FULL PROTOCOL TITLE

FUTILITY STUDY OF DEFEROXAMINE MESYLATE IN INTRACEREBRAL HEMORRHAGE

SHORT TITLE

INTRACEREBRAL HEMORRHAGE DEFEROXAMINE TRIAL
(iDEF TRIAL)

Protocol Version
IV/I

Study Chair:

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Supported by:

The National Institute of Neurological
Disorders and Stroke (NINDS)

(U01 NS074425)

Sponsor of IND:

Magdy H Selim, MD, PhD
IND# 77,306

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STUDY ADMINISTRATIVE ORGANIZATION

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); Aaron Perlmutter, MPH, MSW (Project Manager), Catherine Dillon, CCRP (the Supervisory Data Manager); Andre Thornhill (the Data Manager); and Claudia Moy, PhD (NINDS-appointed liaison).

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 the study documents (including the protocol, case report forms (CRF), and manual of operations); collection, review and oversight of the dissemination of serious adverse event (SAE) occurrences and other important events pertinent to the study; and communication among all components of the study administrative organizations.

THE STUDY CHAIR OFFICE

The Study Chair Office, housed in the Department of Neurology – Stroke Division at the Beth Israel Deaconess Medical Center (BIDMC) in Boston, provides overall scientific coordination and fiscal management of the trial and is responsible for preparing progress reports for the NINDS and FDA. The office is comprised of the trial's Principal Investigator (Magdy Selim, MD, PhD), his Study Coordinator, and a senior research administrator from BIDMC. The Principal Investigator provides overall leadership to the entire Trial to ensure its successful implementation. He will visit all clinical sites on a periodic basis and collaborate with the SDMC in organizing all necessary meetings and conference calls. As the Sponsor of the Investigational New Drug (IND) application, he ensures that the trial is conducted according to FDA's Good Clinical Practice (GCP) guidelines and regulations. The Study Coordinator assists the PI in day-to-day implementation of the trial and serves as a major contact person for investigators and study coordinators at the clinical sites. The senior research administrator, together with the PI, is responsible for the budgetary management of the grant. These responsibilities include preparation of consortium agreements and subcontracts, handling of invoices, and directing disbursement of funds.

THE STATISTICS AND DATA MANAGEMENT CENTER (SDMC)

The Data Coordination Unit (DCU), located in the Department of Public Health Sciences - College of Medicine at the Medical University of South Carolina, will serve as the SDMC for the trial. The SDMC is responsible for statistical design and analysis, database development and maintenance, data and project management activities, as well as interim safety monitoring and report generation.

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 statistician, and an ad hoc expert in pulmonary diseases and critical care medicine. 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 (MSM)

Two experts (a Neurocritical care specialist and a pulmonary critical care specialist with special expertise in Adult Respiratory Distress Syndrome) serve as the Independent Medical Safety Monitors (MSMs) for the study. They will be responsible for monitoring the study with regard to safety on an ongoing basis and reviewing all serious adverse events quickly to identify any safety concerns. The MSMs' task is to review all adverse events and to adjudicate all serious adverse events as recruitment progresses. The MSMs will communicate with the investigators for any questions or clarifications regarding an event, in order to determine whether events are unexpected and related to study drug administration. They will report to the Executive Committee their findings that any SAE is unexpected and suspected to be related to the study drug. They will also review and adjudicate all cases of respiratory compromise to ascertain the underlying cause and to determine whether the event is related to the study drug.

STUDY TEAM ROSTER

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STUDY PROTOCOL SYNOPSIS

Protocol Title	Intracerebral hemorrhage DEFeroxamine (iDEF) trial
Clinical Trial Phase	Phase II
Clinical Sites	>20 North American clinical sites
Statistics and Data Management Center	Data Coordination Unit, Department of Public Health Sciences, College of Medicine, Medical University of South Carolina, Charleston, SC
Sponsor Institution	Beth Israel Deaconess Medical Center, Boston, MA
Study Period	Planned enrollment duration – 36 to 40 months Planned duration of study for each participant – 180 ± 7 days Planned duration of the study – 36-48 months
Study Population	Patients with spontaneous intracerebral hemorrhage (ICH)
Study Design	A prospective, multi-center, double-blind, randomized, placebo-controlled, phase-II clinical trial. Subjects will be randomized to either deferoxamine mesylate (DFO) at 32 mg/kg/day (up to a maximum daily dose of 6000 mg/day), or saline placebo, given by IV infusion for 3 consecutive days. Treatment will be initiated within 24 hours after ICH symptom onset. Randomization will control baseline imbalances associated with baseline ICH score, ICH onset-to-treatment time (OTT), ICH volume, baseline NIHSS score, and warfarin use. All subjects will be followed for 6 months and will receive standard of care therapy while participating in the study. Throughout the study, we will continue to assess the safety of DFO. At the conclusion of the study, the proportion of DFO-treated subjects with a good clinical outcome at 3 months (defined as modified Rankin Scale (mRS) score of 0-2) will be compared to the placebo proportion in a futility analysis to determine if it is futile to move DFO forward to Phase III efficacy evaluation.
Primary Objectives	**1-** TO assess whether it is futile to move DFO into Phase III evaluation as a therapeutic intervention for ICH, by comparing the outcome of DFO-treated subjects to placebo-treated subjects with respect to good outcome (defined as mRS of 0-2 at 90 days), in a futility analysis. The futility hypothesis specifies that if the difference in good outcome proportions is less than 12% in favor of DFO, then it would be futile to move DFO forward to Phase III evaluation. 2- TO assess the safety of DFO infusions (at a dose of 32 mg/kg/day, up to a maximum daily dose of 6000 mg/day), given for 3 consecutive days, in a large cohort of ICH patients. We specifically wish to collect more data on treatment-related adverse events in order to ascertain that patients with ICH can complete this dose given over 3-day duration of infusion without experiencing unreasonable neurological complications, mortality, or other serious adverse events related to DFO use, in particular adult respiratory distress syndrome (ARDS).
Secondary Objectives	**1-** TO explore the differences between early (≤12h) and late (>12-24h) time windows in DFO treatment effect on functional outcome. **2-** TO determine the overall ordinal distribution of scores on mRS at 3 months in DFO- and placebo-treated subjects; and to perform a dichotomized analysis considering the proportion of DFO- and placebo-treated subjects with mRS 0-3 **3-** TO perform dichotomized analyses considering the proportion of DFO- and placebo-treated subjects with mRS 0-2 and 0-3; and to determine the overall ordinal distribution of scores on mRS at 6 months. **4-** TO determine mortality during the 90- and 180-day follow-up periods (all causes and

