The package insert of a drug provides the following information: Description, Clinical Pharmacology, Indications and Usage, Contraindications, Warnings, Precautions, Adverse Reactions, Overdosage, Dosage and Administration, and How Supplied. Package inserts for the Walk-PHaSST study will be included in the Investigator's Brochure for Revatio™. Sites will be notified by Rho® of updates and the inserts will be posted on RhoWeb.

## 18.5 FDA Form 1572 and the Clinical Investigator's Responsibilities

Whether the investigational product is a drug, biologic, or a medical device, the CI commits to the performance of many required activities. For studies with an IND or IDE, these activities may be listed on the signed Form FDA 1572 (for drugs and biologics) or may be described in an Investigative Agreement (for drugs, biologics, and/or medical devices) between the CI and the Sponsor.

While research team members are required to carry out their individual roles competently and in accordance with applicable regulations, the CI bears overall responsibility for member performance, conduct of the protocol, and adherence to regulatory requirements. The CI is expected to ensure that members are qualified, well trained, and accountable for their activities as they participate in the study. When the CI signs a Form FDA 1572, he/she is fully committed to the following:

<sup>2</sup> "Essential Documents for the Conduct of a Clinical Trial." International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (E6).

- Ensuring that the study protocol and any subsequent changes are reviewed and authorized by an official IRB.
- Personally conducting or supervising the clinical investigation.
- Ensuring that all associates, colleagues, and employees assisting in study conduct are informed of their obligations.
- Conducting the study in accordance with the relevant, current protocol and only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights or welfare of subjects.
- Complying with all requirements regarding obligations of Clinical Investigators.
- Informing subjects that drugs and biologics are being used for investigational purposes, and ensure that both informed consent and IRB requirements are met.
- Reporting AEs to the sponsor and IRB in a timely manner.
- Reading and understanding the Package Insert including potential risks and side effects of drugs used in the study.
- Maintaining adequate and complete study records in accordance with regulations and making those records available for inspection by the study sponsor and/or government regulators.

For investigational products, the FDA has summarized the responsibilities of Investigators in 21 CFR 312.60 to 312.69 (drugs and biologics) and 812.100 to 812.150 (devices). These responsibilities include the following:

- Ensuring that the investigation is conducted according to the signed Investigator statement (Form FDA 1572) and/or investigational plan.
- Making sure that applicable regulations are followed pertaining to the rights, safety, and welfare of subjects, including proper and adequate subject informed consent.
- Maintaining control of the investigational product by ensuring that only authorized subjects under the personal supervision of the CI (or under supervision of a Sub-Investigator responsible to the CI) receive the investigational product.
- Establishing ongoing records regarding the disposition of the investigational product (IP), including dates, quantity, use by subjects, and documentation of shipment to sponsor or destruction of unused supplies of the IP.

- Preparing and maintaining subject case histories, including eCRFs and their supporting data, signed and dated Informed Consent Forms (before study participation), medical records, patient charts, physician progress notes, and nurses' notes.
- Retaining study records for at least 2 years following either the discontinuance of clinical study or after a marketing application for the product has been approved (whichever is longest). Study records should not be destroyed without sponsor approval.
- Submitting to the sponsor a variety of reports, including study progress reports (at least annually), safety reports of AEs, a final study report at the conclusion of the study, and financial disclosure reports (for up to one year following completion of the study).
- Ensuring 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.
- Permitting the FDA to inspect study records and study reports made by the Investigator.
- Ensuring the proper handling and storage of substances that are subject to the Controlled Substances Act.

Contact the DCC for a copy of the FDA revised 1572 template for any changes to personnel. These updates should take place as they occur and in a timely manner. The clinical investigator must sign each newly revised 1572, keep a copy on site, and submit the original 1572 to the DCC.

## **18.6 Requirements of IRB Approval and Notification**

Approval of the walk-PHaSST protocol and consents and all amendment/revisions must first be approved by the Principal Investigator (PI) and if necessary, the DSMB (if the potential risk is increased by the protocol amendment – which will be determined by the NHLBI Project Officer). Approval is then required by each site's local IRB and any other oversight committee. Site approved documents must be on file with the DCC before beginning accrual (also known as site activation). No changes to the protocol may be implemented without written permission from the PI.

Because specific language is required, all consents and consent amendments/revisions need review by the DCC and NHLBI prior to submission to the local IRB. The NIH also requires a second review by the DCC once the consent document is locally approved with a notice to NHLBI and the site. All IRB correspondence and approval letters should be included in the Investigator Binder and submitted to the DCC regulatory contact. Contact the DCC for questions regarding the required content.

In addition, sites are required to apply to their local IRB for renewal annually, at a minimum, and the written notification of annual renewal must be on file with the DCC

once approved. Lapses in approval will trigger temporary suspension of the site ensuring that new enrollments during the lapse are not possible (refer to Section 18.3.1 for more details).

### **18.7 Informed Consent Forms**

The Informed Consent Form (ICF) confirms a subject's willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. No study-related procedures on the subject can be performed prior to obtaining documented ICF from the subject or a legally authorized representative. The subject must be notified of any changes to the study procedures or new findings that may impact the subject's willingness to continue participation in the study.

### **18.8 Maintenance of Study Records**

The Investigator's Regulatory Binder maintains all the essential documents required for the conduct of a clinical trial. The Regulatory Binder must be current for monitoring visits by the Clinical Research Associate (CRA) and the FDA, if applicable. Should a site be monitored by the FDA, the Regulatory Binder will be a critical component of a site's adherence to federal guidelines for trials involving human subjects. The Regulatory Binder and all associated source documentation should be kept in an accessible manner for at least 2 years following completion of the study. The study sponsor should be contacted prior to disposal of the study file and its source documents.

### **18.9 Overview of 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. Listed below are basic principles of Good Clinical Practice. 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 the following:

- 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.
- The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
- Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should only be used in accordance with the approved protocol.

## 19                    **PROTOCOL VIOLATIONS/DEVIATIONS AND PROTOCOL WAIVERS**

Compliance with regulations and the protocol is essential both to the protection of the rights and safety of the walk-PHaSST research subjects and to the integrity of the walk-PHaSST study. Walk-PHaSST makes no attempt to differentiate protocol violations from protocol deviations. Protocol violations/deviations will therefore refer to any variance from the current IRB approved protocol and applicable amendments. A protocol waiver refers to an advanced permission to deviate from the protocol, which is granted by the medical monitor after careful consideration of the unique circumstances surrounding the request.

Study site personnel will report site specific protocol violations/deviations on the Protocol Deviation CRF in EDC. The form provides space for the type of deviation, reason for deviation, and steps taken to resolve and prevent recurrence. Each site will report protocol deviations as soon as possible in EDC. In addition, each clinical site is responsible for reporting protocol violations or deviations to the local site's governing IRB in accordance with that IRB's requirements.

An across-study, Electronic Protocol Violations/Deviations and Waivers (EPVDW) Report will be maintained on the walk-PHaSST website and will be reviewed by the Operations and/or Executive Committee at regular intervals. Although the CRA assists the clinical site with the discovery and reporting of protocol deviations/violations at site visits, it is the clinical sites responsibility to report these as soon as they occur, not just at site visits. The Clinical Research Associate (CRA) will instruct sites to report any new events identified during study visits in EDC and will also document compliance issues in the Site Progress Report.

Good clinical practices preclude a CI from deviating from the protocol without prior consent, except under two conditions:

- 1) Where it is necessary to eliminate an immediate hazard for a trial subject(s) or
- 2) If the change involves only logistical or administrative aspects of the trial (ICH E6, 4.5.2).

The granting of protocol waivers is not expected. However, it is impossible to anticipate every circumstance that might arise. Therefore, a Request for Protocol Waiver Form has been provided (see Section 19.1). This form must be completed, dated, and signed by the CI prior to its submission to the Executive Committee.

The completed form will be faxed to the DCC at (919) 287-0128. The original CI signed copy of the Request for Protocol Waiver Form will be kept in the site Regulatory Binder behind the "Protocol Violations/Deviations".

