iDEF

Intracerebral Hemorrhage Deferoxamine Trial

INTRACEREBRAL HEMORRHAGE DEFEROXAMINE TRIAL

FUTILITY STUDY OF DEFEROXAMINE MESYLATE IN INTRACEREBRAL HEMORRHAGE

MANUAL OF PROCEDURES

Version 4

22 January 2015

Supported by:

The National Institute of Neurological Disorders and Stroke (NINDS)

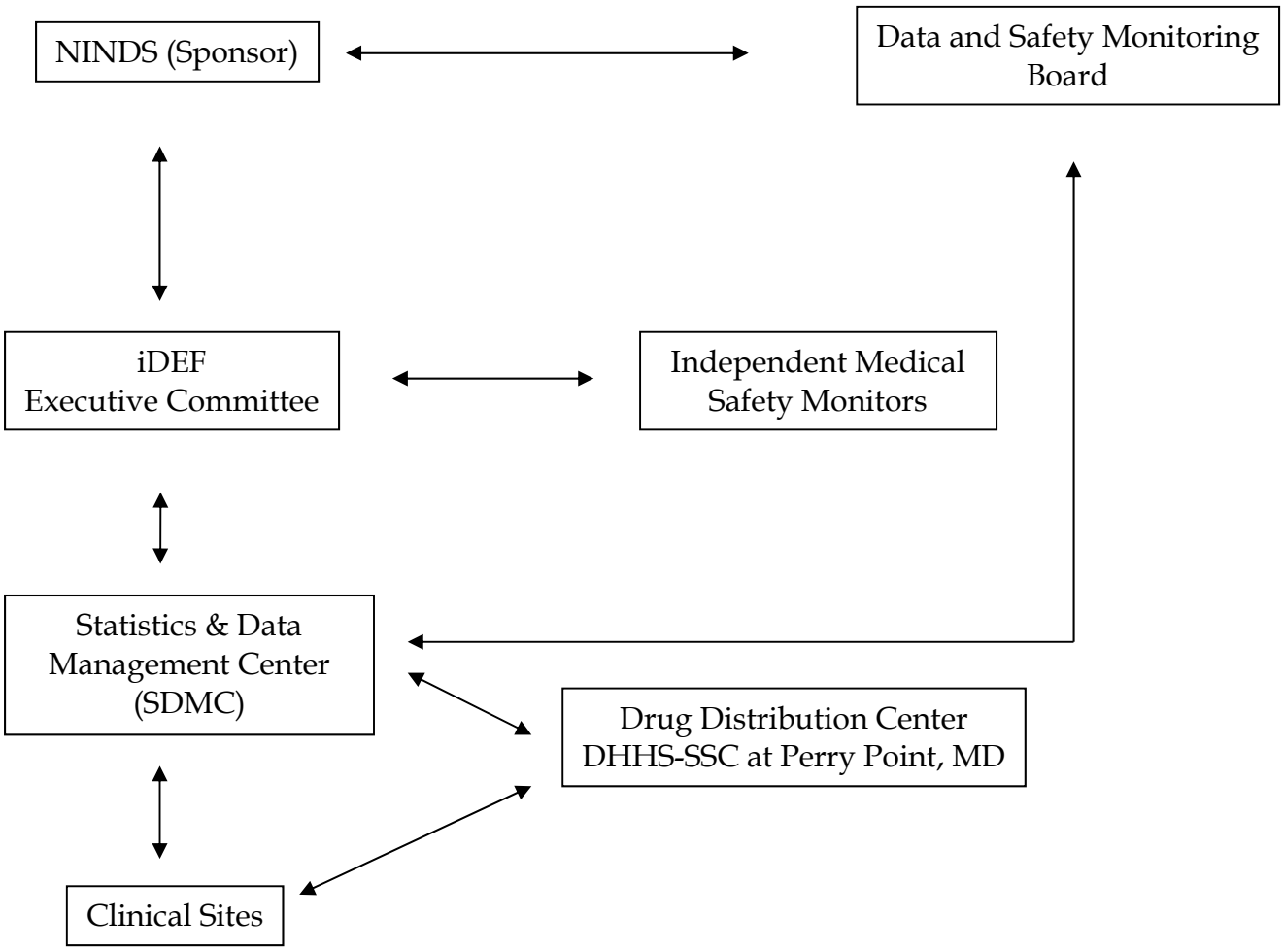
(U01 NS074425)

Contents

1 STUDY ORGANIZATION AND CONTACTS

1.1 STUDY ORGANIZATION

iDEF TRIAL ORGANIZATIONAL CHART



The iDEF Trial is a Phase II multi-center study involving sites from the United States and Canada for subject recruitment. The Trial's Study Chair (Principal Investigator) is Magdy Selim, MD, PhD, located in Beth Israel Deaconess Medical Center, Boston, MA. The Statistics and Data Management Center (SDMC) is the Data Coordination Unit at the Medical University of South Carolina. The Executive Committee, the NINDS-

appointed Data and Safety Monitoring Board (DSMB), and the Medical Safety Monitors (MSMs) will provide oversight and monitoring of the study subjects' safety and the trial's progress. The figure above outlines the infrastructure of the study.

Executive Committee

The Executive Committee consists of Magdy Selim, MD, PhD (the study Principal Investigator and Chair), Sharon Yeatts, PhD (Biostatistician and Principal Investigator of the Statistics and Data Management Center [SDMC]); Yuko Palesch, PhD (Biostatistician); Lydia Foster (Biostatistician), Aaron Perlmutter (Project Manager), Jessica Simons (StrokeNet Project Manager), Claudia Moy, PhD (NINDS-appointed liaison); Catherine Dillon, CCRP (Supervisory Data Manager); and Andre Thornhill (Data Manager). The Advisory Committee members, Drs. Daniel Hanley, Steven Greenberg, Lewis Morgenstern, and Guohua Xi are also expected to participate in the Executive Committee teleconferences, as needed.

The Committee will be responsible for the development and amendment of study documents (including the protocol, case report forms (CRFs), and Manual of Procedures); collection, review and oversight of the dissemination of serious adverse events (SAEs) and acute respiratory distress syndrome (ARDS) occurrences and other important events pertinent to the study; and, communication among all components of the study administrative organizations.

Data Coordination Unit (DCU) and Statistics and Data Management Center (SDMC)

The Data Coordination Unit (DCU), located in the Department of Public Health Sciences at the Medical University of South Carolina, will serve as the Statistics and Data Management Center (SDMC) with responsibility for data processing and management of data obtained from all sites, statistical analyses, generation and distribution of progress reports, and reports to the Data and Safety Monitoring Board. The SDMC also contains the Project Management team for the study, and will be responsible for the collection of all documents required by federal regulation and/or Good Clinical Practice Guidelines and for site monitoring on an ongoing basis.

Data and Safety Monitoring Board (DSMB)

The DSMB is appointed by the Director of NINDS and managed by the NINDS Clinical Trials group. It is comprised of Neurologists with special expertise in stroke and ICH, a hematologist, a critical care pulmonologist, and a statistician. Its responsibility will be the oversight of participant safety, review of the safety reports, requesting additional data/information (if necessary), and advising the NINDS regarding continuation/discontinuation of the study. Peter Gilbert, Sc.M. serves as the NINDS-appointed liaison for the DSMB.

Independent Medical Safety Monitors (MSMs)

The independent Medical Safety Monitors are responsible for monitoring the study with regard to safety on an ongoing basis and reviewing all serious adverse events and cases of respiratory compromise quickly to identify any safety concerns. The MSMs will determine whether events are serious, related to study drug administration, and expected. Due to concerns about respiratory compromise and specifically ARDS, the MSMs will also have a review step in which they determine if the event is ARDS. They will communicate with the investigators by way of the Project Manager for any questions or clarifications regarding an event. Robert Balk, MD and Thomas Bleck, MD will serve as the MSMs for the study.

Clinical Centers

Study participants will be recruited and enrolled at more than 20 clinical centers in the United States and Canada.

1.2 STUDY CONTACTS

Principal Investigator/Study Chair Office, Boston, MA

Role	Name	Address/Fax	Telephone	E-mail
Study Chair	Magdy Selim, MD, PhD	Beth Israel Deaconess Medical Center 330 Brookline Ave. Palmer Bldg – Room 127 Boston, MA 02215 FAX 617-632-8920	617-632-8913	mselim@bidmc.harvard.edu
Study Coordinator	Caroline Feigert, MS		617-632-8919	cfeigert@bidmc.harvard.edu
Senior Research Administrator	Sabrina Heisey	Beth Israel Deaconess Medical Center 330 Brookline Ave. CLS 948 Boston, MA 02215 FAX 617-735-4095	617-735-4094	sheisey@bidmc.harvard.edu

Data Coordination Unit (DCU/SDMC), Charleston, SC

Role	Name	Address/Fax	Telephone	E-mail
Study Statistician and Principal Investigator of the SDMC	Sharon Yeatts, PhD	Data Coordination Unit Department of Public Health Sciences 135 Cannon Street, Ste. 303 MSC 835 Charleston, SC 29425-0835 FAX 843-876-1923	843-513-9085	yeatts@musc.edu
Co-Investigator	Yuko Y. Palesch, PhD		843-876-1917	paleschy@musc.edu
Project Manager	Aaron Perlmutter		843-876-1261	perlmutt@musc.edu
StrokeNet Project Manager	Jessica Simons		843-792-1677	simonsjl@musc.edu
Supervisory Data Manager	Catherine Dillon		843-876-1942	rileycp@musc.edu
Data Manager	Andre Thornhill		843-876-1914	thornhil@musc.edu

NINDS				
Role	Name	Address	Telephone	E-mail
Program Officer	Claudia S. Moy, PhD	Neuroscience Center, Rm 2214 6001 Executive Blvd., MSC 9520 Bethesda, MD 20892	301-496-2789	moyc@ninds.nih.gov
Program Director	Scott Janis, PhD		301-496-9135	janiss@ninds.nih.gov
DSMB Liaison	Peter Gilbert, ScM		301-496-0870	gilbertp@ninds.nih.gov

2 PROTOCOL

Please see most current version of the iDEF Protocol posted on the iDEF WebDCU™ website.