	ICH-related). **5**- TO obtain data on the changes in NIHSS between presentation and day-90, and Montreal Cognitive Assessment (MoCA) and Stroke Impact Scale (SIS)-16 scores at 3 months to explore the effects of DFO on neurological, functional, and cognitive functions.
Exploratory Objectives	**1-** TO explore the effects of treatment with DFO on relative perihematoma edema (PHE) volume progression between baseline and post-treatment CT scans in DFO-treated patients compared to placebo as potential markers of DFO's biological activity on brain tissue. **2-** TO explore whether the effect of DFO on outcome is dependent on initial ICH volume, after adjusting for other confounding variables that can affect outcome, to determine if specific limits for ICH volume should be specified as exclusion/inclusion criteria for future studies. **3-** TO explore the effects of DFO on the size of ventricular enlargement in patients with intraventricular extension of ICH, not requiring an external ventricular drain, as a potential marker of treatment utility in intraventricular hemorrhage. **4-** TO explore the effect of DFO on the incidence of symptomatic cerebral edema (unexplained increase in NIHSS >4 points or decrease in GCS >2 points) during hospitalization, up to day 7 or discharge, whichever is earlier. **5-** TO explore whether progression of PHE can be a radiological/biological marker of activity that can be correlated with clinical outcomes and treatment effect of DFO.
Sample Size	Approximately 294 subjects
Inclusion Criteria	1) Age ≥ 18 and ≤ 80 years; 2) The diagnosis of ICH is confirmed by brain CT scan; 3) NIHSS score ≥6 and GCS >6 upon presentation; 4) The first dose of the study drug is expected to be administered within 24h of ICH symptom onset; 5) Functional independence prior to ICH, defined as pre-ICH mRS ≤1; and 6) Signed and dated informed consent is obtained.
Exclusion Criteria	1) Previous chelation therapy or known hypersensitivity to DFO products; 2) Known severe iron deficiency anemia (defined as hemoglobin concentration < 7g/dL or requiring blood transfusions); 3) Abnormal renal function, defined as serum creatinine >2 mg/dL; 4) Planned surgical evacuation of ICH prior to administration of study drug (placement of a catheter for ventricular drainage is not a contraindication to enrollment); 5) SUSPECTED secondary ICH related to tumour, ruptured aneurysm or arteriovenous malformation, hemorrhagic transformation of an ischemic infarct, or venous sinus thrombosis; 6) Infratentorial hemorrhage; 7) Irreversibly impaired brainstem function (bilateral fixed and dilated pupils and extensor motor posturing); 8) Complete unconsciousness, defined as a score of 3 on item 1a of the NIHSS (Responds only with reflex motor or autonomic effects or totally unresponsive, and flaccid); 9) Pre-existing disability, defined as pre-ICH mRS ≥2; 10) Coagulopathy - defined as elevated aPTT or INR >1.3 upon presentation; concurrent use of direct thrombin inhibitors (such as dabigatran), direct factor Xa inhibitors (such as rivaroxaban or apixaban), or low-molecular-weight heparin; 11) Patients with confirmed aspiration, pneumonia, or evident bilateral pulmonary infiltrates on chest x-ray or CT scan prior to enrollment; 12) Patients with significant respiratory disease such as chronic obstructive pulmonary disease, pulmonary fibrosis, or any use (chronic or intermittent) of inhaled O_2 at home; 13) FiO_2 >0.35 (>4 L/min) prior to enrollment; 14) Sepsis (present source of infection ± lactic acidosis), Systemic Inflammatory Response Syndrome (Temp >100.4F or <96.8F; Heart rate >90; Respiratory rate >20 or $PaCo_2$ <32 mmHg; WBC >12, <4, or bands >10%), or shock (SBP <90 mmHg) at presentation; 15) The presence of 4 or more of the following risk modifiers for ARDS prior to enrollment: a) Tachypnea (respir-

	atory rate >30); b) SpO_2 <95%; c) Obesity (BMI >30); d) Acidosis (pH <7.35); e) Hypoalbuminemia (albumin <3.5 g/dL); or f) Concurrent use of chemotherapy; 16) Taking iron supplements containing ≥ 325 mg of ferrous iron, or prochlorperazine; 17) Patients with heart failure taking > 500 mg of vitamin C daily; 18) Known severe hearing loss; 19) Known pregnancy, or positive pregnancy test, or breastfeeding; 20) Positive drug screen for cocaine upon presentation; 21) Patients known or suspected of not being able to comply with the study protocol due to alcoholism, drug dependency, noncompliance, living in another state or any other cause; 22) Any condition which, in the judgement of the investigator, might increase the risk to the patient; 23) Life expectancy of less than 90 days due to comorbid conditions; 24) Concurrent participation in another research protocol for investigation of another experimental therapy; and 25) Indication that a new DNR or Comfort Measures Only (CMO) order will be implemented within the first 72 hours of hospitalization.
Study Intervention and Follow-up	Each subject will receive an IV infusion of DFO (32 mg/kg/day) or a matching saline vehicle (placebo) for 3 consecutive days. The maximum daily dose will not exceed 6000 mg per 24 hours, regardless of body weight, and the infusion rate will not exceed 7.5 mg/kg/hour. Subjects will be monitored closely and evaluated daily for the first 3 days (during study drug infusion while in hospital) and on day 7 or discharge from the hospital, whichever occurs first. Clinic visits will take place on days 30±7 and 90±7. A telephone interview will be conducted on days 60±7 and 180±7.
Randomization	A combination of minimization and biased coin methodologies will be used to randomize participants to either DFO or placebo in 1:1 ratio. Randomization will control baseline imbalances associated with baseline ICH score, ICH onset-to-treatment time (OTT), ICH volume, baseline NIHSS score, and concurrent use of anticoagulants at the time of ICH onset, as well as clinical site.
Efficacy Outcome Measures	The primary outcome measure is the mRS, dichotomized to define good functional outcome as mRS 0-2 at 90 days.
Safety Outcome Measures	All adverse events (serious and non-serious) will be assessed until day-7 or discharge (whichever is earlier), and serious adverse events (SAEs) until day-90. Safety endpoints will include all DFO-related adverse events until day-7 or discharge (whichever is earlier), and SAEs through day-90. Mortality (all cause and ICH-related) will be assessed through day 180. The following adverse events will be defined as **EVENTS OF SPECIAL INTEREST** for safety surveillance during this study: 1- Anaphylaxis (at any time point during study drug infusion); 2- Hypotension (defined as a decrease in blood pressure requiring medical intervention at any time point during drug infusion that cannot be explained by other causes); 3- Respiratory compromise of any cause during the in-hospital phase; and 4- Development of new and unexplained visual or auditory changes after initiating treatment with the study drug. Analyses of safety data will be carried out on an ongoing basis throughout the trial.

STUDY OBJECTIVES

1.1 PRIMARY OBJECTIVES

- TO assess whether it is futile to move deferoxamine mesylate (DFO) into Phase III evaluation as a therapeutic intervention for spontaneous intracerebral hemorrhage (ICH), by comparing the outcome of DFO-treated subjects to placebo-treated subjects with respect to good outcome (defined as modified Rankin Scale [mRS] score of 0-2 at 90 days), in a futility analysis. The futility hypothesis specifies that if the difference in good outcome proportions is less than 12% in favor of DFO, then it would be futile to move DFO forward to Phase III evaluation.
- TO assess the safety of DFO infusions (32 mg/kg/day, up to a maximum daily dose of 6000 mg/day), given for 3 consecutive days, in a large cohort of ICH patients. We specifically wish to collect more data on treatment-related adverse events in order to ascertain that patients with ICH can complete this dose given over 3-day duration of infusion without experiencing unreasonable neurological complications, increased mortality, or other serious adverse events related to DFO use, in particular adult respiratory distress syndrome (ARDS).

1.2 SECONDARY OBJECTIVES

As secondary analyses of the primary outcome, we also plan to:

- Explore the differences between early (≤12h) and late (>12-24h) time windows in DFO treatment effect on functional outcome.
- Determine the overall ordinal distribution of scores on mRS at 3 months in DFO- and placebo-treated subjects, and to perform a dichotomized analysis considering the proportion of DFO- and placebo-treated subjects with mRS 0-3. Although mRS 0-3 is less favorable than the primary outcome of mRS 0-2, it would still be a desirable effect in patients with ICH given that no treatments exist to reduce disability. The trial is adequately powered to assess the futility hypothesis using mRS 0-3 as the outcome based on an absolute difference in treatment effect <13% in favor of DFO.