The Executive Committee will:

- a) Evaluate the appropriateness of the request
- b) Complete the decision section of the form (including an authorization number, if the request is approved)
- c) Fax a copy of the completed, signed, and dated form back to the site



- d) Save a copy of the form in the central files

The site must store the final response to the Request for Protocol Waiver in the subject's study file, behind the "Protocol Violations/Deviations" tab in the Regulatory Binder, and must document the decision on the Protocol Deviation Form in EDC along with the Executive Committee granted authorization number. Even though it was an **approved** protocol waiver, it still constitutes a protocol deviation and must be recorded as such on the appropriate form in EDC.

## **19.1 Request for Protocol Waiver Form**



**Request for Protocol Waiver Form**

**Fax to: Data Coordinating Center, Rho Federal Systems Division, Inc.**

**Fax Number: (919) 287-0128**

Number of pages in fax:		
Clinical Investigator:		
Site name:		Site #:
Site fax number:		
Date of Request from Site:		
Subject ID, if applicable:		

**Protocol requirement for which a waiver is requested:** (e.g., specific Inclusion/Exclusion criteria)

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**Justification/reason for request:** (if appropriate, you may choose to include supporting patient data herein or attach de-identified subject data as an attachment).

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**Investigator Signature:** \_\_\_\_\_ **Date:** \_\_\_\_\_

<b>FOR EXECUTIVE COMMITTEE USE ONLY</b>	
<b>Approved:</b> <input type="checkbox"/> Yes	<b>Authorization Number:</b> _____ <input type="checkbox"/> No
<b>Comments/Clarification</b>	
_____	
_____	
_____	
_____	

## **20 CLINICAL MONITORING**

The Clinical Research Associate (CRA) will conduct site monitoring visits in accordance with protocol specific requirements, Title 21 of the CFR, ICH/GCP guidelines, and other applicable regulatory documents. Site visits will include Interim Monitoring Visits (IMVs) and a Close-out Visit (COV).

### **20.1 Site Initiation Visit (SIV)**

Sites were pre-selected by NHLBI based a written response to proposal. Centralized training for study staff will be conducted in lieu of the Site Initiation Visit. Each attendee must sign the Training Log at the centralized meeting. Subsequently, the DCC will generate a memo-to-file regarding staff attendance and will forward to the site to be placed in the regulatory binder. A Walk-PHaSST Training Log will be included in the regulatory binder for additional site staff to complete after completing the on-line training modules.

### **20.2 Interim Monitoring Visit (IMV)**

The CRA will conduct IMVs in accordance with protocol and contract specifications. The frequency of IMVs may depend on the study time period (i.e., active enrollment or subject follow-up visits); number of subjects enrolled; sites requiring extra assistance; demand for data collection; and other study management issues. Visits will be conducted at least once annually after enrollment has begun at that site. During the IMV, the following items will be reviewed to ensure that study-required procedures are being conducted appropriately:

- Regulatory binder
- Safety reporting
- Informed consent
- Investigator and site personnel responsibilities
- Source documentation and eCRF
- Protocol deviations
- On-site data corrections
- Data Clarification Forms (DCFs)
- Laboratory supplies
- Investigational study drug accountability
- Facilities

Approximately 2 weeks after the visit, the DCC will provide the site with a letter documenting any issues discovered during the visit; this letter includes a copy of the site progress report. There will be a follow-up teleconference between the DCC, the PI, the Study Coordinator(s), and possibly a representative from NHLBI. This teleconference is intended to check the status of items noted in the letter and will be scheduled for approximately 4 weeks after delivery of the IMV follow-up letter.

### **20.3 Close-Out Visit (COV)**

The CRA will conduct a COV in accordance with protocol and contract specifications. A COV may be conducted in the following circumstances:

- After the last subject has completed the clinical protocol, all data queries have been resolved, and the database has been locked
- Lack of site protocol compliance
- Lack of site subject enrollment
- Premature termination of the trial by the NHLBI

The CRA reviews the following COV items on-site:

- Investigator site file
- Regulatory obligations
- Safety reporting
- Informed consents
- Source documentation and eCRF
- Investigational study drug accountability
- Laboratory supplies
- Study equipment and supplies
- Records retention

### **20.4 Monitoring Process**

Prior to a site visit, the CRA will schedule visits with the Clinical Investigator (CI) or the study coordinator and will follow up with a written confirmation letter. Study coordinators will ensure that all materials requested by the monitor are available within 72 hours of the visit. Should the materials not be available within 72 hours, the study coordinator must notify the CRA to reschedule the visit.

During IMVs, the CRA will generate data corrections identifying discrepancies and protocol deviations/violations uncovered during review of source documentation and eCRFs. The site staff and CRA will resolve as many issues as possible during the visit.

At the conclusion of the site visit, the CRA will meet with the CI and the study staff in a Site Status Meeting to discuss issues identified during the course of the visit. After each visit, the CI will receive a progress report and follow-up letter noting any findings along with action items identified during the visit that must be resolved prior to the next site visit.

### **20.5 Availability of Site Staff**

The study coordinator must be available to the CRA during a reasonable percentage of the time during a site visit. The CI must be available to the CRA for at least a half an

hour near the end of the site visit. If availability changes, the CRA should be notified in advance so that he/she may reschedule the visit.

## 20.6 Source Documentation

According to ICH Guidelines, the CI is responsible for the “accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.” All data reported in the eCRF must be derived from source documents and should be “consistent with the source documents or the discrepancies should be explained.”

Accurate and complete source documentation must be maintained as evidence of the validity of data captured on the eCRFs. Furthermore, if, for any reason, eCRF data is missing or destroyed, the data can be reproduced with the source documents.

The source documentation standards are listed in Table 20-1.

**Table 20-1 – Source Documentation Standards**

Topic	Source Documentation Criteria/Procedures
<b>Addenda to source documentation</b>	When source documentation is found incomplete during a site visit, the circumstances of the deficiency may be documented and filed in the subject’s research record in real-time. If the incomplete documentation is obtained at a later date, the document must be dated and filed in the subject’s research record in real-time. Sites must not modify past-dated research records. Altering past-dated records without appropriately dating the new entry in real-time may be considered unverifiable and fraudulent.
<b>Case Report Forms Templates use as Source Documentation</b>	Source document templates, provided by the DCC and located on the study website, may serve as source documentation for data that <b>cannot</b> be verified by medical records, certified copies of medical records, or shadow files. The following source document templates are most appropriate for use as source documents: <ul style="list-style-type: none"> <li>• Physical Examination</li> <li>• 6-Minute Walk Test</li> <li>• Borg Dyspnea Index</li> <li>• NYHA/WHO Functional Class Assessment</li> <li>• Quality of Life Questionnaire (SF-36)</li> <li>• Pain Questionnaire Inventory (BPI)</li> </ul> All source documents, including those developed from the DCC provided templates must be verified, signed, and dated by the Clinical Investigator completing the assessment.
<b>Certified Copies</b>	Certified copies are copies of the original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Certified copies should be signed and dated to verify it is an exact copy of the original. However, monitors and FDA auditors may request to see the original documents to verify the existence of the original or validity of the copy.

Topic	Source Documentation Criteria/Procedures
<b>Confidentiality</b>	<p>The Code of Federal Regulations (21 CFR 50.25) requires that the confidentiality of records identifying the subject will be maintained and that the subject is informed of the possibility that the FDA may inspect the records.</p> <p>The electronic CRF must contain only the subject's study identification number and site identification data. No personal identifiers (e.g. name, initials, SSN) should be captured on the eCRFs.</p>
<b>Correspondence</b>	<p>Communications with outside clinicians regarding verification of subject diagnoses must be documented by original letters/documents or copies of the same, or contact reports of verbal communication. Letters/documents and contact reports must include appropriate subject identifier(s) and must be signed and dated.</p>
<b>Electronic Medical Records</b>  See also Electronic Signatures	<p>The use of electronic medical records is acceptable in institutions that have adopted electronic medical records systems. The site must provide a printed copy of the electronic medical record in one of the following forms:</p> <ul style="list-style-type: none"> <li>• Printouts of electronic medical records</li> <li>• Screenshots or "print screens"</li> </ul> <p>All printouts must include the institution's name, the subject's name, the date of record, and the date of printout.</p>
<b>Electronic Signatures</b>	<p>The use of electronic signatures is acceptable in institutions that have adopted electronic medical record systems. Electronic signatures are acceptable for the following:</p> <ul style="list-style-type: none"> <li>• Chart Note or Clinic Note</li> <li>• Discharge Summaries</li> <li>• Laboratory Reports</li> <li>• Protocol Deviations</li> <li>• SAE Reports</li> </ul>
<b>Error Corrections</b>	<p>Error corrections made to any source documents must be made by making a single line through the original, incorrect documentation (never obscuring the original entry). The correct data is inserted, and the change is initialed and dated by the person making the correction. An explanation of the changes may be made to the side (if necessary). The use of correction fluid (whiteout) is always prohibited. Corrections should always be made in a way that an audit trail can be maintained.</p>
<b>Inadequate Source Documentation</b>	<p>All source documentation for protocol-related data must be available within 72 hours of the site visit. Should the materials not be available within 72 hours, the study coordinator must notify the CRA to reschedule the visit. The CRA is not responsible for searching for source documents or traveling to another site to obtain source documents. Should the CRA identify missing source documents in the research records, the CRA will request the study coordinator obtain the source documentation during the site visit.</p>
<b>Informed Consent Forms</b>	<p>Per the ICH Guidelines on GCP, prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. Informed consent documents must be signed and dated in</p>