3 SCREENING AND ENROLLMENT

3.1 GENERAL INFORMATION

Study subjects will be recruited from patients seen at the emergency departments (ED) or inpatient services. The majority of patients are expected to be recruited upon initial evaluation in the ED. Therefore, the ED staff, members of the stroke team, and Neurology/Neurosurgery residents should be made aware of this study and in-serviced about its protocol to facilitate recruitment. It is expected that the stroke team and study coordinator (or other designated members of the study staff) will be informed about all patients who present to the ED with ICH, as confirmed by CT; and, that these patients will be reviewed by appropriate members of the study staff as quickly as possible to determine eligibility for participation in the study. All participating sites have an acute stroke response team, and it is expected that potentially eligible candidates will be examined and interviewed within 60-90 minutes of their arrival to the ED. The subjects will be recruited under the responsibility of the principal investigator and sub-investigators at each site. Patients with a diagnosis of spontaneous ICH, as confirmed by CT scan, presenting within 24 hours from symptom-onset will be considered for enrollment into the study, if all other eligibility criteria are met, and the subject does not fall within any of the exclusion criteria. The ICH onset time will be determined from the time the patient was last known to be without presenting deficits. All patients or their legal representative or family member will be required to sign a written informed consent to fulfill the criteria for inclusion in the study.

3.2 SCREENING

In addition to being screened for participation in the study and assessed for inclusion and exclusion criteria, potential subjects will have data collected for the following assessments:
1) Review of Inclusion/Exclusion criteria; 2) Medical history; 3) Review of prior medications; 4) Collect demographic information; 5) Visual and auditory assessment; 6) Neurological examination, including NIHSS and GCS; 7) Vital signs: temperature, heart rate, blood pressure, and respiratory rate; and body weight and

height; 8) Determining the ICH score; and 8) Assessment of baseline functional status [modified Rankin Scale (mRS) score] before ICH onset.

The following laboratory assessments should be conducted at this time:
1) Laboratory tests including hematology, serum chemistries, coagulation parameters, kidney and liver function tests, serum albumin, and urine analysis.
2) CT Scan. A pre-treatment plain (non-enhanced) brain CT confirming the presence of ICH is required to establish the diagnosis of ICH. The head CT should be reviewed by a Radiologist or a stroke-trained Neurologist experienced in the interpretation of CT scans. The need for additional diagnostic tests, such as CTA, conventional angiogram, or MRI/MRA to eliminate secondary causes of ICH in suspected cases will be based on the judgment of the investigators according to the standards of clinical practice at each participating institution and the guidelines from the Stroke Council of the American Heart Association.
3) Pregnancy test, if indicated. A negative pregnancy test will be required for all women of childbearing potential.
4) Chest x-ray. A chest x-ray must be performed before enrollment to exclude pulmonary edema or bilateral infiltrates.

The chest x-ray, CT scan, and results of the routine blood work done at screening should be carefully reviewed as they are needed to determine eligibility (see Section 4 of the Protocol).

For each of the assessments listed above, there is a corresponding Case Report Form (CRF) or a field within a CRF. Each CRF is presented and discussed in detail in Section 6.5 of this MOP.

The investigators at each site will be required to maintain a screening log for ICH patients who are found ineligible to participate in the study or those who are enrolled into another research study, documenting the patients' age, demographics, and the primary reason for exclusion from the study. Please see Section 6.5 – Screen Failure Log for detailed information.

3.3 OBTAINING INFORMED CONSENT

Upon confirmation of patient's eligibility based on the initial screening evaluation above, an informed consent will be obtained. In accordance with US FDA regulations (21 CFR 50) and ICH-GCP Consolidated Guidelines, a written, signed, dated, witnessed, IRB/REB-approved, informed consent is required from all subjects, their legal representative, or family member (as defined in 21CFR50.3(m)) (legal representative and family members are also referred to as surrogates in this protocol) prior to participating in this study. At the initial contact with a potential candidate, the investigator(s) should provide a comprehensive explanation of the purpose, procedures, possible risks/benefits of the study in language that is understandable to a non-medically trained person; as well as, a participant's responsibilities and the fact that his/her participation is voluntary; that he/she may withdraw from the study at any time, and that the decision not to participate or to withdraw will not affect the subject's care in any way. Potential participants or their surrogates should be given ample opportunity to read the document, and to ask questions and to consider their decision. If the subject or the surrogate on behalf of the subject expresses a sustained interest, a signed and dated written informed consent will be obtained. Patients with a known history of dementia should be excluded from self-consent, thereby

minimizing the possibility of invalid informed consent. A copy of the consent form must be given to the participant or the surrogate, and another copy placed in his/her medical record.

The informed consent must be obtained by either the clinical site PI or other members of the study team who are qualified to perform this task and whose names are listed on the Delegation of Authority Log and on the most current FDA Form 1572 submitted in WebDCU™.

Prior to submitting the informed consent documents to a site's IRB/REB, the documents must be sent to the Study Chairman, Magdy Selim, MD, PhD, for review and approval. If a need arises to amend the informed consent at a clinical site (due to local issues) or at all clinical sites due to study-wide modifications/clarifications (e.g., protocol amendment), the clinical sites must follow the same process and submit the proposed amended informed consent documents to Magdy Selim, MD, PhD before submission to their respective IRB/REBs. Following review and approval by the Study Chairman, the site follows the procedures at that site for obtaining IRB/REB approval. Once IRB/REB approval is obtained, the clinical site staff must submit the new informed consent document to the SDMC using the WebDCU™ iDEF Regulatory Document module. It is the responsibility of each clinical site to maintain and use the up-to-date IRB/REB-approved informed consent form for its subjects.

3.4 SAMPLE INFORMED CONSENT

Please refer to the sample ICFs posted in WebDCU™.

3.5 SUBJECT ENROLLMENT AND RANDOMIZATION

Once informed consent is obtained for eligible subjects, the study team member evaluating the subject will be required to log on to the WebDCU™ study database to complete the Subject Enrollment Form, Inclusion/Exclusion CRF (Form 1), the NIHSS (Form 43), the Glasgow Coma Scale (GCS) CRF (Form 6) for the Screening assessment, and the Randomization CRF (Form 2). The WebDCU™ study database will generate a three-digit study subject ID and a four-digit randomization code following successful submission of these CRFs (see section 6.5). The investigator will then be required to provide the site's pharmacy with the final Randomization CRF containing the Randomization Code, or a template developed by the individual clinical site.

4 CLINICAL, LABORATORY, AND RADIOLOGICAL MANAGEMENT

4.1 CLINICAL AND LABORATORY MANAGEMENT

4.1.1 SCREENING

Clinical, laboratory, and radiological assessments are carried out upon screening of potential study subjects and through the course of the study. The assessments carried out at screening are outlined in Section 3.2 of this MOP, and the corresponding CRFs are discussed in Section 6.5 of this MOP.

4.1.2 BASELINE

Subjects who meet eligibility criteria upon initial screening will be reassessed immediately prior to the start of study drug administration to confirm clinical stability and continued eligibility. This assessment will include the NIHSS and GCS to obtain pre-treatment baseline scores. Blood samples for the blood repository (please refer to the Blood Banking Repository Manual in the Project Document Section of the Project Setup component of the iDEF WebDCU™ website) should also be collected prior to the start of the study drug infusion in subjects who agree to participate in this sub-study.

Patients who exhibit significant clinical or neurological deterioration (i.e. develop fixed dilated pupils or GCS decreases to ≤6) prior to administration of the first dose of the study drug should not receive the study drug and will be excluded from the study. Patients who fall into this category, or for some other reason do not receive study drug, are post-randomization screen failures. All available Screening and Baseline CRFs (including the Treatment Confirmation form, which must be submitted within 24 hours of randomization), and the End of Study form should be submitted into iDEF WebDCU™ database for post-randomization screen failures.

4.1.3 STUDY DRUG ADMINISTRATION

After the start of the study drug infusion, the following data should be collected for entry into the WebDCU™ study database: 1) The Study Drug Administration CRF (Form 19), which details the start/stop dates & times of the infusions, the infusion rate and reason(s) for any interruptions, rate changes, or premature discontinuation of the study drug; and whether actual vs. estimated weight is used for the initial dose calculation. The Study Drug Administration Form is a log completed from start of the initial study drug infusion through the end of the final study drug infusion. Please see Section 6.5 – Form 19: Study Drug Administration - for more detailed information. 2) Safety Monitoring data; 3) Concomitant Medications; 4) Concomitant Non-Drug Therapies; and 6) Adverse Events, if any (Serious Adverse Events and respiratory compromise of any cause should be entered into WebDCU ™ within 24 hours of first awareness).

4.1.4 PRIOR TO INFUSION 2 THROUGH 24 HOURS POST LAST INFUSION

Prior to the start of Infusion 2 (from the end of Infusion 1 to the start of Infusion 2), the following assessments must be performed: 1) General physical examination; 2) Visual and auditory assessment; 3) Neurological examination, including NIHSS and GCS; and 4) Vital signs; 5) safety monitoring for adverse events. Urinary output should be recorded every 24 hours.

Prior to the start of Infusion 3 (from the end of Infusion 2 to the start of Infusion 3), the same assessments must be performed: 1) General physical examination; 2) Visual and auditory assessment; 3) Neurological examination, including NIHSS and GCS; and 4) Vital signs; 5) safety monitoring for adverse events. Urinary output should be recorded every 24 hours.

At 24 hours (+/- 6 hours) after completion of the last infusion of study drug, the following assessments must be performed: 1) General physical examination; 2) Visual and auditory assessment; 3) Neurological examination, including NIHSS and GCS; and 4) Vital signs; 5) safety monitoring for adverse events. In addition, the following laboratory studies should be collected: hematology, serum chemistry, coagulation parameters, liver and kidney function tests, and urine analysis. A plain head CT scan should be repeated at the same time point(s). Blood samples for the blood banking repository (please refer to the Blood Banking Repository Manual) should also be collected at this time from subjects who agreed to participate in this sub-study.

Note: If the second infusion is not administered, the "Prior Infusion 2" visit should not be conducted. The next visit to perform would be the "24 Hour Post Last Infusion" visit. Similarly, if the third infusion is not administered, the "Prior Infusion 3" visit should be bypassed for the "24 Hour Post Last Infusion" visit.

4.1.5 DAY 7 or DISCHARGE

The following assessments should occur at Day 7 (+/- 6 hours) or Discharge, (whichever comes first): 1) Vital signs; 2) Visual and auditory assessment; 3) Neurological examination, including NIHSS and GCS; 4) mRS; and 5) Assessment of cognitive functions, using Montreal Cognitive Assessment (MoCA); and 6) any data on Concomitant Medications. During hospitalization, the NIHSS and GCS will be done any time a subject's neurological status deteriorates, or whenever the investigator believes it is prudent to do an assessment.

Concomitant Non-Drug Therapies should be collected through discharge.