In addition, we will:

- Perform dichotomized analyses considering the proportion of DFO- and placebo-treated subjects with mRS 0-2 and 0-3; and determine the overall ordinal distribution of scores on mRS at 6 months.
- Determine mortality during the 90- and 180-day follow-up periods (all causes and ICH-related).
- Obtain data on the changes in NIHSS between presentation and day-90, and Montreal Cognitive Assessment (MoCA) and Stroke Impact Scale (SIS)-16 scores at 3 months to explore the effects of DFO on neurological, functional, and cognitive functions.

1.3 EXPLORATORY OBJECTIVES

Additional planned exploratory analyses include assessments of:

- The effects of treatment with DFO on relative perihematoma edema (PHE) volume progression between baseline and post-treatment CT scans in DFO-treated patients compared to placebo as potential markers of DFO's biological activity on brain tissue.
- Whether the effect of DFO on outcome is dependent on initial ICH volume, after adjusting for other confounding variables that can affect outcome, to determine if specific limits for ICH volume should be specified as exclusion/inclusion criteria for future studies.

- The effects of DFO on the size of ventricular enlargement in patients with intraventricular extension of ICH, not requiring an external ventricular drain (EVD), as a potential marker of treatment utility in intraventricular hemorrhage (IVH).
- The effect of DFO on the incidence of symptomatic cerebral edema (unexplained increase in NIHSS >4 points or decrease in GCS >2 points) during hospitalization, up to day 7 or discharge, whichever is earlier.
- Whether progression of PHE can be a radiological/biological marker of activity that can be correlated with clinical outcomes and treatment effect of DFO.

2 BACKGROUND

2.1 RATIONALE

2.1.1 INTRACEREBRAL HEMORRHAGE IS A MAJOR PUBLIC HEALTH PROBLEM

Intracerebral hemorrhage (ICH) is a major public health problem. Approximately 70,000 patients are diagnosed with ICH in the United States (US), and up to 400,000 in the Far East, each year [Qureshi 2009; Zhang 2003], and the number of patients with ICH is rising with the aging of the population. ICH is a frequent cause of disability and mortality and confers a substantial burden on the healthcare system and society [Russell 2006]; approximately 40% of ICH patients die within one month, and more than 70% of the survivors are left with serious and permanent disability. The financial burden of ICH is enormous; it is estimated that the overall annual costs for ICH patients in the US alone exceed seven billion US dollars.

At present, there is no specific treatment for ICH beyond supportive general medical care. Attention has been focused on medical, endoscopic, and surgical treatments targeting hematoma and its expansion [Mendelow 2005; Mayer 2008]. However, the utility of these approaches alone is likely to be limited to only a selected subset of ICH patients, since ICH expansion often occurs early within the first few hours of onset [Brott 1997; Flaherty 2005]. Although the hematoma gradually resolves after ICH, restoration of function is usually incomplete, indicating that neuronal injury after ICH is not only related to direct tissue damage and hematoma expansion [Brown 2005]. Other processes including apoptosis, necrosis, iron-mediated oxidative stress, inflammation, autophagy, and edema formation contribute to secondary neuronal injury and disability after ICH [Regan 1993-1996; Castillo 2002; Goldstein 2003; Huang 2002; Wu 2003; Wagner 2003; Leira 2004; He 2008].

There is an unmet need for safe and effective neuroprotective strategies to target the secondary effects of ICH in order to limit brain injury, facilitate neuronal repair, and improve functional outcome. The iron chelator, deferoxamine mesylate (DFO), is potentially promising as a candidate therapeutic intervention to improve the overall outcome of ICH patients.

2.1.2 THE ROLE OF HEMOGLOBIN DEGRADATION PRODUCTS AND IRON IN SECONDARY NEURONAL INJURY AFTER ICH

Hemolysed red blood cells release their hemoglobin into the brain parenchyma after ICH. The time course for hemoglobin hemolysis is approximately 2-3 days [Macdonald 2004]. Hemoglobin is a potent neurotoxin, and its toxicity is largely iron-mediated [Regan 1993-2003; Hua 2002; Goldstein 2003; Xi 1998; Huang 2002]. Hemoglobin degradation products include the iron-containing heme, which is metabolized by heme oxygenase to yield ferric iron. The released iron is implicated in neuronal injury and delayed brain edema formation after ICH via several mechanisms including: activation of lipid peroxidation, exacerbation of excitotoxicity, inhibition of Na^+/K^+ ATPase activity, and catalysis of Haber-Weiss/Fenton reaction {$Fe^{++} + H_2O_2 \rightarrow Fe^{+++} + OH^{\circ} + OH^{0}$}, in which superoxide and hydrogen peroxide (H_2O_2) are

converted into highly reactive toxic hydroxyl radicals (OH◦) leading to oxidative stress and cell death [Regan 1993-1996; Winterboum 1995; Goldstein 2003; Huang 2002; Wu 2003; Wagner 2003; Winterbourn1995; Nakamura 2005].

Experimental studies examining the time course of iron's role in brain injury after ICH detected an increase in iron-positive cells, heme oxygenase protein, and markers of DNA damage in the peri-hematoma area within the first day after ICH, peaking by day 3 [Nakamura, 2003-2005; Wu 2003]. Emerging evidence also links iron to neuronal injury in ICH patients. Serum ferritin upon admission correlates with the relative PHE on day-3 (which coincides with the timing for hemoglobin hemolysis), but not at baseline [Mehdiratta 2008], and functional outcome at 3 months [Perez 2010]; and the iron content within the hematoma, estimated by MRI, correlates with the relative PHE volume [Lou 2009]. These studies indicate that iron accumulates in the brain after ICH, and that its toxicity contributes to neuronal injury over many days following ICH. This delayed time window can have important therapeutic implications.

2.1.3 DEFEROXAMINE MESYLATE

2.1.3.1 PHARMACOKINETICS –

Deferoxamine mesylate (DFO) [N-(5-C3-L (5 aminopentyl) hydroxycarbamoyl)-propionamido)pentyl)-3(5-(N-hydroxyacetoamido)-pentyl)carbamoyl)-proprionhydroxamic acid] is a hydrophilic, water-soluble, chelator. It complexes almost exclusively with ferric iron, at physiologic pH values, chelating iron from ferritin and hemosiderin; and forms a stable complex that prevents iron from entering into further chemical reactions. The drug's serum protein-binding rate is less than 10%, and it is distributed throughout all body fluids. It has a volume of distribution of 0.8-1.35 L/kg [Lee 1993]. The initial distribution half-life of DFO is approximately 5-10 minutes in humans [Perrone 2002]. Peak plasma concentrations between 80 and 130 µmol/L are measured 3 minutes after IV injection of DFO at a dose of 10 mg/kg [Allain 1987]. During IV infusion of 50 mg/kg/day, steady state concentrations are generally obtained between 6-12 hours with a mean concentration of 7.4 ± 2.73 µM. The drug has a biphasic elimination pattern; the half-life is 1h in the first rapid phase and 6h in the second slow phase [Allain 1987]. Despite a molecular weight of 560.7 daltons (656.8 as mesylate) and low lipid solubility, the drug can diffuse into the brain down a concentration gradient, and there appears to be specific mechanism(s) of uptake by neuronal cells. DFO accumulates in the brain at a significant concentration quickly after injection [Keberle 1964; Yokel 1991; Palmer 1994; Hershko 1988; Brancaccio 1991] and reduces cerebrospinal fluid free iron level in rats subjected to experimental ICH, indicating that it crosses the blood brain barrier after ICH [Wan 2006-2009].