Topic	Source Documentation Criteria/Procedures
	<p>ink by the subject, parent/guardian, or legally authorized representative.</p> <p>The Screening ICF must be signed and dated before screening commences. Subjects who meet the eligibility screening criteria for the Main Interventional Trial (MIT) must sign and date the MIT ICF before study procedures commence.</p> <p>There should be documentation of the informed consent process within each subject's study file.</p>
<p><b>Laboratory/Ancillary Medical Tests</b></p> <p>See also Electronic Medical Records and Electronic Signatures.</p>	<p>All protocol related laboratory tests must be maintained with the subject's research record. Required laboratory tests include the following:</p> <ul style="list-style-type: none"> <li>• Chemistry</li> <li>• Complete Blood Count</li> <li>• Urinalysis</li> <li>• Serology (optional for pregnancy test?)</li> <li>• Microbiology</li> <li>• Echocardiogram</li> <li>• Right Heart Catheterization</li> <li>• Pulmonary Function Test (PFT)</li> <li>• Chest X-Ray</li> <li>• Arterial Blood Gases Lab Reports, PFT, or Clinic note (O<sub>2</sub> saturation documentation)</li> </ul> <p>The site must provide a printed copy of all electronic laboratory results. All lab reports should be reviewed by the Clinical Investigator (CI) prior to data entry on the eCRF. The CI must initial and date lab reports documenting the CI's review of the lab reports.</p> <p>At baseline, the CI must indicate the clinical significance of out-of-range lab values on the lab reports. The CI will note on the lab report whether or not a lab value outside the normal range is clinically significant in regards to the study. The CI must then initial and date the lab report. If the CI determines a lab value outside the normal range is not clinically significant, it will be considered "normal" for the subject. However, at subsequent study visits, the CI must evaluate any change from the subject's normal, baseline lab value and determine the significance of the change. The degree of change should be evaluated and the CI should indicate on the lab report and on the eCRF whether or not the change constitutes an adverse event. The monitor will use the NIH Common Terminology Criteria for Adverse Events (CTCAE) to determine adverse events as a result of out-of-range lab values.</p>
<p><b>Medical Records</b></p> <p>See also Laboratory Reports</p>	<p>Medical records should be maintained in chronological order and include appropriate subject identifier(s). Acceptable medical records include the following:</p> <ul style="list-style-type: none"> <li>• Chart Note or Clinic Note</li> <li>• Admission/Discharge Summaries</li> <li>• Flow Sheets</li> <li>• Laboratory Reports</li> </ul> <p>Original medical records are required to verify at minimum, the following</p>

Topic	Source Documentation Criteria/Procedures
	data: <ul style="list-style-type: none"> <li>• Endpoints</li> <li>• Entry Criteria</li> <li>• Medical History</li> <li>• Signs/Symptoms</li> <li>• Weight/Height</li> </ul>
<b>Protocol Violation/Deviation</b>	<p>Study site personnel will report site-specific protocol violations/deviations on Protocol Deviation Form in EDC. Each CI is responsible for reporting protocol violations/deviations to the local site's governing IRB in accordance with that IRB's requirements.</p> <p>The granting of protocol waivers is not expected. However, because it is impossible to anticipate every circumstance that might arise, a Request for Protocol Waivers Form has been provided. This form must be completed, dated, and signed by the site CI prior to its submission to the medical monitor. The medical monitor will: a) evaluate the appropriateness of the request; b) complete the decision section of the form (including an authorization number, if the request is approved); c) fax a copy of the completed, signed, dated form back to the site; and d) save a copy of the form in the central files. For situations requiring immediate feedback, telephone contact may precede the faxed form. The site must store the final response to the Request for Protocol Waiver in the subject's study file.</p>
<b>Questionnaires</b>	<p>The protocol requires the subject to complete three questionnaires: the Borg Dyspnea Index, the Quality of Life Questionnaire (SF-36) and the Pain Questionnaire (BPI). The questionnaires must be completed in ink by the subject. Each question must be answered and no question should have more than one response.</p> <p>All pages of the questionnaires must include the subject's ID number and the date the subject completed the questionnaire.</p>
<b>Screening Logs</b>	<p>A screening log must include all subjects screened for the study. The screening log should identify subjects enrolled into the Main Interventional Trial and the subjects who failed screening.</p>
<b>Shadow Files</b>	<p>Original medical records are ideal, but shadow files are acceptable. The CRA and FDA auditors may request the original medical records at any time. If the original records are not available or the site personnel are unable to produce them, the data will be considered as having inadequate source documentation.</p> <p>All source documentation standards for protocol-related medical records apply to shadow files.</p>



## **21 TRAINING AND CERTIFICATION**

Walk-PHaSST is a multi-center clinical trial and requires organized and documented staff training to ensure that findings from each clinical site are comparable and can therefore be analyzed as a whole.

### **21.1 Training**

Before subject enrollment can begin at a clinical site, clinical site personnel must complete instruction and training on every aspect of the trial. Training sessions will be conducted during face-to-face meetings and via regular teleconferences. Topics include, but are not limited to:

- Inclusion/exclusion/randomization criteria
- Study treatments, including drug distribution and treatment initiation
- Study procedures and assessments and appropriate visit windows
- The Rho*RAND*<sup>TM</sup> system, which manages subject randomization
- Electronic Data Capture (Rho*EDC*) system and data entry
- Maintenance of study and subject data files
- The Rho*LAB* system, which manages specimen and radiographic image labeling, shipment, and tracking
- Adverse event reporting
- Study monitoring and clinical site visits

### **21.2 Identification and Certification of Study Personnel**

Each clinical site participating in walk-PHaSST is required to identify at least one individual on the staff who is experienced and/or certified to perform specific functions applicable to their role in the study. The roles involved include:

- Clinical Investigator (CI)
- Study Coordinator (SC)
- Pharmacist
- Cardiologist
- Pulmonologist
- Echocardiogram Technician/Sonographer

In general, training and/or experience is required for all individuals identified as key walk-PHaSST study personnel. Curricula vitae, which document an individual's qualifications, are collected and stored in the site Investigator's Regulatory Binder (see MOO [Section 18.5](#)). Each individual is expected to be familiar with the walk-PHaSST protocol and the sections of the Manual of Operations (MOO) that are applicable to the individual's involvement in the study. All key research staff of NIH sponsored projects are required to document GCP training. The need for other specific training for a particular individual will depend on the study activities for which that individual is responsible.

### **21.2.1 Clinical Investigator**

The CI must be listed on the Form FDA 1572 with signature and date. Each CI must attend a walk-PHaSST training session OR complete the walk-PHaSST Investigator/Coordinator Meetings Training Module on the walk-PHaSST website (see MOO [section 21-3](#)) and submit the signed and dated Training Certification Form (see [Figure 21-1](#)). In order to be authorized to use the RhoRAND System for Registrations, Randomizations, and Blind Break, a CI must complete the practice functions available in RhoRAND.