4.1.6 DAY 30

At Day 30 (+/- 7 days), the following data should be collected in person: 1) General physical examination; 2) Visual and auditory assessment; 3) Neurological examination, including NIHSS; 4) Functional assessment, using mRS and Stroke Impact Scale-16; 4) MoCA; 5) any data on Concomitant Medications and Concomitant Non-Drug Therapies; and 6) Serious Adverse Events.

4.1.7 DAY 60

The Day 60 (+/- 7 days) visit, which will be completed via telephone, is comprised of functional assessment, using mRS; any data on Concomitant Medications and Concomitant Non-Drug Therapies; and, Serious Adverse Events.

4.1.8 DAY 90

At day 90 (+/- 7 days), the following data should be collected in person: 1) General physical examination; 2) Visual and auditory assessment; 3) Neurological examination, including NIHSS; 4) Functional assessments

including mRS and Stroke Impact Scale-16; 5) Assessment of cognitive functions, using Montreal Cognitive Assessment (MoCA); 6) Any data on Concomitant Medications and Concomitant Non-Drug Therapies; and, 7) Serious Adverse Events.

4.1.9 DAY 180

At day 180 (+/- 7 days), a functional assessment will be performed via telephone to obtain a score on the mRS.

4.1.10 OTHER INFORMATION

Laboratory assessments and CT Scans, beyond those required for the study, should be done whenever clinically indicated, and the data recorded on the appropriate CRF.

Study team members certified in NIHSS and mRS and experienced in administering GCS, SIS-16, and MoCA scales should perform the assessments at all time points. Data on the subject's functional status (mRS and SIS-16) may be obtained from a proxy in the event that the subject is unable to provide the information.

4.2 RADIOLOGICAL ASSESSMENTS

The diagnosis of ICH will be based on clinical and radiological findings. A baseline pre-treatment non-enhanced brain CT confirming the presence of ICH is required to establish the diagnosis of ICH. The need for additional diagnostic tests, such as CTA, MRI/MRA, or a conventional angiogram to rule out secondary causes of ICH in suspected cases should be based on the judgment of the investigators according to the standards of clinical practice at each participating institution and the guidelines from the American Stroke Association.

The CT scan must be reviewed by a member of the study team experienced in interpretation of CT scans before completing the Eligibility (Inclusion/Exclusion) and Randomization CRFs in WebDCU™ to determine the following: 1) The presence of ICH; 2) The location of ICH; 3) The presence vs. absence of intraventricular hemorrhage; and, 4) The volume of ICH using the ABC/2 method (please refer to Appendix IV of the protocol or Section 6.5 Form 01: Randomization for instructions).

A baseline chest x-ray confirming the absence of bilateral pulmonary infiltrates or pulmonary edema is required before considering the subject for enrollment into the study. A repeat chest x-ray is required in intubated patients whenever the PaO2/FiO2 ratio is <300.

A repeat non-enhanced brain CT scan should be obtained within 24(+/-6) hours after completion of the last infusion, with the same standard imaging protocols and scanner at a given hospital. Additional CT scans, beyond those required for the study, should be done whenever clinically indicated.

All brain and vascular imaging data from screening to day 90 must be stored on compact discs (CD), coded by the subject's study ID number, and sent to the central imaging laboratory for computerized volumetric measurements by blinded operators. The CDs will be sent via express carrier within 10 days of the completion

of the Day 7/Discharge visit and within 10 days of the Day 90 visit to the central imaging laboratory at the following address:

Magdy Selim, MD, PhD
C/O: Caroline Feigert
Beth Israel Deaconess Medical Center
Dept. of Neurology – Stroke Division
330 Brookline Avenue
Palmer 127
Boston, MA 02215

The data must be entered on the imaging CRF in WebDCU™, and the shipping date must be entered in the CT Scan Shipping interface so that the WebDCU™-generated packing slip can be included with the shipment.

Please refer to the iDEF Imaging Acquisition and Transmission Procedures Manual (Imaging MOP) in the Project Document Section of the Project Setup component of the iDEF WebDCU™ website.

5 DATA COLLECTION AND MANAGEMENT

5.1 GENERAL OVERVIEW

The data collection and management will be conducted according to the process outlined below. The study database was developed in Microsoft SQL Server and allows for a web-based data entry and management. Data are entered at the Clinical Sites and then managed (including data clarification) using a secured study website by the SDMC. During the design of the database, automated consistency checks and validation rules were prepared to check for potential data errors, including missing required data, data out of pre-specified range, data conflicts and disparities within and among worksheets. All validation rules are outlined in the Data Management Plan, which will be prepared by the SDMC.

5.2 WEBDCU™ DATA COLLECTION

The SDMC has established a steadfast infrastructure for web-based data capture and data sharing, including designated web servers and supporting database servers. User-friendly web-based database systems have been developed, validated and used by the SDMC for several clinical trials for on-line subject registration, randomization, data entry, data validation, project progress monitoring, data processing, progress monitoring, user customizable report generation, secure data transfer and coordination of study medication packing, delivering, and acceptance.

Data are directly single-data entered into the database by the Clinical Site staff via a secure internet connection. Secure Socket Layer (SSL) is used for data encryption. Data rules are pre-programmed into the system for automatic data checks. Automatic notifications of rule violations (i.e., out of range values, inclusion deviation, dates) are displayed on the data entry screen for quick and efficient resolution at the site. Although this

requires intense programming in the initial stages of the study, the overall efficiency of being able to resolve data queries at the data entry phase and at the site level with a full audit trail proves to be a valuable system.

All violations require resolution or explanation prior to data submission to the central database. Once data are submitted by the Clinical Site, the Data Manager at the SDMC runs additional cross panel checking and if necessary generates a data clarification request (DCR) to resolve discrepant data. Additionally, monitors may generate DCRs when they find discrepancies between source documentation and the database. Notifications of outstanding queries appear on the screen when the relevant user logs into the system. This notification process facilitates timely response to queries.

The WebDCU™ system combines all study tools into one system that includes the study database, subject calendar, electronic DCR process, case report form and participant tracking system, audit trail, and report generation mechanisms. The reporting mechanism allows the PI to access real-time data that have been entered into the system and validated. In addition the user can retrieve enrollment status, basic demographics and data summaries, such as number of visits completed, number of resolved queries and outstanding queries. Summaries can be broken down by Clinical Site, subject and date. In addition, authorized users can access safety reports containing lists of adverse events.

The most critical part to the success of the WebDCU™ system is the training of the users. All users are trained by the SDMC staff in utilizing the web-based system. The importance of using the system on a regular basis is stressed as it relates to the timeliness of data reporting. Each Clinical Site's use of the system is monitored by the Data Manager. Clinical Sites that are not timely are notified by email, and when necessary, corrective action is taken by the Trial PI. The web system offers speed and efficiency for study conduct while accommodating the field monitors.

6 CRF GUIDELINES

6.1 GENERAL INFORMATION

Worksheets have been developed by the SDMC with input from the Executive Committee. An electronic PDF version of the casebook and individual worksheets are available on WebDCU™ for capturing study data. Since the case book is based upon the data collection schedule defined in the protocol, it is recommended that the clinical sites use these worksheets for data collection. This is not a requirement, provided other source documentation is used in its place.

It is recommended that you print the worksheets, as needed, directly from WebDCU™. **The most current versions of the worksheets will always be posted there.** If any change is made to the study book during the conduct of the study, you will be notified via WebDCU™ and the current version will be posted on the website. For this reason, the study sites may find it practical to print study books as needed.

6.2 CRF COLLECTION SCHEDULE

The CRF collection schedule in WebDCU™ shows the time frame for collection of data for each CRF included in the study. The "Required" (X) in the column for a study visit indicates that data for the CRF identified in

the corresponding row must be collected at that time. Forms that are designated as "Optional" (O) should be completed anytime those data need to be collected, either as required by the study protocol or as per standard care. CRFs marked as "Repeatable" (R) may be used as many times as needed for the indicated time point. CRFs requiring monitor verification will be marked as (M).

There may be changes to the CRF Collection Schedule. You should always refer to the Data Collection Schedule in the protocol most recently approved by your IRB/REB. That Data Collection Schedule will dictate the data you are responsible for collecting and entering into the WebDCU™.

6.3 GENERAL INSTRUCTIONS FOR COMPLETION OF WORKSHEETS

The following section contains general guidelines for the completion of iDEF CRFs:

- Paper worksheets are not required and are not recommended if alternate source documentation exists. If the paper worksheet is the first place the data is recorded, it is source documentation, and thus should be signed and dated by the person collecting the data, and retained as specified by Good Clinical Practice Guidelines.
- eCRFs should be completed utilizing documentation from the legal medical record or other source data whether it is paper or electronic.
- Missing data are not acceptable, except as allowed by a skip pattern. However, if the data value is unknown and permanently unavailable, leave it blank and dismiss the warning.
- If a CRF was not collected or when there is no information to include in the CRF, check 'no' for 'Data Collected' in the header of the CRF.
- If a numerical data item is unknown or missing, leave it blank. Do not enter 0 (zero).
- Circles or radio buttons O indicate that you must choose only one answer.
- Boxes □ indicate that you should 'check all that apply'.
- Use the following format for all date fields: DD-MMM-YYYY (e.g., 31-JAN-2010)
- Complete dates should be entered, whenever possible, for all date fields. If the complete date is not known, partial dates are allowed for select data points.
- When multiple valid sources for a data item are available, such as heart rate from pulse oximetry and cardiac monitoring, then either: (1) All available data values must be used, such as for the maximum and minimum SBP readings within the hour; (2) a decision must be documented regarding which values will be used consistently and why; or (3) a decision must be documented regarding why one value or a set of values was chosen for a particular subject. Ultimately, it is up to the site PI to

determine the most valid source for data items to be used for subjects enrolled at his/her site when multiple valid values exist.

6.4 DATA ENTRY TIMELINES

Data required to be collected must be entered and submitted into WebDCU according to the timeline below:

Visit/Event	**Timeline for Submitting Data into WebDCU™**
Screen Failure Log	10th of the following month
Subject Enrollment, Eligibility Form, Glasgow Comma Scale and NIHSS scores, and Randomization Form	Prior to randomization
Treatment Confirmation Form	Within 24 hours of randomization
SAEs and respiratory compromise	All subject data related to the serious adverse event or respiratory compromise must be entered within 24 hours of the site's first awareness of the event
All other data	Within 5 calendar days of collection
Responses to Data Clarification Requests (DCRs/queries)	Within 5 calendar days of DCR (query) generation

If there will be a delay in entering the information in the study database, the Study Coordinator should notify the SDMC by e-mail with a brief explanation of the circumstances for the delayed data entry. It is critically important to the effective and efficient conduct of the study that ALL data be entered in a timely manner.