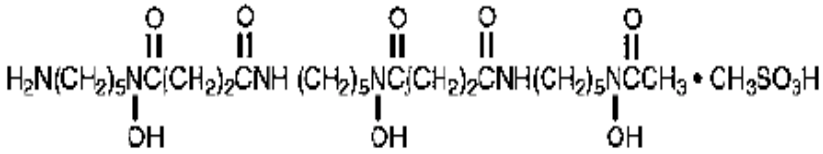

Figure 2.1.3.1: Chemical Structure of DFO

2.1.3.2 SAFETY CONSIDERATIONS –

Deferoxamine mesylate is approved by the Federal Drug Administration (FDA) for the treatment of acute iron intoxication and chronic iron overload and has been extensively used in clinical practice for more than 40 years. Safety studies indicate that it is relatively well tolerated. The following adverse reactions have been observed, but there are not

enough data to support an estimate of their frequency: At the injection site: localized irritation, pain, burning sensation, swelling, induration, infiltration, itching, erythema, or wheal formation. These injection site reactions may be associated with arthralgia, fever, headache, myalgia, nausea, or abdominal pain. Systemic allergic and hypersensitivity reactions: rash, urticaria, anaphylactic reaction with or without shock, or angioedema. Cardiovascular system: tachycardia, hypotension, and shock. Impairment of cardiac function has also been reported in patients with severe chronic iron overload following concomitant treatment with DFO and vitamin C in excess of 500 mg per day. Digestive system: abdominal discomfort, nausea, vomiting, or diarrhea. Hematologic system: thrombocytopenia and leucopenia. Musculoskeletal system: muscle cramps. Nervous system: dizziness, paresthesias, tinnitus, high-frequency sensorineural hearing loss, or visual disturbances, such as blurred vision, decreased visual acuity, pigmentary retinopathy, visual field defects, and cataracts. The ocular and auditory disturbances were reported when DFO was administered over prolonged periods of time, at high doses, in patients with low ferritin levels. These disturbances were reversible upon immediate cessation of treatment, in most cases. Respiratory system: acute respiratory distress syndrome has been reported following treatment with excessively high doses of intravenous DFO in patients with acute iron intoxication or thalassemia. Urinary system: dysuria and impaired renal functions. In addition, rare infections, such as Yersinia and Mucormycosis have been reported in patients with iron-overload. These are thought to be attributed to iron-induced increased susceptibility to infections particularly in patients with low ferritin levels, and are unlikely to occur in patients without iron overload. In a recent study, the most frequent adverse events of DFO (40-50 mg/kg/day, 5 days/week, for 48 weeks) in adult patients with transfusion related iron overload were abdominal pain (34%), diarrhea (26%), fever (26%), joint pain (13%), vertigo (13%), and dyspepsia (8.7%) [Piga 2006]. Other less frequent adverse effects of DFO were local reactions at the site of injection, such as pain, swelling, or erythema. There were no serious adverse events related to DFO use, and the gastrointestinal symptoms were mild and resolved spontaneously within a few days without drug interruption.

Serious adverse effects are uncommon and are seen primarily with IV doses higher than 125 mg/kg/day, daily doses exceeding 6000 mg, and chronic long-term use [Porter, 1989]. Hypotension and shock have been reported in up to 2% of patients using IV DFO [Westlin 1971]. They were mostly seen with rapid intravenous infusions, and rarely reported when the drug is given at a rate ≤1 mg/kg/minute, and a dose ≤125 mg/kg/day [Westlin 1971; Porter 1989]. We will use a slower infusion rate ≤7.5 mg/kg/hour and limit the maximal dose that any subject can receive to 6000 mg per day in the current study.

Small studies have investigated the use of DFO in patients without systemic iron overload who have similar comorbidity profile to that of stroke patients, such as patients with coronary artery disease, diabetes mellitus, and elderly subjects with Alzheimer's disease [Duffy, 2001; Hattori, 2002-2003; Crapper, 1991], and healthy volunteers [Allain; 1987]. The doses used varied from 10 to 80 mg/kg body-weight-adjusted or 250 to 500mg fixed-dose regimens, and the duration of treatment varied from a single treatment to repeated daily dosing up to one year. Previous studies in cardiopulmonary bypass patients and in thalassaemia patients with cardiac disease used IV DFO doses of 50 to 100 mg/kg [Tamary 1994; Davis, 2000; Ioannis, 2004]. Gordeuk et al. also used DFO infusions (100 mg/kg per day for 72 hours) in non-iron overloaded volunteers with asymptomatic Plasmodium falciparum parasitemia and patients with cerebral malaria [Gordeuk, 1992]. These various dose regimens resulted in no serious adverse events to treatment in these studies.

Because DFO is not approved by the FDA for the treatment of patients with ICH, the primary investigator was granted a research (non-commercial) Investigational New Drug (IND) by the FDA to investigate the use of DFO in this patient population (IND #77,306). The supporting data section below (section 2.2.4) details our experience with DFO use in ICH patients. Our Phase I study indicated that repeated IV infusions of DFO in doses up to 62 mg/kg/day with a maximum daily dose of 6000 mg/day in patients with ICH were largely safe and tolerable. The most observed adverse events were injection site reaction (irritation, pain, or erythema; 15%), IV infiltration (20%) and a modest decrease in blood pressure which did not require any medical intervention (40%). While hypotension may be an undesirable side effect in patients with ischemic stroke, a modest reduction in blood pressure may prove to be beneficial, and is often advocated, in

patients with ICH. One subject developed visual hallucination during IV infusion of DFO. Almost all of these adverse events were mild, self-limited, did not require specific treatment, and resolved spontaneously. There were no deaths or serious adverse events related to DFO use.

In the first part of phase II investigation of DFO in ICH (HI-DEF trial, where subjects were treated with a continuous infusion of DFO at 62 mg/kg/day for 5 consecutive days), however, we observed 7 cases of ARDS among the first 42 participants; 6 of these cases were in the DFO treatment arm, and 2 of these were fatal. An expert blinded to treatment assignment reviewed all these cases and concluded that a plausible cause for ARDS, other than the study drug or ICH itself, was identified in 4 cases, while no other explanation, other than the study drug or ICH, was apparent for the remaining 3 cases. HI-DEF was terminated due to safety concerns, given the imbalance in the frequency of ARDS between the DFO- and placebo-treated groups. This prompted further review of 2 cases of respiratory failure, reported as the result of aspiration pneumonia, in Phase I study; both in the 62 mg/kg/day dose-tier. An expert review concluded that one of these cases was an undiagnosed case of ARDS, and that aspiration was a plausible explanation for it. We have undertaken considerable precautions to minimize the potential pulmonary toxicity of DFO and ARDS risk and to enhance the safety of future participants in the current modified protocol by reducing the daily dose of DFO from 62 mg/kg/day to 32mg/kg/day, decreasing the duration of treatment from 5 to 3 days, and excluding subjects at high risk for ARDS.

The effects of DFO on the fetus are unknown. It is also not known if DFO is excreted in human milk. Therefore, women who are pregnant and those who are breast-feeding will be excluded from this study.