### **21.2.2 Study Coordinator and Backup Study Coordinator**

Requirements for certification of the SC apply equally to the designated backup SC(s). The requirements focus on the SC's primary role in assuring the quality and completeness of data entered into the walk-PHaSST database via the EDC. These requirements include:

- Being listed on either the Form FDA 1572 or the Delegation of Responsibility Log with signature and date.
- Attendance at face-to-face walk-PHaSST training sessions OR successful completion of the walk-PHaSST Investigator/Coordinator Meetings Training Module available on the walk-PHaSST website and submission of the signed and dated Investigator/Coordinator Meetings Training Certification form (see [Figure 21-1](#)).
- Successful completion of the 7 RhoRAND Practice Functions within the RhoRAND system. Study Coordinators should use Chapter 3 as a reference tool and guide for completing the 7 unique practice functions. The system will generate an email notification to the SC (or designee) that the practice functions have been successfully completed. The study coordinator must receive 7 different email notifications completing the successful completion of each function in order to receive access to the live RhoRAND system.
- Successful completion of the face-to-face RhoLAB training or self-study review of the RhoLAB training presentation on the walk-PHaSST website and submission of the signed and dated RhoLab Training Certification form (see [Figure 21-2](#)). Additionally, study coordinators will have access to the RhoLAB demo site and

can practice enrolling subjects, adding specimens, and shipping specimens to each of the central labs before using the live system.

- Successful completion of the RhoEDC Practice Data Entry Functions. This activity is supported by the RhoEDC Training Module available on the walk-PHaSST website. Sites are not required to submit a certification form because proficiency is demonstrated by successfully performing practice data entry (see MOO [Section 21.6.1](#)).

### **21.3 Walk-PHaSST Investigator/Coordinator Meetings Training Module**

Face-to-face project meetings occur yearly. These meetings provide on-going training and progress updates for walk-PHaSST CIs and SCs. Each topic on the meeting agenda is presented using MS PowerPoint slides. The slides are posted on the walk-PHaSST website. They contain enough detail to serve as training material for personnel that were not able to attend a particular meeting. Attendance at the meetings is strongly recommended. However, for CIs and SCs unable to attend the meeting, a review of the meeting slides is mandatory.

Documentation of training for individuals who attended a face-to-face meeting is captured via the meeting attendee sign-in sheet maintained by the DCC. Current CIs and SCs who did not participate in a walk-PHaSST face-to-face meeting must review the slides from that meeting within 1 month of the meeting and must complete the Investigator/Coordinator Meeting Training Certification Form for Non-attendee (see [SAMPLE<sup>1</sup>](#) in [Figure 21-1](#)). Please fax the completed form to the DCC's study coordinator at 919-287-0128 and file the original in the site Investigator's Regulatory Binder.

It is not necessary for new CIs and SCs to review slides from previous face to face meetings, unless explicitly requested by the DCC.

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<sup>1</sup> The current version of all Forms are stored on the Forms page of the walk-PHaSST website.

**Figure 21-1: Investigator/Coordinator Meeting Training Certification Form for Non-attendee (SAMPLE)**

The form is enclosed in a black rectangular border. At the top left is the walk-PHaSST logo, which consists of a stylized red and grey figure resembling a person walking. To the right of the logo, the text 'walk PHaSST' is written in red. Further to the right, the title 'Investigator/Coordinator Meeting Training Certification Form for Non-attendee' is written in red, with 'Investigator/Coordinator Meeting' on the first line, 'Training Certification Form' on the second line, and 'for Non-attendee' on the third line. Below the title, there are three lines of text for personal information: 'NAME \_\_\_\_\_', 'POSITION IN STUDY \_\_\_\_\_', and 'SITE NAME \_\_\_\_\_ SITE # \_\_\_\_\_'. A paragraph of bolded text follows: 'By signing and dating below, I confirm that I have reviewed ALL PowerPoint presentations contained in the Investigator Meetings Training Module and any corresponding handouts which are currently posted on the walk-PHaSST website. It also verifies that any questions I may have had have been answered by this review.' Below this is a blue italicized instruction: 'Please print, sign, date, and fax to Jamie Spencer at the DCC (287-0128). Place original in the site Investigator's Regulatory Binder.' Another blue italicized instruction follows: 'This signature page must be filed at the DCC before site certification is complete.' At the bottom, there are two lines for 'Signature \_\_\_\_\_' and 'Date \_\_\_\_\_'.

## 21.4 Manual of Operations (MOO) Review

The MOO details all important study procedures. As such, it is a critical resource to SCs and CIs, who should review all sections of the MOO. Other site staff should review relevant MOO sections as appropriate.

## 21.5 RhoLAB Training Module

There is a RhoLAB training module regarding the topics of general labels, shipping of specimens, and simulation of the live RhoLAB system. This training module is located on the walk-PHaSST website home page under '**Training**' and can be viewed by new site personnel who will be shipping specimens of any kind using the RhoLAB system.

Attendees of the August 2007 in-person training are not required to review this module because attendance at the meeting, documented by signature on the meeting attendees list, confirms that RhoLAB Training occurred. All others must review the module prior to being granted access to the RhoLAB system.

### 21.5.1 Access to the RhoLAB system

Access to the RhoLAB system will be granted by the DCC to each new user, upon the completion of the RhoLAB training module. Print and complete the final page of the module (see SAMPLE<sup>2</sup> in Figure 21-2), indicating your review of this module, and fax it to the walk-PHaSST website administrator per instructions on the form. Please note that the DCC must receive this form prior to granting access to the RhoLAB system and should be done 24 hours PRIOR to needing the system. Upon completion of this training and the receipt of this form, the walk-PHaSST website administrator will provide electronic access to the production version of the RhoLAB system. An email message will be sent by the website administrator confirming that the trainee is certified. A printed copy of this email notification should be stored in the site Investigator's Regulatory Binder.



The form features a vertical red bar on the left side. At the top left is the walk-PHaSST logo, which consists of a stylized red and grey figure resembling a person or a molecule. To the right of the logo is the text 'RhoLAB Training Certification' in a large, bold, black font. Below the title, there is a horizontal grey line. The main body of the form contains several lines of text with blank lines for input: 'When you have completed this training module, print this last page. Complete the information, sign and date where indicated, and fax to the DCC.', 'Name: \_\_\_\_\_', 'Walk-PHaSST Website User Name: \_\_\_\_\_', 'Site Name: \_\_\_\_\_', 'Signature: \_\_\_\_\_', and 'Date Training Completed: \_\_\_\_\_'. At the bottom, it says 'Fax to: Christopher Woods (919) 287 - 0128'.

<sup>2</sup> The current version of all Forms are stored on the Forms page of the walk-PHaSST website.

## 21.6 RhoEDC Training Module

An overview of the RhoEDC system was presented during the walk-PHaSST Study meeting in Bethesda in August 2007. This overview included a live demonstration of the study in the RhoEDC system. The demonstration covered the following topics:

- Basic navigation
- Registering a new subject in RhoEDC using the subject number provided by RhoRAND
- Viewing the Case Report Form (CRF)

CRFs by study visit

“Ongoing” CRFs such as Adverse Events that are used throughout the study

- Opening CRFs and entering study data
- Submitting forms
- Changing study data, including deleting a completed form
- Responding to automatic queries

A self-study training module of this general information has been developed to provide the same instruction for using the functions of RhoEDC. This training module is located on the walk-PHaSST website on the home page under ‘**Training**’ and may be viewed by all site personnel who will be entering study data using the RhoEDC system.

### 21.6.1 RhoEDC Practice Session Certification

Site personnel who will be responsible for entering data in RhoEDC are required to successfully complete a practice session in the EDC demo site. These individuals will be given a mock subject ID number to use when completing the practice session. This practice session consists of entering mock data in a sample set of CRFs. The mock data and instructions for data entry are included in the training module.

Study Coordinators must enter a set of 3 mock CRFs to earn certification. Because CI’s have write access to the data and because their electronic signature is required on all SAEs submitted via the EDC, each CI must also enter mock EDC data to earn certification. CIs are only required to enter data from the sample AE (SAE) form and to use the Signature function on that page in order to earn certification. Site personnel who need only “View” access to data in RhoEDC are not required to complete a practice session.

Once a user has completed the practice data entry, he/she must send an email notification indicating that he/she has completed the practice session to the DCC Data Manager Vickie Coble, ([Vickie\\_Coble@rhoworld.com](mailto:Vickie_Coble@rhoworld.com)), copying Christopher Woods ([christopher\\_woods@rhoworld.com](mailto:christopher_woods@rhoworld.com)) and Jamie Spencer ([jamie\\_spencer@rhoworld.com](mailto:jamie_spencer@rhoworld.com)),. The DCC Data Manager will work with each user to resolve any confusion that may arise during the practice sessions. After the user has successfully completed the practice session, the DCC will grant access to the production version of the system and will send the user an email notification of this production system access. A printed copy of this email notification acts as documentation of certification. As such, it should be stored in the site Investigator's Regulatory Binder.