6.5 INSTRUCTIONS FOR COMPLETION OF SPECIFIC WORKSHEETS

> ***The CRF instructions in this section may be revised during the course of the trial. Please always refer to the most recent Study Book posted on the iDEF WebDCU™ website.***

SCREEN FAILURE LOG

The Screen Failure Log is used to help identify the number of potential iDEF subjects who flow through a site's Emergency Department. Only subjects that meet the following criteria should be entered on to the Screening Log:

1. Age 18 years or older.
2. Diagnosis of intracerebral hemorrhage confirmed by a brain CT scan.
3. Presentation within 48 hours of ICH symptom onset
4. Actively screened by your site's iDEF Study Team for participation in the Study, but were not randomized.

Subjects who are randomized but do not receive study drug infusion should **not** be included on the log as they will be otherwise captured in the database.

If a subject meets the above criteria, only the site number, date that the subject is screened and his/her gender, race, ethnicity, age (in years), and primary reason for ineligibility are collected. A Code List identifying the primary reasons for exclusion is at the bottom of the form. If the "Other" category is used, please include as much specificity as possible in the next column. Please do not use the "Other" category unless the primary reason for exclusion is not one of those specified in the code list. The Clinical Site staff should enter the Screen Failure Log into WebDCU™ by the 10th day of the following month.

It is recommended that you print the screen failure log, as needed, directly from iDEF WebDCU™. The most current version will always be posted there.

SUBJECT ENROLLMENT FORM

Subjects must be enrolled and assigned a subject ID prior to randomization. Click on [Add New Subject] and enter the subject's gender, race, ethnicity, age, date of informed consent, and date of enrollment. After saving the form, WebDCU™ will assign the subject ID. The information collected on this form will be pre-populated and viewable on the appropriate corresponding CRFs (e.g. Gender will be pre-populated on Form 09: Demographics.) If an item on this form requires editing, the item must be edited via 'Subject Enrollment' in [Study Progress].

One of the items on the subject enrollment form is race. The racial categories are as follows:

Racial Categories:

American Indian or Alaska Native: A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American: A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or Other Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White: A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Gender and race will be pre-populated from the information entered on the Subject Enrollment Form. If these data items need to be edited, it must be edited via 'Subject Enrollment' in [Study Progress].

FORM 1: INCLUSION/EXCLUSION CRITERIA

This form is intended to document the subject's compliance with the protocol inclusion and exclusion criteria. All items in the Inclusion Criteria section must be answered YES, and all items in the Exclusion Criteria section must be answered NO for a subject to be eligible for randomization. Missing responses are not allowed anywhere on this form. **If all eligibility criteria are not met, randomization will be blocked.**

If any eligibility violations are discovered after randomization, the eligibility violation must be documented on this form. Should you enter YES to an exclusion criteria or NO to an inclusion criteria, you will receive a protocol violation error message on the eCRF screen. Enter a concise description of the situation when dismissing the rule violation. Age and date of signed informed consent will be pre-populated on this form from the information entered on the Subject Enrollment Form. If these data items need to be edited, they must be edited via 'Subject Enrollment' in [Study Progress].

FORM 2: RANDOMIZATION

GENERAL INFORMATION

A patient will be randomized into the iDEF trial once all eligibility criteria are met following the screening assessment, and informed consent is obtained. It is important to point out that a patient is considered to be included in the modified intent to treat population for the primary analysis when he or she receives the initial study drug infusion.

Successful completion of randomization requires entry of subject's ICH score, anticipated ICH onset-to-treatment time, reporting whether the subject was using warfarin at the time of ICH onset, entry of the Screening GCS and NIHSS score, and completion of the Inclusion/Exclusion Criteria Form.

The formula for calculating the ICH Score is summarized in the table below.

COMPONENT	ICH SCORE POINTS
Glasgow Coma Score	
o 3-4	2
o 5-12	1
o 13-15	0
ICH Volume on CT Scan (measured by ABC/2 method*)	
o Greater than or equal to 30 cc	1
o Less than 30 cc	0
Intraventricular Hemorrhage	
o Present	1
o Absent	0
Infratentorial Hemorrhage	
o Yes	1
o No	0
Age	
o Greater than or equal to 80 years	1
o Less than 80 years	0
TOTAL ICH SCORE (0-6)	

The ABC/2 Method for measuring ICH volume:

- A = The greatest hematoma diameter on CT scan
- B = The diameter perpendicular to A
- C = The number of CT slices with hemorrhage multiplied by slice thickness (in centimeters)

To successfully randomize a patient, data enter the Subject Enrollment form. Then data enter and submit the Inclusion/Exclusion Criteria, Glasgow Coma Scale and NIHSS scores, and the Randomization forms. If there are errors or rule violations on any of these forms, randomization will be blocked. Links will be provided to edit forms with rule violations that prevent randomization.

If the subject is eligible for randomization, data enter and submit the Randomization Form. WebDCU™ will perform the randomization and the randomization number will be displayed.

Please print, email or fax a copy of your randomization screen to your pharmacy.

FORM 3: PRIOR MEDICATIONS

This form is used to capture medications taken by the subject within one month prior to randomization, including any medications received while in the ED.

FORM 4: SCREENING VISUAL AND AUDITORY ASSESSMENT

This form must be completed at screening, prior to randomization. For other abnormal findings not specified in Q01-Q-05, please enter a brief description in Q06. Some items may not be easily assessed in all subjects. For example, assessment for color blindness, visual field cut, tinnitus, or hearing loss might not be possible in patients with severely depressed level of consciousness. In these cases, mark unable to assess/unknown.

The visual and auditory assessments are based on simple bedside clinical evaluation. Please use Ishihara test (laminated Ishihara plates have been provided to your site for your convenience) to assess for color blindness.

FORM 5: MEDICAL HISTORY

This form is intended to document both the data obtained from the patient, his/her family, and any medical records available while screening the patient, as well as pre-existing conditions that are discovered after enrollment into the study.

When completing the CRF, indicate yes, no or unknown for each listed medical problem in the systems/areas listed. Additional history should be entered into the spaces provided.

The date and time of ICH symptom onset (or the last time the patient was known to be in his usual state of health, if the exact time of ICH onset is unknown) should be reported on the first line (Q01) of the form. In addition, the date and time of presentation to your ED should be extracted from your ED triage records and reported on the second line (Q02) of the form.

FORM 6: GLASGOW COMA SCALE (GCS)

The Glasgow Coma Scale should be completed at Screening; Baseline (prior to randomization); Prior to Infusion 2; Prior to Infusion 3; 24 Hour Post Last Infusion; and Day 7 or discharge, whichever occurs first. The scale should also be completed whenever a subject's neurological status deteriorates or whenever the investigator believes that it is indicated.

The Glasgow Coma Scale, or GCS, is a neurological scale which aims to give a reliable, objective way of recording the conscious state of a person, for initial as well as continuing assessment. A patient is assessed against the criteria of the scale, and the resulting points give a patient score between 3 (indicating deep coma) and 15 (normal state of consciousness and awakening).

The scale comprises three dimensions: best eye, verbal and motor responses. The three values separately as well as their sum are considered.

It is important to stop sedatives or paralytics, whenever feasible, for sufficient time before performing GCS.

Tracheal intubation makes it impossible to test the verbal responses. Use the provided algorithm to derive the predicted verbal score based on motor and eye opening scores in intubated patients.

The GCS Score

	1	2	3	4	5	6
EYES	Does not open eyes	Opens in response to pain	Opens in response to voice	Opens eyes spontaneously		
VERBAL	Makes no sounds	Makes incomprehensi-ble sounds (moaning)	Utters inappropriate random words	Confused & disoriented	Oriented & converses normally	
MOTOR	Makes no spontaneous movements	Decerebrate (extension) response to pain	Decorticate (flexion) response to pain	Flexion withdrawal to pain	Localizes to pain	Obeys commands

Algorithm for calculating predicted verbal score for intubated subjects					
Motor Score	Eye Opening Score				Predicted Verbal Score
	1	2	3	4	
1	1	1	1	2	
2	1	2	2	2	
3	2	2	3	3	
4	2	3	3	4	
5	3	3	4	4	
6	3	4	4	5	

FORM 7: MODIFIED RANKIN SCALE (mRS)

The mRS is completed at screening (pre-ICH mRS), Day 7 or discharge, whichever occurs first, Day 30, Day 60 Day 90, and Day 180. Data on the subject's functional status (through the use of the mRS) may be obtained from a proxy in the event that the subject is unable to provide the information.

The Modified Rankin Scale (mRS) is a functional disability scale heavily weighted toward neurological disability. It is widely used and has strong face validity worldwide. The scale is best scored by medical personnel in person; however, a structured interview has been shown to have good reproducibility by telephone. Note that only symptoms arising since the ICH should be considered. Walking aids or other necessary mechanical devices are disregarded provided that the patient can use these without external assistance.

If two options appear equally valid and if further questions are considered unlikely to clarify the correct choice, then the more severe category should be selected. When in doubt between 2 categories, always stick to the key discriminators of the scale. Thus, if the patient has any remaining symptoms (even if minimal), he/she scores at least 1. If the patient is unable to undertake previous activities, score 2. If the patient is dependent upon others in activities of daily living, he/she must score at least 3. If the patient is unable to walk without the assistance of another person, score at least 4.

To access the mRS training video and certification test, go to the WebDCU™ training website at https://webdcu.musc.edu/campus/.

FORM 8: LABS

Hematology, coagulation, serum chemistry, kidney function, liver function and urine analysis must be completed at Screening and within 24 hours following completion of the study drug infusion. Serum albumin is also required at screening to determine eligibility. Any labs that are abnormal and clinically significant after the start of the initial study drug administration should be recorded as an adverse event.

FORM 9: DEMOGRAHICS

The purpose of this form is to capture basic demographic information, such as gender, race, and ethnicity of the subject and is collected at the Screening/Subject Enrollment visit. It is important that all demographic information be verified either by self-report by the subject, by medical records, or by a reliable individual accompanying the subject. Please note that some information for this form will be derived from the Subject Enrollment Form, and changes to those derived fields need to be made on the Subject Enrollment form under Study Progress.

Ethnicity is a self-reported or self-identified data field that is required by the NIH. This field should be marked 'Unknown' unless the subject/family members/medical records can provide the information. You should first ask the subject, or the proxy, to indicate the subject's ethnicity as either Hispanic or Latino or not Hispanic or not Latino and indicate the response in one of the two options provided in Question 2.