2.1.3.3 NEUROPROTECTIVE EFFECTS OF DFO –

By forming a stable complex with ferric iron, DFO decreases free iron's availability for the production of hydroxyl radicals. DFO also alters iron regulatory genes and proteins binding activity, thereby reducing cellular vulnerability to iron [Chen 2010; Messer 2010]. However, DFO has multiple and diverse neuroprotective properties, which may be only partly related to its iron chelating abilities. DFO also prevents apoptosis induced by glutathione depletion and oxidative stress in embryonic cortical neuronal cultures by activating a signal transduction pathway leading to activation transcription factor 1/cAMP response element-binding protein (ATF-1/CREB) and hypoxia inducible factor (HIF-1), and expression of genes known to compensate for oxidative stress [Zaman 1999]. It inhibits prolyl 4-hydroxylase activity, which may lead to protection from oxidative stress-induced cell death [Siddiq 2005; Ratan 2008]; induces transcription of heme oxygenase-1; suppresses the upregulation of activated c-Jun N-terminus kinase (JNK) seen after ICH [Wan 2009]; exerts anti-inflammatory effects by stimulating cyclooxygenase [Tanji 2001]; blocks the neurotoxic effects of hemoglobin via inhibition of glutamate-mediated excitotoxicity [Regan 1996]; and exerts anti-phagocytic effects in animal models of ICH [He 2008]. Our phase I study also suggests that DFO has a modest blood pressure lowering effect when administered by IV infusion, which might be beneficial in patients with ICH [Anderson 2008; Suri 2008].

2.2 SUPPORTING EVIDENCE

2.2.1 SUPPORTING EVIDENCE THAT DFO ATTENUATES NEURONAL INJURY AFTER ICH

2.2.1.1 IN VITRO STUDIES

Several studies have shown that DFO can reduce hemoglobin-induced neurotoxicity in experimental models of ICH. Regan and Rogers [Regan, 2003] showed that delayed treatment with DFO markedly attenuates the production of reactive oxygen species and neuronal death induced by adding hemoglobin to mixed neuronal/astrocyte cell cultures. In another study, Regan and Panter [Regan, 1993] showed that DFO completely blocked hemoglobin-induced neuronal death in neocortical cultures derived from fetal mice. Regan and Panter [Regan, 1996] also showed that hemoglobin potentiates the neurotoxicity of glutamate agonists in primary murine cortical cultures, and that this effect was

attenuated by DFO. Goldstein et al [Goldstein, 2003] showed that treatment with DFO significantly reduces the production of reactive oxygen species and cell death induced by hemin in human neuron-like cells. Similarly, Levy et al [Levy, 2002] showed that DFO diminishes hemin-induced cell death in pheochromocytoma (PC12) and neuroblastoma (SH-SY5Y) cell lines.

2.2.1.2 IN VIVO STUDIES

Bilgihan et al [Bilgihan, 1994] studied the effects of DFO on lipid peroxidation and Na-K ATPase activity after experimental ICH in guinea pigs, and found that DFO treatment reduces brain malondialdehyde content and induces recovery of Na-K ATPase activity, suggesting that DFO can exert potential neuroprotective effects to counteract the deleterious effects of ICH. Pelit et al [Pelit, 2003] examined the effects of systemic treatment with DFO on the pathological changes in the optic nerve after experimental retrobulbar hematoma in rabbits, and were able to detect ultrastructural changes and abundant iron pigment accumulation in the orbital fat tissue following induction of hematoma. These microscopic changes were significantly less pronounced in DFO-treated rabbits. Huang et al [Huang, 2002] examined the effects of intraperitoneal administration of DFO (500 mg/kg) on brain edema in rats pre-treated with hemoglobin degradation products via stereotactic infusion into the brain; they found that DFO significantly attenuated the brain edema induced by hemoglobin and its breakdown products. In similar studies, Nakamura et al [Nakamura, 2004] investigated the effects of repetitive administration of DFO (100 mg/kg intraperitoneally every 12 hours), starting 2, 6, and 24 hours after induction of ICH in rats, on markers of DNA oxidative damage and repair. They found that treatment with DFO ameliorated ICH-induced changes in 8-hydroxyl-2'-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage, and increased levels of apurinic/apyrimidinic endonuclease/redox effector-factor 1 (APE/Ref-1), a protein involved in DNA repair following oxidative damage, indicating that DFO may be a potential therapeutic agent for ICH by reducing the oxidative stress caused by the release of iron from the hematoma.

Several experimental studies investigated whether DFO can reduce ICH-induced brain injury, by examining its effects on brain edema, severity of neurological deficits, and performance on sensorimotor behavioral tests [Nakamura, 2003-2004; Wan 2006-2009; Gu, 2009; Okauchi 2009]. In a piglet ICH model, ICH resulted in development of a reddish perihematoma zone, and iron accumulation, ferritin upregulation, and neuronal death within that zone, which were all reduced by intramuscular administration of DFO at 50 mg/kg bid for 3 or 7 days after ICH [Okauchi 2009] (Figure 2.2.1.2-A-C).

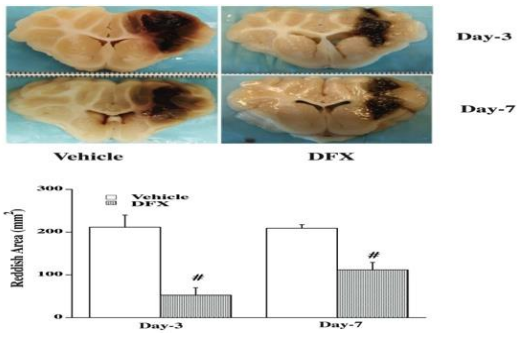

Figure 2.2.1.2- A: Deferoxamine (DFX) reduces the reddish zone around the hematoma after 3 and 7 days of treatment in a pig model of ICH.

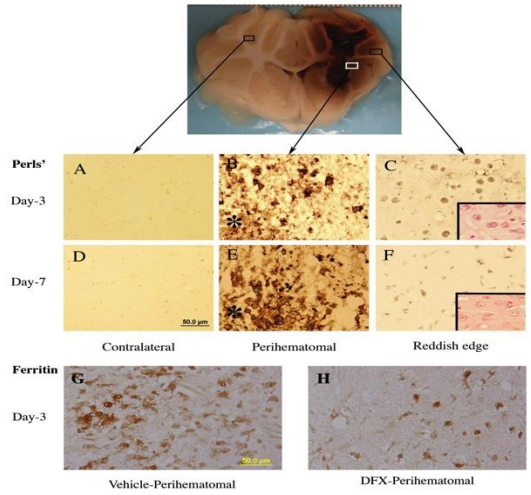

Figure 2.2.1.2- B

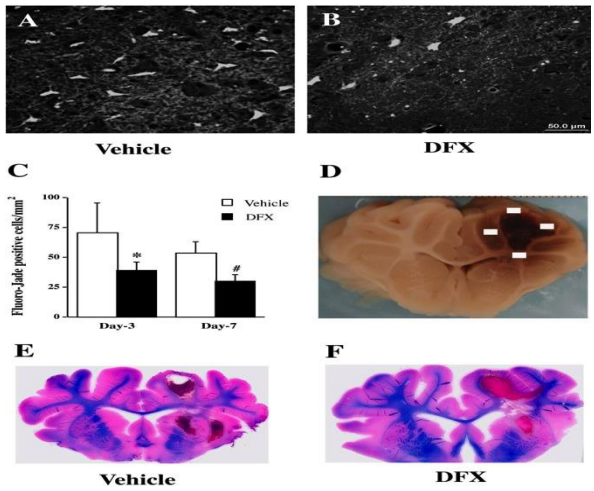

Figure 2.2.1.2- C

Figures 2.2.1.2- (B-C): B shows iron histochemistry (Perls staining) and ferritin immunoreactivity in the brain after ICH (* in D & E indicates the hematoma; inserts in C & F indicates hematoxylin and eosin staining). C shows Fluoro-Jade C-positive cells, which indicates neuronal degeneration, in the perihematoma area [A-C]; D shows 4 sampled field for Fluoro-Jade C cell counting); and Luxol fast blue staining of the white matter [E & F]. Courtesy of Dr. Guohua Xi.