Please note that because of the effort required to review the data and grant access, the practice session must be executed at **least 3 business days** prior to actual use of RhoEDC. If problems are identified during the practice session, contact the Rho Help Desk Support Team at 1-800-905-0460.

## **21.7 RhoRAND Certification**

All individuals who intend to use RhoRAND to a) register, enroll, randomize, discontinue, or log study visits for a subject; b) conduct an emergency unblinding; c) log the shipment or receipt of study drug; or d) request additional open-label sildenafil must successfully complete the relevant RhoRAND practice functions. See MOO Chapters 3 and 8 for further details about completing the practice functions.

Once a user completes all relevant practice functions, he/she should store the practice function email notifications in the Regulatory Binder. The DCC will provide access to the non-practice functions in 1 business day from completion of the full set of practice functions.

### **21.7.1 RhoRAND Unmasking Function for Clinical Investigators**

Only a clinical investigator is authorized to use the unmasking function in RhoRAND. This option does not appear on the RhoRAND menu for study coordinators. A clinical investigator must have successfully practiced this function in order to be certified to use the production system to unmask a subject at the site. See MOO Chapter 17 for more information on the unmasking procedure.

## **21.8 Certification of Personnel: Transthoracic Echocardiography (TTE) Examiner**

The designated transthoracic echocardiography (TTE) examiner at every clinical site must complete a training session with Dr. Vandana Sachdev ([sachdevv@nhlbi.nih.gov](mailto:sachdevv@nhlbi.nih.gov)) prior to participation in the walk-PHaSST Trial. The presentation at the in-person central training is located on the website and should be reviewed by any new staff echo staff members that join the study.

## **21.9 Human Subjects Training**

All staff listed on Form FDA 1572 or the Delegation of Responsibility Log must complete human subjects training prior to enrolling a subject. Access to an online training is available at <http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp>. A link is also provided on the walk-PHaSST website under 'Links'. Documentation of this training must be filed in the Investigator's Regulatory Binder. Non-US sites may complete an alternate Human Subjects Training if the training has been approved by the NHLBI Project Officer or the DCC.



## **22 SITE STAFF RESPONSIBILITIES**

### **22.1 Role of the Clinical Investigator (CI)**

The Clinical Investigator (CI) is the individual at each participating study site who is responsible for the scientific and technical conduct of the trial. Specific responsibilities of the CI are as follows:

- Direct the activities of the center personnel
- Coordinate the scientific and administrative operations of the center personnel
- Represent his/her center in meetings or on teleconferences for the walk-PHaSST trial
- Obtain approval from his/her center's Institutional Review Board (IRB) to conduct the protocol
- Create and maintain budget
- Provide annual reports
- Supervise data quality
- Ensure center personnel adhere to the protocol and follow procedures described in the Manual of Operations (MOO)
- Guarantee the timely reporting of Serious Adverse Events (SAEs)
- Report protocol deviations to the governing IRB

### **22.2 Role of the Study Coordinator**

The Study Coordinator is responsible for overseeing the daily operations for the walk-PHaSST trial at his/her participating center. Specific duties include the following:

- Recruit and screen participants for the study
- Ensure that study participants receive adequate information regarding informed consent
- Make certain that the participant signs the most recent version of informed consent approved by that center's IRB
- Schedule appointments
- Enroll study participants into the electronic data capture (EDC) system
- Ensure regulatory compliance and maintain the center's regulatory binder
- Serve as primary point of contact of the participating center when communicating with Data Coordinating Center (DCC) about recruitment, screening, drop-outs, missed visits and data queries

- Notify the DCC immediately when an SAE occurs and report the SAE to the appropriate IRB
- Maintain a current roster of site personnel including pertinent contact information (addresses, phone numbers and email)
- Notify the DCC of changes to the roster
- Maintain a file of all correspondence with the DCC
- Maintain a current version of the MOO
- Maintain and update the site's regulatory binder
- Follow procedures described in the protocol and the MOO
- Meet with site monitor during site visits
- Submit accurate and complete data to the DCC via the RhoRAND and RhoEDC systems
- Respond to data queries in a timely manner
- Report all protocol deviations to the DCC
- Attend monthly study coordinator teleconferences chaired by the DCC

### **22.3 Oversight of Study Procedures**

The walk-PHaSST study coordinator along with the Clinical Investigator will be responsible for insuring that all procedures are performed according to the protocol while adhering to Good Clinical Practice (GCP) guidelines. In order to maintain the integrity of the study, the study coordinator must oversee the following: recruitment, eligibility, informed consent, protocol interventions, data collection and data entry, adverse event reporting, study staff education and communication.

### **22.4 Retention of Documents**

Study documents must be maintained at the research center or a local storage facility for at least seven years following the completion of the study. Study documents that must be retained include all source documentation for information entered into the eCRFs, laboratory reports, IRB approval documentation and related correspondence, signed informed consent forms, and other required regulatory documents. During the course of the study, all participant documents must be maintained in a locked file cabinet and/or locked room to maintain confidentiality. After that time, the sponsor will be notified to establish plans for disposition of records. Because the walk-PHaSST trial is being conducted under an IND (Investigational New Drug Application), it is important to maintain the appropriate Regulatory documents in a separate Regulatory Binder. Each Study Coordinator/Study Investigator will receive one of these binders from the DCC. The binder should be kept in a locked room, preferably the Study Coordinator's or

Clinical Investigator's office. The contents of the binder will include: Updated Form 1572s, curriculum vitae required for 1572 forms, site personnel log, updated protocol and amendments, financial disclosure forms, updated IRB approvals, updated IRB approved consent forms, IRB approval and correspondence, lab reference ranges, drug dispensing records, IND Safety reports, site visit reports and correspondence. Along with monitoring of the source documentation for this study, the contents of this binder will also be monitored so it must be kept updated.

## **22.5 Communication with the Data Coordinating Center (DCC) – Rho**

Interaction with the DCC will be essential during the course of this trial. During the initial months of the study, the DCC will conduct regular conference calls in which all study coordinators from all sites will be required to participate. These calls will serve to answer any questions which arise as well as to inform the study team members of any changes, serious adverse events, or other protocol issues which come up during the study. These calls may lessen in frequency as the study progresses. If at any time outside of a regularly scheduled meeting a study coordinator or any staff member has any questions, he/she may contact the DCC either by telephone and/or email and a response will be sent as soon as possible (ideally with one business day).

It is important not to make any changes to the procedures/instructions in the protocol or Manual of Operations without first contacting the DCC. Any deviation may affect the results of the trial. Standardization and consistency in a multi-center trial is key to the accuracy and reliability of the results.

## **22.6 Availability for Site Visits**

The DCC will provide written confirmation of scheduled visit date(s) and time to the study coordinator and/or study investigator. The availability of the study coordinator will be required during the site visits. The investigator must also be available for at least 30 minutes, late in the day of the scheduled site visit. The pharmacist should also be contacted by the site coordinator and an appropriate time to visit the pharmacy must be established and confirmed. The study coordinator should also ensure the DCC and NHLBI (if in attendance) staff are provided with ample space for monitoring activities. In addition, the study coordinator will need to have essential documents, source documents, patient charts, etc., readily available for the DCC.

## **22.7 Preventing Study Drop-outs**

Subjects enrolled in the walk-PHaSST trial have a burdensome disease (i.e., SCD) and are at increased risk of mortality due to pulmonary hypertension. By participating in this important trial, these individuals offer the scientific community and others who suffer from SCD the opportunity to improve the quality of life. Missing data are a threat to the

integrity of the walk-PHaSST trial and the reasons for missing data will be closely monitored by the MCC, the DSMB, and NHLBI.