Hispanic or Latino: A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

FORM 10: SUBJECT INTUBATION

This form documents each time the subject was intubated or worsened while intubated from the ICH onset through Day 7/Discharge (whichever comes first). If the subject is not intubated, check 'No' for 'Data Collected?' in the header of the form.

FORM 11: HOSPITAL DISCHARGE

This form is to be completed upon the subject's discharge from the hospital. This form should be completed for all subjects except those who withdraw consent prior to discharge. If the subject dies prior to discharge, answer 'Morgue/Funeral home' for question 2 and complete the End of Study Form. If the subject withdraws consent prior to discharge, check 'No' for 'Data Collected?' in the header of the form.

FORM 12: TREATMENT CONFIRMATION

This form is collected to ensure that balance is retained in the randomization stratification variables across subjects who receive study drug, since subjects that don't receive study drug will not be followed or included

in the analyses. This form is also collected to maintain a more accurate and current assessment of study drug inventory.

This form must be submitted within 24 hours of randomization to confirm whether or not the subject was a post-randomization screen failure defined as a subject who is randomized but does not receive any study drug. If the subject is a post-randomization screen failure, indicate whether or not study drug was prepared for the subject in question 2 and complete the End of Study form.

FORM 15: CT SCAN

CT Scans are required to be completed at Screening and within 24 hours of completion of the last dose of study drug. Any additional imaging scans (CT, CTA, MRI, MRA, or conventional angiography) conducted for safety or other reasons must be documented on Form 32: Additional Imaging.

In most cases, the screening CT scan will serve as the baseline scan. However, in cases where CT scan is repeated before the start of study drug infusion, the last scan before randomization should be considered as the baseline CT scan.

Submission of this form in WebDCU™ generates an image tracking number with which the de-identified scan should be labeled. Refer to the Imaging Acquisition and Transmission Procedures Manual (Imaging MoP) for detailed instructions regarding preparation and shipment of images.

The coordinator of the Central Imaging Laboratory at Beth Israel Deaconess Medical Center will serve as the central reader for CT scans and be responsible for entering findings in a Central Reader interface in WebDCU™. The central reader form will be completed for the screening CT scan and CT scan obtained within 24 hours following completion of the study drug infusion.

FORM 18: BLOOD SAMPLE COLLECTION

This form will be completed only for subjects who agree to participate in the Blood Banking Repository Sub-study. The samples will be collected at Baseline prior to randomization and within 24 hours following completion of the study drug infusion.

FORM 19: STUDY DRUG ADMINISTRATION

The Study Drug Administration form is a log form completed from the start of the initial study drug infusion through the end of all study drug infusions. This form captures completion status of the infusion, the weight measurement used for the initial dosing (either estimated or actual) and actual weight measured within 24 hours of randomization used for subsequent dosing.

Enter a new row in the log section of the form (Question 9) anytime an infusion is started/changed (including bag changes, infusion rate changes, and interruptions).

FORM 22: VITAL SIGNS

Vital signs (BP, pulse, respiratory rate, and temperature) are collected at Screening, Baseline (prior to randomization) and Day 7 or discharge, which occurs first. Height and weight (actual or estimated) should also be collected at screening to calculate body mass index (BMI).

The standard BMI calculator can be accessed by clicking on the following link:
http://www.nhlbi.nih.gov/guidelines/obesity/BMI/bmicalc.htm

The metric BMI calculator can be accessed by clicking on the following link:
http://www.nhlbi.nih.gov/guidelines/obesity/BMI/bmi-m.htm

FORM 23: MONTREAL COGNITIVE ASSESSMENT (MoCA)

The MoCA CRF should be completed at Day 7 or discharge, whichever occurs first, Day 30, and Day 90.

The MoCA test is a one-page 30-point test administered in approximately 10 minutes. The MoCA assesses several cognitive domains. The short-term memory recall task (5 points) involves two learning trials of five nouns and delayed recall after approximately 5 minutes. Visuospatial abilities are assessed using a clock-drawing task (3 points) and a three-dimensional cube copy (1 point). Multiple aspects of executive functions are assessed using an alternation task adapted from the trail-making B task (1 point), a phonemic fluency task (1 point), and a two-item verbal abstraction task (2 points). Attention, concentration and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each). Language is assessed using a three-item confrontation naming task with low-familiarity animals (lion, camel, rhinoceros; 3 points), repetition of two syntactically complex sentences (2 points), and the aforementioned fluency task. Finally, orientation to time and place is evaluated (6 points).

The MoCA was validated in the setting of mild cognitive impairment, and has subsequently been adopted in numerous other settings clinically. The sensitivity and specificity of the MoCA for detecting mild cognitive impairment were 90% and 87% respectively, compared with 18% and 100% respectively for the Mini-Mental State Examination.

FORM 24: STROKE IMPACT SCALE-16 (SIS-16)

The SIS-16 assessment is done at Day 30 and Day 90. Data on the subject's functional status (through SIS-16) may be obtained from a proxy in the event that the subject is unable to provide the information.

The SIS-16 is a 16-item questionnaire developed as a short instrument to assess stroke physical function 1-3 months post-stroke. The SIS-16 is more discriminative than other indices (such as the Barthel Index) in patients

with mild to moderate strokes. There is less of a ceiling effect with fewer patients scoring at or near maximum values. However, it only measures the physical aspects of stroke.

FORM 25: CONCOMITANT MEDICATIONS

Concomitant medications will be collected from randomization through Day 90. For the Day 7/Discharge visit, enter any medications that the subject has taken since randomization through Day 7 or discharge, whichever comes first. At subsequent follow up visits, only enter medications the subject is currently taking.

FORM 26: CONCOMITANT NON-DRUG THERAPIES

Concomitant procedures (non-drug therapies, e.g. surgery or rehabilitation) will be collected from the Baseline through the Day 90 visit. At the Day 7/Discharge visit, enter all non-drug therapies that the subject has received since baseline through discharge. At subsequent follow up visits, enter any non-drug therapies received since the last assessment.

FORM 27: ADVERSE EVENTS

The Adverse Event form is intended to document serious (SAE) and non-serious adverse events (AE). You should use this form to enter all adverse events occurring from randomization through Day 7 or Discharge, whichever comes first. This form should also be completed for all Serious Adverse Events that occur from the start of the initial study drug infusion through the Day 90 visit or end of study, whichever comes first.

All AEs (Serious and Non-serious) that occur between screening and the start of the initial study drug infusion should be recorded on the Form 02: Medical History and are not considered adverse events. A report listing all Adverse Events by subject is available from the WebDCU™. It is recommended that the clinical site print this report prior to subjects' visits to aid in tracking new adverse events, as well as the resolution of previous events.

NAME AND DESCRIPTION OF THE ADVERSE EVENT

Provide the name of the adverse event without the use of abbreviations or extra words.

SEVERITY

Enter the appropriate designation for the severity of the event. Please note that severity and seriousness are two separate terms. Severity is used to describe the intensity of the event; the event itself, although severe, may be of relatively minor medical significance, e.g., a severe stomach ache. The following are definitions of severity:

Mild: Awareness of sign or symptom, but easily tolerated by the subject, causing minimal discomfort and not interfering with regular daily activities.

Moderate: Discomfort enough to cause interference with regular daily activities.

Severe: Incapacitating with inability to work or do regular daily activities. It may necessitate additional therapy and could place the subject in immediate risk of harm.

Life-Threatening: Any adverse event that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred.

Fatal: Any adverse event that results in the subject's death.

SERIOUS

Indicate whether or not the adverse event was serious by selecting 'No' or 'Yes' as appropriate. A serious adverse event is an adverse event that results in any of the following outcomes:

(1) death;
(2) life-threatening AE;
(3) in-patient hospitalization;
(4) prolongation of existing hospitalization;
(5) a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
(6) a congenital anomaly/birth defect;
(7) an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

If a subject experiences a serious adverse event or an adverse event associated with respiratory compromise, the adverse event form and all data relevant to that event must be entered and submitted in WebDCU™ within 24 hours of FIRST knowledge of the event.

DATE AND TIME OF ONSET

Indicate the date and time of event onset. If the onset time is unknown, leave it blank and enter an explanation in the General Comments section. Do not enter "0" for unknown times.

OUTCOME

Indicate the best category for each AE:

(1) Resolved;
(2) Resolved with sequellae;
(3) Continuing (follow-up required);
(4) Continuing at end of study (no follow-up required);
(5) Continuing at time of death.

If outcome is 'Continuing', then the "Date of resolution" field will be skipped. Mark 'Continuing - No follow up is required' if the SAE is ongoing at the End of Study visit.

In the event that a subject has several adverse events at the time of death, please do the following:

1. For the AE that actually caused the death (if known), mark outcome as 'Continuing at time of death' and severity as fatal. Date of resolution should be left blank.
2. For the remaining AEs (that were not resolved prior to death but were not responsible for causing the death), mark outcome as 'Continuing at time of death' and severity as not fatal. Date of resolution should be left blank.

DATE OF RESOLUTION

Indicate the date of resolution. (If outcome is 'Continuing', this field will be skipped.) Please see the section above (Outcome) for instructions in determining the appropriate date to report the resolution of an event.

RELATIONSHIP

Enter the appropriate code for the adverse event's relationship to the study drug:

Unrelated:

- Adverse event is clearly due to extraneous causes (e.g., underlying disease, environment)

Unlikely - Should have two of the following:

- Does not have temporal relationship to the intervention,
- Could readily have been produced by the subject's clinical state,
- Could have been due to environmental or other interventions,
- Does not follow known pattern of response to intervention,
- Does not reappear or worsen with reintroduction of intervention

Possible - Should have two of the following:

- Has a reasonable temporal relationship to the intervention,
- Could not readily have been produced by the subject's clinical state,
- Could not readily have been due to environmental or other interventions,
- Follows a known pattern of response to intervention

Probably - Should have three of the following:

- Has a reasonable temporal relationship to the intervention,
- Could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions,
- Follows a known pattern of response to intervention,
- Disappears or decreases with cessation of intervention

Definitely - Should have all four of the following:

- Has a reasonable temporal relationship to the intervention,
- Could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions,
- Follows a known pattern of response to intervention,
- Disappears or decreases with cessation of intervention and recurs with re-exposure

ACTIONS TAKEN FOR THIS EVENT

Select all of the actions that were taken to resolve the adverse event.