2.2.2 SAFETY AND TOLERABILITY OF DEFEROXAMINE IN PATIENTS WITH ACUTE CEREBRAL HEMORRHAGE (R01 NS 057127)

OVERVIEW AND OBJECTIVES - This was a prospective, open-label, multiple-tier, dose-finding, multi-center, preliminary clinical study to evaluate the safety and tolerability of repeated treatments with DFO in patients with ICH. The study was planned to evaluate DFO dose-tiers ranging from 7 to 125 mg/kg/day (up to a maximum dose of 6000 mg/day) using the Continual Reassessment Method (CRM). The initial dose of the drug was administered within 18h after stroke symptom onset by IV infusion at a rate of 7.5 mg/kg/hour and repeated daily for 3 consecutive days. Four clinical sites participated in the study (Beth Israel Deaconess Medical Center, Massachusetts General Hospital, Medical College of Wisconsin, and Hartford Hospital). The Division of Biostatistics and Epidemiology at the Medical University of South Carolina served as the Statistics and Data Management Center for the study. Subject recruitment began in July 2008.

THE PRIMARY OBJECTIVES were: 1) To evaluate the safety and tolerability of repeated IV infusions of DFO in patients with spontaneous ICH; and 2) To determine the maximum tolerated dose (MTD) of DFO (highest dose regimen ≤ 125 mg/kg that can be safely administered and tolerated) in patients with ICH to be adopted in subsequent studies to test the efficacy of DFO in ICH.

Enrollment into every dose tier, starting with 7 mg/kg daily for 3 days, was completed before enrollment into the next tier began. Each subsequent dose level was determined using the Piantadosi-modified CRM (Piantadosi 1998). The dose-toxicity curve was re-estimated based on safety data generated throughout the study. At least 3 patients were enrolled in each dose-tier. The safety information, guiding transition from one dose tier to the next, was based on the number of subjects in a cohort who experienced pre-defined dose-limiting toxicities (DLT) during the first 7-day period or until discharge, whichever occurred first, following initiation of DFO treatment. The acceptable probability of DLT

was set at 0.40. The dose-limiting toxicity (DLT) was pre-defined as any of the following adverse events, fatal or non-fatal, occurring within 7 days or until discharge, whichever occurs first, of treatment initiation: 1) Anaphylaxis (at any time point during DFO infusion); 2) Hypotension (defined as a decrease in SBP > 20 mm Hg or DBP > 10 mm Hg, or a SBP ≤ 85 mm Hg, confirmed by 3 consecutive readings, requiring medical treatment at any time point during DFO infusion that cannot be explained by other causes); 3) Worsening neurological status (defined as an increase ≥ 4 points on NIHSS, or a decrease of ≥ 2 points on GCS, that cannot be explained by other causes, compared to baseline values occurring at any point during DFO infusions); 4) Mortality within 7 days of hospitalization; and 5) Any adverse event prolonging hospital stay, resulting in emergent medical therapy, or resulting in death. All of these events were considered SAEs for the purpose of this study. Patients underwent repeated clinical (neurological, visual and auditory, and general physical examinations) and laboratory evaluations at regular intervals throughout their participation in the study, from the day of enrollment until day 90, for adverse events. The 30-day neurological and functional status was determined by NIHSS, extended Glasgow outcome scale (eGOS), Barthel index (BI), and mRS. The patients or their surrogates were contacted by phone on day 90±7 days to compute mRS, eGOS, and BI, and to assess 3-month mortality.

STUDY STATUS AND RESULTS: Enrollment was completed in January 2010; the last subject completed the 90-day assessment in April 2010. A total of 20 subjects were enrolled into 5 DFO dose tiers, ranging from 7 mg/kg/day to 62 mg/kg/day. Because the recommended subsequent dose was within 5% (a pre-specified convergence criterion) of the 62 mg/kg/day dose, the study was concluded with the 62 mg/kg/day dose as the recommended MTD.

Number of subjects enrolled by dose-tier**:** 7 mg/kg = 4; 32 mg/kg = 3; 47 mg/kg = 3; 57 mg/kg = 4; 62 mg/kg = 6. An additional cohort of 3 subjects was treated at 62 mg/kg once it was determined to be the MTD to ascertain the safety and tolerability of this dose before proposing its use in the current study). The detailed results are included in Appendix I. The main results are summarized below.

SAFETY DATA: Sixteen non-serious adverse events were possibly or probably related to the study drug. The most common were injection site irritation and IV infiltration. Six subjects experienced 12 SAEs and 3 subjects had 4 DLTs. Three subjects (15%) died during the 90-day follow-up period: one subject died in hospital within 7 days of ICH onset and two between 7-30 days after ICH onset. None of the SAEs, DLTs, or mortalities was adjudicated to be related to the study drug. There were 2 cases of respiratory failure; both in the 62 mg/kg/day dose-tier and were thought to be related to aspiration pneumonia and adjudicated as being unrelated to the study drug. However, a recent expert review found that one of these cases was an undiagnosed ARDS, and agreed that aspiration was a plausible explanation for it.

PHYSIOLOGICAL DATA: Laboratory data - There were no differences in routine laboratory values and in the incidence of abnormalities and change from baseline in EKG parameters. Overall, daily DFO infusions at a rate of 7.5 mg/kg/hour up to 62 mg/kg/day (up to a maximum of 6000 mg/day) were well tolerated without significant alterations of hemoglobin or hematocrit, hematological parameters, and renal or hepatic functions. Treatment with DFO for 3 consecutive days at all 5 dose-tiers did not result in iron deficiency. Overall, the median values of the change in iron parameters from baseline to after the 3rd DFO infusion were as follows: serum iron (3.5 ug/dl; 95% CI -23, 45); transferrin (-18 ng/ml; 95% CI -43, 5); total iron binding capacity (8.5 ug/dl; 95% CI -47, 30); and ferritin (32.5 ng/ml; 95% CI 6, 74). We found no relationship between DFO dose and changes in serum iron studies. Vital signs (heart rate; respiratory rate; oxygen saturation; and temperature) - Overall, DFO administration did not result in important alterations in these variables. Blood pressure: DFO had a moderate BP-lowering effect. Overall, the median mean BP at baseline was 95.8 mmHg (95% CI 84, 100.3) vs. 93.2 mmHg (95% CI 87.6, 98) during the infusions. A total of 8 patients (40%) experienced a maximal drop in mean BP >20% (median 0.29; 95%CI 0.27, 0.39) at some point during the infusions compared to baseline values. One subject required vasopressors; his hypotension was thought to be related to intubation and anesthesia. None of the remaining 7 subjects required any medical treatment.

RADIOLOGICAL DATA: We found no radiological evidence to suggest that treatment with DFO exacerbates the natural enlargement of ICH or PHE over 72h after treatment. The overall median change in relative PHE volume from screening to post-3rd DFO infusion was 0.48 (95% CI 0.10, 0.76) and from screening to day-7 or discharge (whichever

occurred first) was 0.87 (95% CI 0.51, 1.28). These exploratory results contrast with previous studies of the natural history of relative PHE evolution [Mehdiratta 2008; Gebel 2002], which showed that the relative PHE volume almost doubles by 72h.