Strategies to prevent study drop-outs include:

- Maintain up-to-date contact information for subject and family
- Foster supportive relationships
- Maintain availability via telephone or pager
- Provide reimbursement for transportation, meals, and lost wages (per executed contract with NHLBI)

## **22.8 Scheduling Study Participants**

Clinical sites are responsible for scheduling walk-PHaSST subjects for all required study visits and evaluations. Scheduling of study visits will be unique to each subject and to each clinical site. After a subject has been enrolled into the EDC system, the DCC (via RhoRAND) will issue a study schedule for all follow-up visits for that individual. The study schedule will identify the target appointment dates including a maximum and minimum window of time for a particular subject's follow-up visit. It will be the clinical site's responsibility to schedule the follow-up visits to fall within the appropriate time windows.

## **22.9 Monitoring for Priapism**

CI and Study Coordinators are responsible for monitoring subjects for adverse events. Priapism is an adverse event that requires special attention in this study. Priapism is defined as a sustained painful erection lasting more than 3 hours or intermittent painful unwanted erections lasting less than 3 hours. Males will be monitored for priapism for 6 hours after sildenafil therapy in the catheterization laboratory (for subjects with TRV • 3.0 m/s) **and** in the clinic after the first dose of study drug during the double-blind phase for subjects with TRVs between 2.7 m/s and 2.9 m/s. In addition, all male participants will be monitored in the clinic for priapism after their first dose of sildenafil during the Open-label Follow-up phase.

Males will be specifically monitored for priapism during their study visit interviews. They will be instructed to contact a member of the study team at the onset of any degree of priapism and will be admitted for immediate evaluation and treatment. Each site will have a priapism management plan in place. Possible therapeutic interventions are listed below and will be individualized as clinically appropriate for each episode of priapism. For specific details regarding priapism management, see MOO Chapter 10.

## **23 WEBSITE AND OTHER ELECTRONIC SYSTEM ACCESS**

### **23.1 Overview of website purpose and structure**

The walk-PHaSST website is the central location for all study-specific information including:

- Study announcements
- Study document storage and development (e.g., protocol, consent forms, case report forms, the manual of operations, relevant study articles, meeting presentations, etc.)
- Staff and committee directories
- Meeting agendas and minutes
- Study calendar with important dates and events
- Study status reports (e.g., enrollment status by site)
- Frequently Asked Questions (FAQs)
- Links to study software systems (e.g., Rho*RAND* & Rho*EDC*)

### **23.2 Website and Electronic Systems Access**

All study personnel who need access to the walk-PHaSST website or any of the electronic systems must complete a System Access Request Form located on the Forms page of the website and fax it into the walk-PHaSST website administrator at (919) 287-0128. Study personnel will be notified by e-mail when they have been granted website access.

To log into the website, go to the URL <https://www.rhoworld.com/login>. Enter your username and password and select “Login” then select “Walk-PHaSST” to navigate to the walk-PHaSST Home Page.

#### **23.2.1 System Access Request Form**



6330 Quadrangle Drive | Chapel Hill, NC | 27517

(919) 408-8000 FAX (919) 287-0128

**Fax To: Data Coordinating Center, Walk-PHaSST Study      Attn: Christopher Woods**  
**Fax Number: 919-287-0128**

**System Access Request Form**  
**Project: Pulmonary Hypertension and Sildenafil Therapy**

**CONTACT INFORMATION**

Name: \_\_\_\_\_ Position/Role: \_\_\_\_\_

Email: \_\_\_\_\_ Phone: (\_\_\_\_) \_\_\_\_\_ - \_\_\_\_\_ Fax: (\_\_\_\_) \_\_\_\_\_ - \_\_\_\_\_

Company/Institution: \_\_\_\_\_

Address: \_\_\_\_\_

\_\_\_\_\_

Receive Study Notifications via (circle one):      EMAIL      FAX

In order to access the Pulmonary Hypertension and Sildenafil Therapy website, you must provide a username and password. Your username is your first initial followed by your last name and can be up to 32 characters long. (Examples: Malcom Reed=mreed; Travis Mayweather=tmayweather) Your password **must have eight or more characters** and **must include a numeric digit** somewhere in the middle. Both the **first and last character of the password must be a letter**. (Examples: blue1bird, one2three.)

Print your username here: \_\_\_\_\_

Print your password here: \_\_\_\_\_

Re-print your password: \_\_\_\_\_

Fax this completed form per the fax header above. This secure Rho fax is password protected to prevent unauthorized viewing of documents. For security reasons, please do not email this document back as an attachment.  
**If you have any questions, contact the Rho Help Desk at 1-800-905-0460.**

Web Systems Access (for Content Admin use only)						
√	Web Application	Role		√	Web Application	Role
	RhoNET				RhoEDC	
	RhoRAND				RhoLAB	

**Nondisclosure Obligations:** Receiving party promises and agrees to hold in confidence any Confidential Information and Trade Secrets of Rho, Inc., (Rho) to which Receiving party may become privy either through deliberate disclosure by Rho or through observation or accident. Receiving party further promises and agrees (1) to protect and safeguard such Confidential Information against unauthorized use, publication, or disclosure; (2) not to use any of the Confidential Information except for the Business Purpose agreed to by the Parties; (3) not to reveal, report, or publish, directly or indirectly, or in any way, disclose, transfer or otherwise use any Confidential Information to anyone, including other employees of Receiving Party, unless specifically authorized by Rho; (4) not to use any Confidential Information to unfairly compete or obtain unfair advantage vis-à-vis Rho in any commercial activity; and (5) to comply with any other reasonable security measures requested in writing by Rho. All information on and concerning the RhoNET™ website is considered confidential.

**I hereby agree to all of the above obligations. Signature:** \_\_\_\_\_

**Content Administrator or Project Manager Signature:** \_\_\_\_\_

## **23.3 Website Features**

### **23.3.1 Documents in Development**

The Documents in Development section of the website provides a forum for people to review and edit study documents such as the protocol and manual of operations. Using the check-in/out feature only one person can make edits to a document at a time, thus providing version control.

To access the documents in development section of the website, click on one of the Administration links on the right side of the page (e.g., CRF Design Dev., MOO Development, Protocol Development, etc.). To add a new document select the “Add a New Document” button and fill in all the required information on the next page then hit “Submit.”

To make changes to an already existing document, click on the document title. This will take you to the Check-in/out page. The version on the top of the list is the most current version of the document. To make changes to a document, you must first check it out by clicking the “Check Out” button. This will prevent another person from making changes to the same document at the same time. A pop-up box will appear asking you to provide a reason for the check-out and select a length of time you will have the document (e.g. 1 day, 3 days, or 7 days). Click the View/Download link to save the file to your computer so you can edit it. To check a document back in, click the “Check In” button and attach the file on the check-in page. Once you have checked the document back in, others may now make changes.

## **23.4 Website Troubleshooting**

If you have any problems accessing or navigating the walk-PHaSST website, you may e-mail the website administrator at [christopher\\_woods@rhoworld.com](mailto:christopher_woods@rhoworld.com). In addition, questions may be submitted using the “Submit a Question” feature on the Frequently Asked Questions page.

The Rho Help Desk can be reached at **(800) 905-0460**, Monday thru Friday, 9AM to 6PM Eastern Time. Help desk representatives will be able to immediately reset your password and answer basic questions about the study. If answers are not available in the MOO or in the Frequently Asked Questions section of the website you may contact the Help Desk with questions regarding website issues, Rho*RAND* and Rho*EDC*. The Help Desk is available to answer the questions or direct your call to the appropriate resource for resolution.

## **23.5 Website Access Removal**

Sites are responsible for letting the DCC know when site personnel leave the study. When a user leaves the study and no longer requires website access, a website access removal request form should be completed and faxed to the website administrator who will then remove the user's permissions from the RhoNET website, as well as the Rho*RAND* and Rho*LAB*, and Rho*EDC* software systems. Once all access has been removed an e-mail notification will be sent. The System Access Removal Request form is located on the Forms page of the website.

### **23.5.1 Website Access Removal Form**





6330 Quadrangle Drive | Chapel Hill, NC | 27517

(919) 408-8000 FAX (919) 287-0128

**Fax To: Data Coordinating Center, Walk-PHaSST Study      Attn: Christopher Woods**  
**Fax Number: 919-287-0128**

**System Access Removal Form**  
**Project: Pulmonary Hypertension and Sildenafil Therapy**

**CONTACT INFORMATION**

Name: \_\_\_\_\_ Position/Role: \_\_\_\_\_

Email: \_\_\_\_\_ Phone: (\_\_\_\_) \_\_\_\_\_ - \_\_\_\_\_ Fax: (\_\_\_\_) \_\_\_\_\_ - \_\_\_\_\_

In order to remove your access from the Pulmonary Hypertension and Sildenafil Therapy website, please provide your username and sign the removal statement below. You will receive an e-mail notification once your access has been removed.