SERIOUS ADVERSE EVENT AND RESPIRATORY COMPROMISE DESCRIPTION

For serious adverse events and cases of respiratory compromise, you are required to enter a description of the event in the field titled "Describe the event or problem" section of the Adverse Event CRF. The narrative is relied on by the Medical Safety Monitors (MSMs) in their review of the SAE or respiratory compromise. As such, the narrative must be adequate to allow the MSMs to make a determination on the relationship of the SAE or respiratory compromise to the study drug (as well as whether the event was unexpected). It is extremely important that the narrative be completed by a physician and include, at a minimum, the subject's age, gender, and presenting information; followed by a description of what happened and a summary of all

relevant clinical information (medical status prior to the event, signs and/or symptoms, differential diagnosis for the event in question, clinical course, treatment outcome, etc.), and, the Investigator's opinion of the relationship of the SAE or respiratory compromise to the study intervention.

Because cases of respiratory compromise, and specifically ARDS, are of particular concern, additional data points will be collected on the AE CRF when the adverse event category selected is respiratory compromise. This information will be used by the Medical Safety Monitors to determine if the event being reported is ARDS, and, as such, it is critical that these questions be answered as accurately and completely as possible.

Finally, the last name of the reviewing site investigator and the date of the site investigator review must be provided. Each serious adverse event or respiratory compromise CRF also must be signed by the clinical site Investigator reporting or reviewing the event.

FORM 29: END OF STUDY (EOS)

The End of Study (EOS) form is required for all randomized subjects once the subject has completed the study (i.e., Day 180, post-randomization screen failure, withdrawal of consent, lost to follow up, or death.) If the participant completes the study in its entirety, the EOS form is to be completed at the Day 180 visit.
The site PI, listed on the 1572, must review and affirm (by providing a signature and date the forms were reviewed) the accuracy of the information reflected in **ALL** of the case report forms for the study subject.

FORM 30: VISUAL AND AUDITORY ASSESSMENT FOLLOW-UP

This form must be completed Prior to Infusion 2; Prior to Infusion 3; , 24 hours post last infusion, Day 7 or discharge, whichever is earlier, and Day 30.

For other abnormal findings not specified in Q01-Q05, please enter a brief description in Q06. Some items may not be easily assessed in all subjects. For example, assessment for color blindness, visual field cut, tinnitus, or hearing loss might not be possible in patients with severely depressed level of consciousness. In these cases, mark unknown/unable to assess.

The visual and auditory assessments are based on simple bedside clinical evaluation. Please use Ishihara test (laminated Ishihara plates have been provided to your site for your convenience) to assess for color blindness.

The emergence of new abnormalities that were not detected on previous assessments (assuming that the assessment was adequately completed) should be recorded as an adverse event.

FORM 32: ADDITIONAL IMAGING

This form is optional and should only be completed if additional imaging (beyond the protocol-required CTs collected at Baseline and 24 Hour Post Last Infusion) was performed per standard care. Otherwise, this form should be left blank. Submission of this form in WebDCU™ generates an image tracking number with which the de-identified scan should be labeled. Refer to the iDEF Imaging MoP for detailed instructions regarding preparation and shipment of images.

FORM 43: NIH STROKE SCALE

The NIHSS is a well-validated clinical tool to score the stroke neurological examination. The scale can be administered in about 10 minutes. All health care personnel can be certified in the use of the scale. The NIHSS must be assessed in person by a clinical investigator at the site who has current NIHSS certification and is included on the FDA Form 1572. Certification is available through the National Stroke Association (https://secure.trainingcampus.net/uas/modules/trees/windex.aspx?rx=nihss-english.trainingcampus.net). This link can be accessed through the WebDCU™ training site at https://webdcu.musc.edu/campus/. For information regarding certification, please contact Aaron Perlmutter (perlmutt@musc.edu).

The NIHSS should be completed at Screening (at presentation to the enrolling center); Baseline (prior to randomization; Prior to Infusion 2; Prior to Infusion 3; 24 Hour Post Last Infusion; and Day 7 or discharge, whichever occurs first; Day 30; and Day 90. The scale should also be completed whenever a subject's neurological status deteriorates or whenever the investigator believes that it is indicated.

It is important to stop sedatives or paralytics, whenever feasible, for sufficient time before performing the NIHSS.

1a. Level of Consciousness: The investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation. For coma, score 3.

0 = Alert; keenly responsive.
1 = Not alert, but arousable by minor stimulation to obey, answer, or respond.

2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped).
3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, areflexic.
Unknown

1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues. For coma, score 2.

0 = Answers both questions correctly.
1 = Answers one question correctly.
2 = Answers neither question correctly.
Unknown

1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to them (pantomime) and score the result (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored. For coma, score 2.

0 = Performs both tasks correctly
1 = Performs one task correctly
2 = Performs neither task correctly
Unknown

2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI) score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness or other disorder of visual acuity or fields should be tested with reflexive movements and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy. For coma, score as examined.

0 = Normal
1 = Partial gaze palsy. This score is given when gaze is abnormal in one or both eyes, but where forced deviation or total gaze paresis are not present.

2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.
Unknown

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat as appropriate. Patient must be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction patient receives a 1 and the results are used to answer question 11. Score as examined.

0 = No visual loss
1 = Partial hemianopia
2 = Complete hemianopia
3 = Bilateral hemianopia (blind including cortical blindness)
Unknown

4. Facial Palsy: Ask, or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barrier obscures the face, these should be removed to the extent possible.

0 = Normal symmetrical movement
1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling)
2 = Partial paralysis (total or near total paralysis of lower face)
3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)
Unknown

5 & 6. Motor Arm and Leg: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder or hip may the score be "UN" and the examiner must clearly write the explanation for scoring as a "9". For coma, score 4.

0 = No drift, limb holds 90 (or 45) degrees for full 10 seconds.
1 = Drift, Limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support.
2 = Some effort against gravity, limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity.
3 = No effort against gravity, limb falls.
4 = No movement
9 = Amputation, joint fusion explain: _____
Unknown

5a. Left Arm
5b. Right Arm

0 = No drift, leg holds 30 degrees position for full 5 seconds.
1 = Drift, leg falls by the end of the 5 second period but does not hit bed.
2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity.
3 = No effort against gravity, leg falls to bed immediately.
4 = No movement
9 = Amputation, joint fusion explain:_____
Unknown

6a. Left Leg
6b. Right Leg

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion may the item be scored "UN", and the examiner must clearly write the explanation for not scoring. In case of blindness, test by touching nose from extended arm position. For coma, score 0.

0 = Absent
1 = Present in one limb
2 = Present in two limbs
9 = Amputation, joint fusion explain: _____
Unknown

8. Sensory: Sensation or grimace to pin prick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas [arms (not hands), legs, trunk, face] as needed to check accurately for hemisensory loss. A score of 2, "severe or total," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will therefore probably score 1 or 0. The patient with brain stem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in coma (item 1a=3) are automatically given a 2 on this item.

0 = Normal; no sensory loss.
1 = Mild to moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick but patient is aware he/she is being touched.
2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.
Unknown

9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. The patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences (see the end of this section for the attachments). Comprehension is judged from responses here as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in coma (question 1a=3) will automatically score 3 on this item. The examiner must choose a score in the patient with stupor or limited cooperation but a score of 3 should be used only if the patient is mute and follows no one step commands.

0 = No aphasia, normal
1 = Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided material difficult or impossible. For example, in conversation about provided materials examiner can identify picture or naming card from patient's response.
2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response.
3 = Mute, global aphasia; no usable speech or auditory comprehension.
Unknown

10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barrier to producing speech, may the item be scored "UN", and the examiner must clearly write an explanation for not scoring. Do not tell the patient why he/she is being tested. For coma, score 2.

0 = Normal
1 = Mild to moderate; patient slurs at least some words and, at worst, can be understood with some difficulty.
2 = Severe; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric.
9 = Intubated or other physical barrier, explain_____
Unknown

11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable. For coma, score 2.

0 = No abnormality.
1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities.

2 = Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space.
Unknown

7 ADVERSE EVENT REPORTING

7.1 DEFINITION OF ADVERSE EVENTS

Definition of Adverse Events - - Adverse events are any *untoward* medical occurrences whether or not they are considered related to the study drug. An adverse event can be any unfavorable and unintended symptom, sign, disease or clinically significant abnormal test result occurring during the study which were either not present at baseline, or if present, worsened during the study in terms of either severity or frequency.

Each subject is monitored closely from study drug start through Day 7/Discharge (whichever comes first) for adverse events (AEs). SAEs are assessed from study drug start through Day 90 of the study
(See Section 6.5 – Form: 27 Adverse Events - for more detail on the information required to be reported for a SAE.)

All adverse events or complications will be assigned to a system-organ class using the MedDRA coding dictionary preferred terms, and will be recorded in an adverse event data collection table.

7.2 REPORTING OF ADVERSE EVENTS

In order to ensure prompt reporting of adverse events, we require that all **adverse events** (as well as all related study data) be entered into the WebDCU™ data base within 5 calendar days following the completion of the Baseline through Treatment study phase and the Day 7 or discharge (whichever occurs first) study phase. All adverse events occurring throughout the study period will be recorded on the Adverse Event Case Report Form.

For all **serious adverse events** (SAEs) and respiratory compromise of any cause, you are required to report the event in the WebDCU™ database within 24 hours of the study site being made aware of the occurrence of the event. The 24-hour reporting requirement for SAEs applies to all study phases. The 24-hour reporting for respiratory compromise applies to the inpatient phase of the study. The investigators are required to provide relevant information such as description of the adverse event, date/time of onset and resolution, severity and seriousness, action taken, and suspected relationship to the study drug.

Reporting of SAEs or respiratory compromise will trigger notification of the event to the Project Manager (PM) and appropriate members of the Executive Committee (EC). After reviewing the event for completeness and accuracy, the PM will forward the SAE to the MSMs who will conduct independent reviews of each event to determine its relationship to the study drug along with other elements. Within 72 hours of receipt of the event for review, the MSMs will enter into the trial's database their opinions as to seriousness, and if it is unexpected and related to the study drug. They will also make a determination as to whether the event is ARDS. If necessary, an expedited safety report (MedWatch) will be filed with the FDA within the stipulated regulatory guidelines; for fatal or life-threatening SAEs no later than 7 calendar days after the sponsor's initial receipt of information, and for SAEs outside those categories, no later than 15 calendar days after the sponsor determines that the event requires expedited reporting. If the study site investigator(s) and the MSMs are not in agreement on these issues and fail to resolve their disagreement after communication, the opinion of the MSMs will be considered as the final adjudication. When a MedWatch Report is filed with the FDA, a copy of the MedWatch Report (or a link to a secure file in the trial data base) will be sent to the DSMB through the NINDS liaison.