FUNCTIONAL OUTCOME DATA: Two subjects withdrew consent, one after the 7-day visit (mRS =5), and one after the 30-day visit (mRS =1). Among the remaining 18 subjects, 9 subjects (50%) had mRS scores of 0-2; 2 (11%) had a score of 3; and 7 (39%) had scores of 4-6.The 90-day mortality rate was 15%.

CONCLUSIONS: Repeated daily infusions of DFO at doses up to 62 mg/kg/day (up to a maximum of 6000 mg/day) in patients with acute spontaneous ICH for 3 consecutive days after ICH onset are feasible, well tolerated and do not increase serious adverse events or mortality.

2.2.3 HIGH DOSE DEFEROXAMINE IN INTRACEREBRAL HEMORRHAGE (HI-DEF IN ICH) (U01 NS074425)

OVERVIEW AND OBJECTIVES - Part 1 of the current study was a prospective, multi-center, double-blind, randomized, placebo-controlled, phase-II clinical trial. Subjects were randomized to either DFO at 62 mg/kg/day (up to a maximum daily dose of 6000 mg/day), or saline placebo, given by continuous IV infusion for 5 consecutive days. Treatment was initiated within 24 hours after ICH symptom onset. Randomization controlled for baseline imbalances associated with baseline ICH score (0-2 vs. ≥3), ICH onset-to-treatment time (OTT) window (≤12h vs. >12-24h), and concurrent warfarin use. All subjects were followed for 3 months and received standard of care therapy while participating in the study.
THE MAIN OBJECTIVES WERE: **1-** TO assess whether it is futile to move DFO forward as a therapeutic intervention for ICH into Phase III evaluation, by comparing the outcome of DFO-treated subjects to placebo-treated subjects with respect to good outcome (defined as mRS of 0-2 at 90 days), in a futility analysis; and **2**- TO assess the safety of DFO infusions (at a dose of 62 mg/kg/day, up to a maximum daily dose of 6000 mg/day), given for 5 consecutive days, in a large cohort of ICH patients. We specifically wished to collect more data on treatment-related adverse events in order to ascertain that patients with ICH could complete this dose given over 5-day duration of infusion without experiencing unreasonable neurological complications, mortality, or other serious adverse events related to DFO use.

STUDY STATUS AND SAFETY RESULTS - Throughout the study, we continued to assess the safety of DFO. Enrollment was placed on hold after enrollment of 42 subjects to investigate a potential safety concern – Adult Respiratory Distress Syndrome (ARDS). ARDS is reported as a potential side effect of prolonged intravenous infusions of high dose DFO in the product's package insert. Five cases of ARDS were reported. An expert in ARDS, blinded to treatment assignments, reviewed all 5 cases as well as 3 cases reported as respiratory failure and 3 cases reported as pulmonary edema. The expert concluded that 2/3 cases reported as pulmonary edema were possibly/probably ARDS, suggesting a total of 7 ARDS cases. The expert review identified a plausible cause for ARDS, other than the study drug or ICH itself, in 4 cases, while no other explanation was apparent for the remaining 3 cases. After careful review of the data, the DSMB unblinded the investigators to the treatment assignment. Six of the 7 cases of ARDS occurred in the DFO-treated group. Three of the 42 enrolled subjects died (7%); all had ARDS, and the cause of death was attributed to ARDS in 2 subjects. No other safety concerns emerged. A total of 36 SAEs were reported in 15 subjects; 22 of which occurred in 9 DFO-treated subjects. One MedWatch report was submitted for hypophosphatemia as it was judged to be severe, unexpected, and possibly related to the study drug. Overall, hypophosphatemia was reported as an AE in 3 subjects (2 in the DFO- and 1 in the placebo group). Other analyses are yet to be performed.

CONCLUSIONS - The NINDS-appointed DSMB concluded that: "although the ARDS cases in the treatment group were in the ballpark frequency of at least one paper in the literature on ARDS in patients with ICH [Elmer 2013], the imbalance in the frequency of ARDS cases between the treatment and placebo groups suggested that pulmonary toxicity of the

drug was highly likely". HI-DEF was therefore terminated due to safety concerns, and the initial protocol has been modified to minimize the potential for pulmonary toxicity of DFO and to enhance the safety of future participants.

2.3 SUMMARY OF BACKGROUND AND RATIONALE

Collectively, the above data indicate that: 1) extensive preclinical investigations, in vitro and in vivo, by different investigators and in different species, show that treatment with DFO confers neuroprotection after ICH; 2) although DFO may work directly by chelating iron, it also has several other neuroprotective properties which can be beneficial after ICH; 3) repeated daily administrations of IV infusions of DFO to ICH patients is feasible and largely well-tolerated; and 4) the potential for pulmonary toxicity and ARDS is higher in ICH patients treated with continuous IV infusions of DFO at 62 mg/kg/day (up to a maximum total dose of 6000 mg/day), for 5 consecutive days; a lower dose and shorter duration of treatment might help to ameliorate this toxicity to improve the benefit/risk ratio.

These findings indicate that DFO is a potentially promising candidate intervention to target the secondary effects of ICH, and provide a rationale for its therapeutic use to improve the overall outcome in patients with ICH, particularly if the safety concerns encountered in part 1 (HI-DEF) of this study can be ameliorated by lowering the daily and total dosage of DFO and improved selection of subjects to exclude those at high risk for ARDS. Because hemoglobin degradation starts hours-days after ICH onset, the potentially delayed and slow pace of hemoglobin- and iron-mediated injury may facilitate treatment at a delayed time window after ICH onset. This could extend the potential utility of DFO as a therapeutic intervention to a large proportion of ICH patients. DFO is relatively inexpensive and is likely to be a highly cost-effective therapy for ICH and complementary to ongoing efforts targeting hematoma and its expansion. We generally hypothesize that treatment with DFO would minimize ongoing neuronal injury after ICH, via several diverse mechanisms, and would improve the outcome in these patients. As a prelude to test this hypothesis, this Phase II study will assess the futility of DFO as a therapeutic intervention in ICH before embarking on a large Phase III trial. In addition to allowing us to assess the futility of moving DFO forward to phase III efficacy testing as a potential therapeutic intervention in ICH, this study will allow us to gain experience with logistical aspects of trial conduct, and the data and results from this study will be used to guide our planning for a possible future Phase III study.

2.4 SIGNIFICANCE

This study will provide a crucial "go/no-go" signal to determine if embarking on a large-scale, costly phase III trial to investigate the efficacy of DFO as a treatment for ICH is worthwhile. This study will also provide important information to guide the planning and conduct of a future phase-III trial, if it is determined that the treatment with DFO is not futile. It will allow us to gain experience with logistical aspects of trial conduct, such as blinding and randomization, prior to phase-III testing. Furthermore, results from this study can provide valuable information regarding the dichotomized mRS outcome rate among control subjects, the potential for a differential treatment effect in the ≤12 vs. >12-24 hour time windows, and appropriate inclusion and exclusion criteria (HI-DEF has been already informative in this regard); information which can guide the design of a potential future Phase III trial. In addition, we plan to collect data on various outcome scales (mRS, NIHSS, SIS-16 [Duncan 2003], and MoCA [Pendlebury 2010]), which will allow us to explore the utility of these various outcome measures in phase-III.