Print your username here: \_\_\_\_\_

I request that my access to the walk-PHaSST website and any electronic systems be removed.

**Signature:** \_\_\_\_\_

Fax this completed form per the fax header above.  
**If you have any questions, contact the Rho Help Desk at 1-800-905-0460.**

**Content Administrator or Project Manager Signature:** \_\_\_\_\_

## **24 NUMBERED MEMOS AND MANUAL OF OPERATIONS (MOO) UPDATES**

### **24.1 Purpose and Objectives of Numbered Memos**

The objective of numbered memos is to document and communicate important study information to all investigative sites in a consistent manner.

The numbering of the memos is intended to facilitate reference to the memos, as well as tracking and archiving of the memos.

#### **24.1.1 Scope**

This document covers all numbered memos that are generated by members of the Operations and Executive Committees.

#### **24.1.2 Responsibilities**

##### **24.1.2.1 Operations Committee and Principal Investigators**

- Either the Operations Committee or the Executive Committee may identify issues that require across-site communication/clarification above and beyond discussion during a Study Coordinator or Steering Committee meeting.
- The Operations Committee or Executive Committee will identify an author and reviewer(s) for the memo.
- A PI (either from the Operations Committee or Executive Committee) or designee is responsible for approving the memo. (Approval may be communicated via email from a PI or by signature on a version of the memo itself.)
- The facilitators of the Steering Committee and Study Coordinator Meetings are responsible for including a discussion of each new numbered memo on the agenda for the corresponding meeting.

##### **24.1.2.2 Data Coordinating Center (DCC)**

- The Site Correspondence Manager or designee will be responsible for the email distribution of the numbered memos.
- The Webmaster will store the numbered memo tracking spreadsheet and all numbered memos under “Numbered Memos” on the left margin menu of the walk-PHaSST website homepage.

### **24.1.2.3 Clinical Sites**

- All Clinical Investigators and Study Coordinators are responsible for reviewing each numbered memo. In addition, all other individuals identified in the “TO” or “CC” lines of the memo are responsible for reading the memo (i.e., site pharmacists, echo techs, etc).
- Study Coordinators will ensure that all relevant site staff members are aware of the memo and that all numbered memos are stored in the site’s regulatory binder.

### **24.1.3 *Procedures***

#### **24.1.3.1 Identifying the need for and the owners of a numbered memo**

- DCC. The DCC may issue a numbered memo in order to release a final protocol amendment or Manual of Operations or to alert the clinical sites of an expedited safety report requiring submission to the IRB. Neither of these numbered memos require review and approval from either the Operations or Executive Committees.
- PI. A PI may identify the need for a numbered memo.
- Non-PI. Alternately, anyone involved in the study may suggest the need for a numbered memo to someone on the Operations or Executive Committees (see Staff Directory on the walk-PHaSST website for a complete list of committee members.)
- The request will be brought forward to either Committee for approval.
- The Operations Committee or Executive Committee will consider whether the issue is something that could be communicated sufficiently during Steering Committee and Study Coordinator teleconferences and in the resultant minutes.
- If a memo is not required and the requesting individual is not a member of the Operations Committee, then the individual making the request will be informed of the reasons for the decision.
- If the issue is of enough complexity and importance to require a numbered memo, then the Operations Committee or Executive Committee will identify an author and the reviewers for the memo. Examples of items that may trigger the generation of a numbered memo are 1) establishing a new process for distribution

of study drug or 2) an update to the process for communicating Serious Adverse Events.

- The Site Correspondence Manager will track all aspects of the generation, review, approval, and distribution of the numbered memos.

#### **24.1.3.2 Creating, Reviewing, and Approving a New Numbered Memo**

- Structure of Memo: Memos will be numbered consecutively, starting with #001. The numbered memo will include a standard memo heading with TO, CC, RE, and the date of issuance. It will also contain a “Site Action Required” section in the header. This section is designed to communicate whether the memo requires some action on the part of the site or whether it is being provided for informational purposes only. The body of the memo will provide the details of the information. The Numbered Memo Template is displayed in Figure 24-1.
- The author will identify the required time frame for completion of the numbered memo and will be responsible for managing the production, review and approval process. The author is responsible for confirming that he/she is using the appropriate number for the memo.
- All memos must be approved prior to electronic distribution to the sites. It is not necessary to distribute the signed version of the memo to the sites.
- A copy of the original numbered memo with the PI/designee’s email and signed approval will be kept in the study file at the DCC.

#### **24.1.3.3 Distributing a New Numbered Memo**

- An electronic version of each numbered memo will be emailed to the study coordinator(s), clinical investigators (CIs), and other relevant study personnel, including the walk-PHaSST webmaster. (Note: It is not necessary to email the signed version of the memo.)
- Each memo will also be posted on the website under “Numbered Memos” on the left margin menu of the homepage.

#### **24.1.3.4 Reading and Archiving Numbered Memos**

- The CIs and study coordinators will read each numbered memo.

- Copies of the numbered memos will be stored in each site's regulatory binder or in a separate numbered memo study file or binder.

#### **24.1.3.5 Amending Information in a Numbered Memo**

- If it becomes necessary to correct a numbered memo, a new memo will be distributed with the same memo number and will include a \_Corrected\_Date designation (eg, Memorandum #005\_Corrected\_20JULY2007).
- The nature of the corrections will be identified in the header of the memo.
- If a study decision changes the guidance in a previous numbered memo, a new numbered memo will be issued and will refer to the numbered memo being superseded. This status of the previous numbered memo will be highlighted on the website as well.

**Figure 24-1: Numbered Memo Template**



**MEMORANDUM #xxx**

To:

From: Roberto Machado, MD  
Mark Gladwin, MD  
Principal Investigators, walk-PHaSST

Date:

Re:

Site Action Required:

---

INSERT BODY OF MEMO HERE.

*cc: walk-PHaSST Investigator Binder or Numbered Memo File/Binder  
RhoWebsite  
DCC Numbered Memo File*

## **24.2 Manual of Operations (MOO) Updates**

As the study progresses, the DCC will be responsible for documenting any recommended and approved changes to the MOO. The DCC will incorporate all of approved changes and will update the MOO periodically. When the revisions are final, the MOO will be posted to the study's secure website. All clinical sites will be notified that the MOO has been updated and is on the website via a numbered memo, which will also summarize the changes that were made. Additionally, study coordinators will be reminded of the MOO update during the regularly scheduled monthly teleconference.

The author of an updated MOO chapter will ensure that all necessary changes are captured in the update and that the version date of the updated chapter is adjusted.

The author of the updated MOO chapter will also be responsible for preparing the associated numbered memo that describes the content of the MOO updates.

The DCC Webmaster is responsible for document control of the MOO on the walk-PHaSST website and for filing updates in a timely manner.

Study Coordinators are responsible for on site document control of the MOO and for filing updates in a timely manner.

### **24.2.1 Procedures**

The majority of procedures associated with MOO chapter updates will be handled via the numbered memo procedures. For instance, the need for a MOO chapter update may be identified by anyone in the study. The request will be brought to the Operations Committee for decision and implementation.

A numbered memo will accompany the distribution of updated MOO chapters. The memo will summarize the changes to the chapter and will identify the version date of the updated chapter (this summary will not include typographical error corrections).

As with all numbered memos, study coordinators will ensure local distribution of the memo to study staff along with the updated MOO chapter and that the numbered memo is stored in the site's regulatory binder.

In addition to filing the numbered memo per guidance,

- the Study Coordinator will file the updated chapter in the study binder, remove the outdated chapter from the binder, and file that obsolete version in another file location clearly marked "obsolete."
- the webmaster will post updated MOO chapters on the website within 2 business days of receipt.

## **25 PROCESS TO ADJUDICATE SECONDARY ENDPOINTS**

### **25.1 Purpose**

The purpose of this chapter is to establish a scientifically sound process for evaluating and categorizing the potential secondary endpoints of acute chest syndrome (ACS), clinical deterioration of PH, and right heart failure (RHF).