Each clinical site PI and primary Study Coordinator will receive an email notification that a MedWatch Report has been filed with FDA. The email notification will contain a link to a secure file in the trial data base. It is the responsibility of each clinical site PI to file these reports with his/her IRB/REB in compliance with their institution's local requirements. After the submission of the initial MedWatch Report, the principal investigator at the corresponding clinical site will be responsible for obtaining follow-up information about the event, and reporting it in the WebDCU™.

7.3 INTERIM MONITORING OF ADVERSE EVENTS

Two independent Medical Safety Monitor (MSMs), appointed in consultation with the NINDS program director, will monitor the study with regard to safety on an ongoing basis to identify any safety concerns. The MSMs will review all cases of respiratory compromise and all SAEs to determine whether they are related to study drug administration, and to ascertain the diagnosis of ARDS in cases of respiratory compromise. They will communicate with the investigators for any questions or clarifications regarding an event. Periodically throughout the study, the EC and the MSMs will review reports on the incidence rates of all reported adverse events, whether serious or not, with particular attention to SAEs, respiratory compromise including ARDS, and mortality during the first 7 days of hospitalization (or until discharge, whichever is earlier). Should such monitoring uncover issues that may threaten subject safety (e.g. unexpectedly high rate of adverse events), the study statistician and principal investigator will prepare a report to be submitted to the DSMB for their review and further actions to be taken, if any.

Two statistical reports will be generated semiannually (unless requested at a more frequent interval by the MSMs or DSMB) – an open report to be distributed to the Executive Committee and MSMs, and a closed report to be distributed only to the NINDS-appointed DSMB. Each semi-annual report will provide cumulative summary statistics on enrollment, subject status in the study, baseline characteristics, protocol violations, safety data (including a summary of the most frequent and most serious adverse events, a summary of all MedWatch Reports, and a listing of all subjects who were terminated from the study and the reason for termination), and data management/quality information. The statistics will be provided for the overall study. An annual report will be submitted to the FDA and Health Canada.

The occurrence of ARDS will be continuously monitored during the course of the trial, in order to facilitate thorough review of the data by the DSMB and to stop enrollment into the trial if sufficient evidence of imbalance in the rate of ARDS exists. The ARDS cases will be reviewed on an ongoing basis throughout the trial by the MSMs (who will adjudicate all cases together to provide a consensus opinion about the diagnosis, severity, and possible/plausible causes other than the study drug). . The DSMB will be notified of each individual ARDS occurrence upon confirmation by the MSMs, per their request. Given that a common definition for the diagnosis of ARDS will be used, we do not anticipate much discrepancy between the site's assessment and the MSM's assessment. However, in the event of disagreement, the MSM's assessment will be used.

7.4 iDEF EMERGENCY MEDICAL CONTACT

The Principal Investigator for the iDEF Study (Magdy Selim, MD, PhD), or a member of his study team, is available 24 hours a day, 7 days a week throughout the year via the emergency phone number 617-667-7000 - ask the operator to page Beeper # 39636, and **TELL THE OPERATOR "I HAVE A QUESTION REGARDING THE IDEF TRIAL"**

Sites should contact Dr. Magdy Selim to discuss the following:

- Questions regarding the Inclusion or Exclusion Criteria.
- To report or discuss any deviation from the protocol.
- Any other clinical questions that may be of concern.

7.5 WebDCU™ EMERGENCY RANDOMIZATION HOTLINE

If you encounter a problem randomizing a subject in WebDCU™, contact the WebDCU™ Emergency Randomization Hotline at 1-866-450-2016. The hotline is available 24 hours a day, 7 days a week, but it should only be used for randomization emergencies.

8 INVESTIGATIONAL DRUGS

8.1 GENERAL INFORMATION

The study site Principal Investigator (PI) will have overall responsibility for drug accountability, which will be carried out in accordance with ICH/GCP and the individual study site's Standard Operating Procedures. The study site PI may delegate some or all of the investigational product duties to a Pharmacist, Study Coordinator or another appropriate individual who is under the supervision of the study site PI or is accountable through other lines of responsibility established by the clinical site. Any delegation of authority must be reflected on the Delegation of Authority Log.

The duties that may be assigned include:

- Investigational study drug accountability and reconciliation

- Appropriate storage of all investigational study drugs
- Investigational study drug preparation in accordance with the protocol
- Investigational study drug use in accordance with the protocol

8.2 STUDY DRUG SUPPLY

8.2.1 STUDY DRUG SOURCE

The active study drug, Deferoxamine, will be purchased periodically from the manufacturer by the Department of Health and Human Services, and shipped to the Supply Service Center (DHHS-SSC) in Perry Point, MD. The DHHS-SSC will serve as the drug distribution center and supply the clinical sites as recruitment progresses.

8.2.2 STUDY DRUG LABELING/PACKAGING

The active study drug (DFO) will be supplied to the research pharmacy at each site in non-blinded, open label vials. Labeling will comply with FDA requirements for investigational drug supplies. Each vial of study medication will contain 2 g of sterile lyophilized, powdered deferoxamine mesylate.

The following information will be contained on the vial label:

- Drug name and strength
- Lot number
- Expiration date
- Unique 4-digit Vial Tracking ID number on the "Investigational Use Only" label.
- "INVESTIGATIONAL DRUG TO BE USED BY QUALIFIED INVESTIGATORS ONLY. DROGUE DE RECHERCHE-RESERVEE UNIQUEMENT A L'USAGE DE CHERCHEURS COMPETENTS."

Prior to being released to enroll subjects, each site will be provided with IDEF study drug labels to be applied to the IV bag. This label will contain the following information:

- IDEF Study Drug: Deferoxamine or Saline [0.9% sodium chloride]
- Subject Study ID: __ __ __
- Randomization number: __ __ __ __
- Investigational drug to be used by qualified investigators only. Drogue de recherche-réservée uniquement a l'usage de chercheurs compétents.
- Do not administer any other drugs through the study drug IV line. Please contact the IDEF study team for questions.

8.2.3 DFO STORAGE

DFO must be stored in a pharmacy.
DFO vials are to be stored in a secure, limited-access, locked location.
DFO vials must be stored in a cool location, 15°C – 25°C (68°F – 77°F).

DFO vials should be kept away from direct light and heat.

Storage room temperature should be recorded at least daily on a Temperature Log. A Sample Temperature Log can be found at the end of this Manual. Copies of these logs may be requested during monitoring visits and at the end of the study.

Deviations from the recommended storage conditions should be documented on the Temperature Log and communicated to the Project Management team at the SDMC, who will forward the information to the DHHS-SSC for assessment with regard to the use or destruction of the affected DFO.

8.3 STUDY DRUG SHIPPING AND SUPPLY

8.3.1 INITIAL DEFEROXAMINE (DFO) SHIPMENT

Initially, each study site will receive 12 vials of deferoxamine (enough to treat at least 1 subjects randomized to the DFO treatment for 3 days). Each shipment will be preceded by an e-mail or phone call notifying the primary study pharmacist of the shipment date. Once DFO is received in house, the primary study pharmacist, or designee, will confirm receipt of the study drug in the WebDCU™.

Should any of the study drug vials arrive in a damaged or non-useable condition, the primary study pharmacist, or designee, will document this in WebDCU™. This will trigger an automatic email requesting resupply of DFO to the drug distribution center. The drug distribution center will ship replacement vials on the next available shipment date.

8.3.2 RESUPPLY OF INVESTIGATIONAL DRUG

As a subject is randomized to the DFO arm, the WebDCU™ system will automatically alert the DHHS-SSC to ship replacement vials of DFO to the enrolling site's pharmacy, as needed.

As with the initial shipment of DFO, the primary study pharmacist, or designee, will confirm receipt of DFO in the WebDCU™.

8.4 STUDY DRUG PREPARATION AND DOSAGE CALCULATION

Each vial of DFO will contain 2 g of sterile lyophilized, powdered deferoxamine mesylate. The contents of each vial will be dissolved in 20 ml of sterile water. This will result in approximately a 100mg/ml solution. The reconstituted drug will be further diluted in normal saline (NS) to achieve a final concentration of 7.5 mg per ml to be administered by IV infusion at a rate of 1 ml/kg/hour to achieve a total dose of 32 mg/kg/day (up to a maximum daily dose of 6000 mg).

The pharmacist will verify the **subject's weight in kg** - actual or estimated (The facsimile or other order from the MD investigator should identify the weight). The weight can be rounded to the nearest whole number (e.g. 70 kg for 70.3 kg & 74 kg for 73.6 kg). It is expected, however, that all subjects will have their actual body

weight determined and recorded within 24 hours of admission, and that subsequent dosing will be based on actual body weight.

For subjects randomized to DFO, the site pharmacist will complete a **Pharmacy Worksheet** to calculate the weight-based dose for this subject, volume of the reconstituted DFO to be used (in ml), and volume of normal saline to be added to an empty IV bag or bottle. The **Pharmacy Worksheet** and additional, more detailed information on dose calculation, study drug preparation, and administration are contained in the **iDEF Pharmacy Manual** which is posted in the Project Document Section of the Project Setup component of the iDEF WebDCU™ website.

The drug will be reconstituted immediately prior to use to ensure microbiological safety. The reconstituted solution, however, may be stored at room temperature for a maximum period of 24 hours before use.

8.5 STUDY DRUG ADMINISTRATION INSTRUCTIONS

The study drug will be administered using an intravenous cannula, dedicated to drug infusion, inserted into an antecubital vein preferably in a non-paralyzed limb, and a variable speed infusion pump. Alternatively, a central line, with a port dedicated to the drug infusion, may be used. **It is important to maintain a dedicated line for the study drug infusion because it may be incompatible with other drugs.**

Applying warm compresses to the site of IV injection throughout each infusion period is strongly encouraged as a precaution to minimize the potential for local injection site reactions. The initial dose of the study drug must be administered within 12-24 hours (as appropriate) of ICH symptom onset. Every effort should be made to initiate drug administration in consenting subjects as soon as possible after their arrival to the ED.

The infusion of the diluted study drug will be administered daily during hospitalization for 3 consecutive days by IV infusion at a rate of 1 ml/kg/hour. The infusion start time should be the same each day. The date and time of drug preparation and administration, as well as rate of infusion, will be recorded. Ideally, the daily IV infusions of the study drug should occur without any interruptions. However, it is possible that interruptions will occur, for example to replace the IV access site. In such cases, the occurrence and duration of these interruptions will be documented on the Study Drug Administration CRF (Form 19). An explanation of the reason for the interruption should be included in the General Comments section at the bottom of the form.