### **25.2 Scope**

The adjudication process will include potential events that begin a) on or after the date that a subject receives his/her first randomized dose of study medication and b) no later than the date of completion/discontinuation from the double-blind portion of the MIT.

### **25.3 Responsibilities**

#### **25.3.1 *Clinical Sites***

Clinical sites will

- A. record subject data in the EDC, ensuring that all adverse events occurring during the MIT have been reported
- B. use the EDC to flag events that should be included in the adjudication process and provide additional details about these events
- C. ensure that that required information (see Adjudication Information Form, supplemental to the AE form, in the EDC) has been captured for those events flagged for adjudication
- D. if asked, provide additional source documentation necessary to thoroughly evaluate a qualifying event
- E. redact subject names from any requested source documentation prior to sending it to the DCC

#### **25.3.2 *Data Coordinating Center (DCC)***

The DCC will

- A. prepare a plan for electronically evaluating the clinical database to identify potential secondary endpoints to be adjudicated. The plan will include an identification of the relevant EDC fields and specification of any algorithms that will be required
- B. prepare masked Potential Event Reports that list all relevant EDC fields and distribute the report to the reviewers
- C. add relevant data fields to the EDC to enable reporting of potential events; these Potential Event Reports will differ in content depending on the type of



event being considered (ie, clinical deterioration of PH vs. RHF vs. ACS; see Attachment A for a draft SAMPLE form.)

- D. gather additional clinical information from the sites, when necessary, and redact any patient identifying information prior to distributing it to the adjudication panel
- E. create a form (likely to be EDC form) to capture reviews from individual panel members as well as the group adjudication decision, when necessary
- F. provide a mechanism to track each potential event from identification through the recording of the adjudicated decision in the clinical database
- G. maintain the adjudication tracking tool
- H. provide a mechanism for sending chest radiographs to the Central Radiographer, as needed
- I. provide summary reports of adjudication progress, and coordinate the data review according to a pre-established schedule
- J. analyze the adjudicated secondary endpoints based on protocol and Statistical Analysis Plan specifications

### **25.3.3            *Secondary Endpoint Adjudication Panel***

The Adjudication Panel will

- A. review the DCC plan to identify potential events via a pilot test of the process and reports
- B. participate in 1 or more masked data reviews to categorize potential secondary endpoints
- C. provide decision via paper form or the EDC

### **25.3.4            *Central Radiographer***

If requested by the adjudication panel, the Central Radiographer will review the chest radiographs and will complete the Central Radiographer review form. The form will clarify the presence/absence of infiltrates, location and extent of consolidation and presence/absence of pulmonary edema.

## **25.4                *Identifying Potential Events***

The clinical site will use the EDC to flag AEs that should be evaluated by the adjudication team as potential ACS, RHF, or Clinical Deterioration of PH. For each flagged potential ACS or RHF, the site will complete a supplemental adjudication form that captures information about associated signs, symptoms, and treatments. The DCC may also identify some additional fields in the database that would trigger a site query to ask if a non-flagged AE should be considered for evaluation.

The DCC will generate a computer algorithm to aid in the identification of potential Clinical Deterioration of PH from within the EDC data.

All potential events will be evaluated by the adjudication panel to determine which events qualify as secondary outcomes.

## **25.5 Clinical Considerations**

### **25.5.1 *Clinical Deterioration of PH (Time to)***

In order to determine clinical deterioration of PH, the adjudication panel will evaluate the subject if the site flags an AE as a potential Clinical Deterioration of PH **OR** if either of the following conditions is true:

- 20% decrease in six-minute walk distance, on two successive evaluations taken at least 2 weeks apart while not in VOC (and not impaired by a non-PH related event, such as a sprained ankle), plus deterioration in NYHA/WHO functional class
- Initiation of additional PH specific therapy, that is, prostanoid analogue, endothelin receptor antagonist or PDE 5 inhibitor

Time to Clinical Deterioration of PH will be defined as the number of days from first dose of study drug to the earliest of a) the date of the second 6 minute walk that represents the 20% decrease OR b) the date of initiation of additional PH therapy.

### **25.5.2 *Acute Chest Syndrome***

The adjudication panel will **consider** the following signs/symptoms to determine whether or not a potential event is an acute chest syndrome:

#### Signs/Symptoms:

- Chest pain
- Cough
- Wheezing
- Rales
- Temperature  $\geq 38.5^{\circ}\text{C}$  Tachypnea (per age-adjusted normal)
- Intercostal retractions, nasal flaring, or use of accessory muscles of respiration
- $>2\%$  decrease in  $\text{SpO}_2$  ( $\text{O}_2$  saturation) from a documented steady-state value in room air
- $\text{PaO}_2 < 60$  mmHg (if available)
- Radiographic evidence of consolidation [A new\* segmental radiographic pulmonary infiltrate (involving at least 1 complete segment)]
- Cardiac enzymes
- BNP value
- Administration of transfusion
- Mechanical ventilatory support

The following assessments are required for each potential ACS:

- Evaluation of signs and symptoms
- Vital signs
- Chest radiograph
- Pulse oxymetry

### **25.5.3      *Right Heart Failure***

The adjudication panel will consider the following signs/symptoms/test results and therapeutic administrations to determine whether or not a potential event is a right heart failure:

Signs/Symptoms:

- Shortness of breath
- Swelling of feet and/or ankles
- Fatigue
- Fainting
- Abnormal heart sounds (including murmurs)
- Abnormal lung sounds (including rales)
- Irregular or rapid heartbeat
- Weight gain
- Abdominal distension
- Distended neck veins
- Enlarged liver
- Ascites
- PaO<sub>2</sub> <60 mmHg (if available)

Drug/therapy administrations:

- Diuretics
- inotropic agents
- oral nitrates
- implanted device (i.e., pacemaker, defibrillator)

Drug/therapy results:

- Did drug/therapy result in symptomatic improvement?
- Did drug/therapy result in weight loss?

The following assessments are required for each potential RHF:

- Evaluation of signs and symptoms
- Vital signs
- Chest radiograph
- Pulse oxymetry

## 25.6 Tenets of the Adjudication Process

- A. Clinical investigators should use the special adjudication request field on the AE form to flag ANY adverse events that could potentially be considered a Clinical Deterioration of PH, an ACS, or RHF, even if the physician does not use one of these terms in his/her diagnosis.
- B. The adjudication panel will consist of a minimum of 6 members. This membership should remain as consistent as possible throughout the adjudication phase of the trial.
- C. The panel will include at least 2 cardiologists, 2 pulmonologists, and 2 hematologists/sickle cell experts
- D. Chest radiographs of potential ACS events will be reviewed by the Central Radiographer, if requested by the panel.
- E. The DCC will report potential events to the adjudication panel in a treatment masked manner.
- F. Adjudication panel members may be walk-PHaSST clinical investigators. However, no panel member may evaluate his/her own subjects' potential events as part of the adjudication panel.
- G. To begin, 3 panel clinicians will independently review each event and record their yes/no decisions.
  - Each potential ACS event must be reviewed by at least 1 pulmonologist and 1 sickle cell disease expert
  - Each potential RHF must be reviewed by at least 1 cardiologist or pulmonologist and 1 sickle cell disease expert
  - Each potential clinical deterioration of PH must be reviewed by at least 1 pulmonologist and 1 sickle cell disease expert
- H. An event will be deemed a qualifying endpoint if 2 of the 3 reviewers deem it as such. However, if any of the reviewers believes that the event is worthy of a full panel review, then it will be reviewed by all available panel members who are not affiliated with the subject being reviewed. The majority vote will determine the classification of the event.
- I. To be categorized as one of the secondary endpoints, each event requires agreement between 2 of the 3 independent reviewers **OR** discussion and adjudication by the full panel.
- J. There will be a final quality control (QC) re-review of a select set of events to confirm consistency of evaluation. Additional actions of the committee may be required, based on the results of that QC review

## **25.7 Timing of the Review Process**

Potential event reports will be sent to the initial reviewers on an approximately monthly schedule. This schedule will be reevaluated and modified (if necessary) after the review process has proceeded for several months.

Full panel reviews will occur up to twice annually. An effort will be made to schedule at least 1 review per year to occur in conjunction with a face to face walk-PHaSST meeting.

Potential events will be reviewed only after that patient's participation in the MIT has ended.