8.6 HANDLING OF USED AND UNUSED STUDY DRUG

Any materials (including used study drug) remaining after each infusion should be discarded by the study site staff in accordance with that study site's standard clinical practices.

Used DFO vials, however, should be maintained on site for verification purposes until the next scheduled monitoring visit. After verification by the monitor, these vials can be discarded in accordance with standard clinical practices and the established practices at each study site. At the conclusion of the study, the study Sponsor will communicate the procedures to be followed with regard to the destruction or return of unused DFO.

If DFO expires during the course of the study, the primary study pharmacist, or designee, will be notified by the Project Management team and a determination as to the method of destruction of the unused DFO will be included in any communications. As DFO vials expire, the primary study pharmacist, or designee, will document expiration in WebDCU™.

9 SOURCE DOCUMENTATION AND MONITORING

9.1 SOURCE DOCUMENTATION

Source documents are any documents on which study data are recorded for the first time. Source documents include but are not limited to medical records (inpatient and outpatient), worksheets developed for study use, standardized test forms, and laboratory reports.

Source documents are necessary to validate the information that has been entered into WebDCU™. All source documents must be readily available during site monitoring visits and must be retained in accordance with federal and local guidelines.

Source documents should be:

- Attributable- It should be clear who has documented the data. Best practice includes a legible signature and signature date by the person who collected the data. Acceptable practice includes the name of the person who collected the data, with indication of the data collection date. Documents that are not attributable are unacceptable practice.
- Legible- Readable and signatures identifiable.
- Contemporaneous- The information should be documented in the correct time frame along with the flow of events. If a clinical observation cannot be entered when made, chronology should be recorded. Acceptable amount of delay should be defined and justified.
- Original- Original, if not original should be exact copy; the first record made by the appropriate person. The investigator should have the original source document.
- Accurate- Accurate, consistent and real representation of facts.
- Enduring- Long-lasting and durable.
- Available and accessible- Easily available for review of treating physicians and during audits/inspections. The documents should be retrievable in reasonable time.
- Complete-Complete until that point in time.
- Consistent-Demonstrate the required attributes consistently.
- Credible- Based on real and reliable facts.
- Corroborated-The data should be backed up by evidence.

(http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3121265/**)**

9.2 SITE MONITORING

The rationale for monitoring visits is to ensure that the conduct of the trial is in compliance with the current version of the IRB/REB approved protocol, the GCP/ICH Guidelines and all applicable regulatory requirements. It is paramount that the trial is performed in accordance with all regulatory requirements and protocol criteria and that the rights and well-being of human subjects are protected.

Experienced clinical research monitors will be contracted through the SDMC to perform on site source document verification (SDV) during the study. A checklist of key outcome and safety data variables requiring SDV will be developed based on the trial's endpoints. Visits to each site will take place at intervals to be determined by patient recruitment and other study and clinical site related factors. Monitoring will also involve, as appropriate, correspondence and telephone contacts. In addition to data verification, the monitor will evaluate drug accountability and site facilities. The CRFs and corresponding source documents should be made available to the study monitor at each site visit. It is also expected that the PI, or a designated member of the research staff, will be available during the monitoring visit to review the data and resolve questions and/or issues. The close out monitoring visit will take place after the study is completed.

At each monitoring visit, the investigator(s), study coordinator(s) and other study staff members should be available to meet with the monitor. The monitor will review:

- Adequacy of study facilities
- Drug dispensing, accounting, and storage procedures
- Regulatory binder including the presence of current regulatory documents
- Evidence that SAEs are being appropriately reported to the study site's IRB/REB
- Subject-specific documents of enrolled subjects, including documentation of signed informed consent forms, enrollment worksheets, serious adverse events, source documents, and other data items.

A Monitoring Log will be signed and dated by the Monitor and a member of the study site staff at each visit and maintained in the Regulatory Binder.

9.3 REGULATORY BINDER

Each site should maintain a Regulatory Binder to document submission of all required and/or essential documents. The following regulatory documents must be submitted to the SDMC. If the documents are submitted in WebDCU™, they do not necessarily need to be maintained in the site files. However, if the documents are not in WebDCU™ (for example, IRB/REB correspondence regarding AEs), they need to be in the site files.

- FDA Form 1572 signed by the Principal Investigator.
- Current curriculum vitae (signed and dated within 1 year of the date on the 1572) for all site personnel listed on the FDA Form 1572, including Investigators (primary and sub-investigators), Study Coordinators, and any other personnel who are directly involved in the study.
- Current copies of Investigator/s and Study Coordinator/s licenses.

- Written documentation of the IRB/REB approval of the protocol with clear documentation of the protocol version and approval date.
- Written documentation of the IRB/REB approval of the consent forms with clear documentation of the IRB/REB approval date.
- Written documentation of the IRB/REB review and approval of any advertising materials to be used for study recruitment, if applicable.
- Current laboratory certifications of the laboratory performing the analysis (examples include the CAP or CLIA)
- Copies of NIHSS certification for Investigators and Coordinators who will be completing the NIHSS assessment of subjects.
- Copies of Modified Rankin Scale (mRS) certification for Investigators and Coordinators who will be completing the mRS assessments of subjects.
- Delegation of Authority Log
- IRB Federal Wide Assurance (FWA)
- For Canadian sites
    - Qualified Investigator Undertaking
    - Research Ethics Board Attestation
    - Clinical Trial Site Information, Protocol #
-

The following document should be on file at Beth Israel Deaconess Medical Center and the clinical site:

- A signed contract with Beth Israel Deaconess Medical Center.

The SDMC Project Management team will review all required documents for completeness and accuracy based on regulatory and iDEF study requirements. The SDMC Project Management team also will communicate to the sites any corrections or additions that need to be made to their documents prior to the site beginning enrollment in the study.

Throughout the study, periodic review of these regulatory documents is conducted and reminders of expiration dates will be sent to the sites. These reminders include, but are not limited to, PI and other staff license expirations, NIHSS certification, mRS certification, laboratory certification expirations, FWA expiration, IRB/REB approval renewal and/or expiration, and outstanding regulatory documents. The site is contacted to request outstanding materials and to remind them of upcoming expirations approximately 3 months in advance of expirations. All communications regarding expirations are documented. It is the responsibility of the clinical site to renew the expiring documents, prior to the expiration date, and enter the documents into the iDEF WebDCU™ regulatory data base.

Additionally, any protocol amendments, protocol extensions, changes to consent forms, changes to previously approved advertising, or changes to any other document previously approved by a site's IRB/REB requires documentation of IRB/REB approval. The regulatory binder should contain written documentation of the approval with clear documentation of the approval date

9.4 CHANGE IN STUDY PERSONNEL

When there are any changes to site personnel during the study, it is the site's responsibility to notify the Project Management team at SDMC. The site must submit the following information:

For additions/changes:

- Amended 1572
- Curriculum Vitae (signed and dated within 1 year of the date on the 1572)
- Medical license (required for all investigators)
- Updated Delegation of Authority Log

For deletions:

- Amended 1572 (required **only** for personnel listed on the 1572)
- For changes in Primary Investigator, IRB/REB approval for change in PI. Any proposed change in the PI for a clinical site, must be presented to the study Sponsor (Dr. Magdy Selim) who will notify NINDS for approval of the change prior to any notification to an individual IRB/REB.
- Updated Delegation of Authority Log

WebDCU User Accounts:

It is the responsibility of the clinical site staff to notify SDMC when personnel are no longer working on the study so that the WebDCU™ user account can be deactivated. This is a critical step to prevent unauthorized access to the database.

9.5 ESSENTIAL DOCUMENTS

Several essential documents that are not submitted in WebDCU™ must be retained in the site's files. These include:

- Advertisements used for subject recruitment, if used.
- Contracts, financial agreements, etc.
- Signed informed consent forms
- Source documents
- Subject identification code list
- IRB correspondence, excluding IRB approval of protocol/ICFs/amendments (such as MedWatch Report submission)

10 TRAINING

Principal investigators, sub-investigators, study coordinators, and other study personnel will be trained in the protocol and study procedures, worksheet completion, WebDCU™ procedures, etc. at site initiation sessions. The goal of the training is two-fold: 1) to ensure a full understanding of the protocol; 2) to standardize the methods of data collection to help ensure comparability of data across sites. At the training sessions, the iDEF PI and personnel from the SDMC will initiate the study site PI and other site personnel involved with the study to the protocol (generally with a Power Point or comparable presentation), the WebDCU™, and other forms and instructions, as necessary. The protocol, the Manual of Procedures, and the Regulatory Document Parameters Guidelines all are available on the iDEF WebDCU™ database. Once the study site's team has received their training, it is the responsibility of each person to maintain updated copies of any iDEF study materials as they are amended. Notice of updates and amendments to these materials will be sent from the SDMC, as necessary.

When a new study coordinator is added during the trial, the existing coordinators at that clinical site should train the new study coordinator on entering data into the WebDCU™ system prior to starting work in the study. SDMC personnel will be available to provide any assistance/training that may be helpful. The experiences of the existing study coordinator, however, are likely to provide the best basis for training the new study coordinator.

The SDMC will perform a regular review of training of site personnel on an 'as needed' basis to ensure that coordinators remain current in WebDCU™ procedures.

11 RETENTION OF STUDY RECORDS

In June 2005, a new Federal law was implemented that extends the statute of limitations to six (6) years to bring forward an allegation of research misconduct. In response to this extension, research records must be retained for a sufficient period to investigate an allegation of research misconduct - - **a minimum period of six (6) years.** An agreement must be in place between the clinical site Principal Investigator and the study Sponsor regarding records that may be destroyed.

For Canadian sites, research records must be maintained for twenty-five (25) years.

Federal regulations [56 CFR 56.115(b)] require that IRB records be retained for at least 3 years, and records relating to research which is conducted be retained for at least 3 years after completion of the research. All records must be accessible for inspection and copying by authorized representatives of HHS and FDA at reasonable times and in a reasonable manner. At the end of three years, records are boxed, labeled and sent to central storage for another 7-10 years. A log of stored records should be maintained in the study site's IRB office for retrieval if files are needed for audit or other purposes.

12 ICH GUIDELINES FOR GOOD CLINICAL PRACTICE

The core principles of ICH/GCP are the following:

1. Clinical trials should be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety and well-being of the trial subjects are the most important considerations and should prevail over interest of science and society.
4. The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/ independent ethics committee (IEC) approval/favourable opinion.
7. The medical care given to, and medical decisions made on behalf of subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. 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).
12. Investigational products should be manufactured, handled and stored in accordance with applicable Good Manufacturing Practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

(http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3097692/)