If successful, this study can potentially result in new means to improve the outcome of patients with ICH. A successful study demonstrating the efficacy of DFO in ICH would be of considerable significance to the field and the society. A wealth of data, generated from various planned exploratory analyses in this study, can still help to advance our knowledge and understanding of the pathophysiology of ICH, such as the relationship between PHE volumes and outcome and the relationship between ICH and cognitive function, even if DFO is found to be futile. These additional analyses can generate novel hypotheses for future investigations in ICH. The potential advantage of novel treatments for ICH and better understanding of its pathophysiology and relationship to outcome with regard to patients' welfare, public health and cost containment is noteworthy.

3 STUDY DESIGN

3.1 STUDY OBJECTIVES

THE STUDY HAS TWO PRIMARY AIMS: 1- To determine if it is futile to move DFO forward to Phase III evaluation, using mRS 0-2 at 90 days as the outcome based on an absolute difference in treatment effect ≥12% in favor of DFO; and 2- To further assess the safety of DFO infusions, at a dose of 32 mg/kg/day, given over a consecutive 3-day period, in particular serious adverse events including ARDS.

THE SECONDARY AIMS are to: 1- Explore the differences between early (≤12h) and late (>12-24h) time windows in DFO treatment effect on functional outcome; 2- Determine the overall distribution of ordinal scores on mRS at 3 months in DFO- and placebo-treated subjects, and to perform a dichotomized analysis considering the proportion of DFO- and placebo-treated subjects with mRS 0-3; 3- Perform dichotomized analyses considering the proportion of DFO- and placebo-treated subjects with mRS 0-2 and 0-3; and to determine the overall ordinal distribution of scores on mRS at 6 months; 4- Determine mortality during the 180-day follow-up period (all causes and ICH-related); and 5- Obtain data on the changes in NIHSS between presentation and day-90, and MoCA and SIS-16 scores at 3 months to explore the effects of DFO on neurological, functional, and cognitive functions.

ADDITIONAL PLANNED EXPLORATORY ANALYSES include assessments of: 1- The effects of treatment with DFO on relative PHE volume progression between admission (i.e. screening) and post-treatment CT scans in DFO-treated patients as potential markers of DFO's biological activity on brain tissue [Gebel 2002; Mehdiratta 2008; Leira 2004; Okauchi 2009-2010]; 2- Whether the effect of DFO on outcome is dependent on initial ICH volume, after adjusting for other prognostic variables, to determine if specific limits for ICH volume should be specified as exclusion/inclusion criteria for future studies; 3- The effects of DFO on the size of ventricular enlargement in patients with intraventricular extension of ICH , not requiring EVD, as a potential marker of treatment utility in IVH [Chen 2011]; 4- The effect of treatment with DFO on incidence of symptomatic cerebral edema (unexplained increase in NIHSS >4 points or decrease in GCS >2 points) during hospitalization, up to day 7 or discharge whichever is earlier; and 5- Whether progression of PHE can be a radiological/biological marker of activity which can be correlated with clinical outcomes and treatment effect of DFO.

3.2 OVERVIEW OF STUDY DESIGN

This is a prospective, multi-center, double-blinded, randomized, placebo-controlled, phase-II clinical trial. The total sample size required is 294 subjects with ICH. Subjects will be randomized in a 1:1 ratio to receive either DFO at 32 mg/kg/day (up to a maximum daily dose of 6000 mg/day), or a matching saline vehicle (placebo), given by IV infusion for 3 consecutive days, in a blinded manner. Treatment will be initiated within 24 hours after ICH symptom onset. Subjects will undergo repeated clinical, imaging, and laboratory evaluations at regular intervals throughout their participation in the study, from the day of randomization until day 180. All adverse events will be assessed until day-7 or discharge (whichever is earlier), and new SAEs until day-90. Mortality and continuing SAEs will be assessed until day 180. Functional status will be determined by mRS scores, in person at 30±7 and 90±7 days; the patients or their surrogates will be contacted by phone on days 60±7 and 180±7 to assess mRS [Merino, 2005].

3.3 RATIONALE FOR STUDY DESIGN AND PROTOCOL MODIFICATIONS

The rationale for the proposed dose regimen, therapeutic time window, duration of treatment, study design, inclusion of a placebo group, and surrogate measures of DFO efficacy is as follows:

Dose Reduction and New Dose Selection: The 62 mg/kg/day dose was identified in our Phase I study as the MTD in ICH subjects and was the dose used for the 42 participants enrolled in HI-DEF. This was based on safety data from the phase I study, where DFO did not appear to increase the overall rate of SAEs or mortality compared with placebo-treated patients in previous ICH trials [Mayer 2005; Mayer 2008; Lyden 2007; Haley 2005], and the notion that the efficacy of a drug often has a monotonically non-decreasing dose-response relationship. However, the observation of 6 cases of ARDS among DFO-treated participants in HI-DEF, and the reported association of prolonged high-dose intravenous infusions of DFO with the development of ARDS [Tenenbein 1992] prompted us to reduce the dose to 32 mg/kg/day (up to a maximum daily dose of 6000 mg per day) in the current protocol to maximize safety and minimize harm. Pre-clinical studies in aged rats compared 3 dose regimens of DFO; 10 mg/kg, 50 mg/kg, and 100 mg/kg every 12 hours [Okauchi 2009]. Based on mass constant conversion factors and the FDA guidance for the industry for estimating the human equivalent dose (HED) in clinical trials, the calculated HEDs are approximately 3, 16 and 32 mg/kg/day, respectively [http://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInfmation/Guidances/ ucm078932.pdf]. The latter dose regimens (HEDs 16 and 32 mg/kg/day) were superior to the first dose regimen in improving performance on sensorimotor behavioral tests at days 28 and 58 following induction of experimental hemorrhage. We now opt for a dose of 32 mg/kg/day based on the following considerations:

I. This dose, while assuring increased tolerability and safety of the drug, represents the upper limit of effective doses in animal models - Data from rat models of ICH indicate that HEDs ranging from 16 to 32 mg/kg/day are effective in reducing brain edema formation and brain tissue atrophy, and improving neurological and functional recovery [Okauchi 2009].
II. This dose provides a better safety margin - No cases of respiratory failure or distress were reported in any of the 10 participants who received DFO in doses ranging from 32 to 57 mg/kg/day in our Phase I study (32 mg/kg/day, n=3; 47 mg/kg/day, n=3; 57 mg/kg/day, n=4).
III. Equivalent dose in piglet model of ICH exerts biological activity on the brain tissue. It reduced the perihematomal reddish zone, white matter injury, iron accumulation, ferritin upregulation, and neuronal death within that zone [Gu 2009].

The 6000 mg/day limit, irrespective of body weight, is based on FDA recommendations and the manufacturer's brochure to avoid the risk of serious adverse effects of higher dose-regimens.

TIME-TO-TREATMENT WINDOW: The decision to initiate DFO treatment up to 24h after ICH symptom onset and not beyond, and to balance randomization based on OTT, is based on data from animal studies. Okauchi et al [Okauchi 2010] examined the effects of DFO when administered within 2h, 4h, 12h, 24h, and 48h after the induction of ICH on brain edema formation, forelimb placing and corner turn scores, and brain atrophy in aged rats. They found that: 1) Regardless of the time-to-treatment window, DFO improved forelimb placing and corner turn scores compared to vehicle treatment, and the differences in rats' performance of these tests between these various time points were not significant; 2) DFO effects on functional recovery, however, were seen faster when the treatment was begun within 24h as

opposed to 48h (28 days vs. 56 days); and 3) DFO reduced brain tissue loss and atrophy when administered within 24h after induction of ICH compared to 48h delayed treatment. The faster improvement of function noted in these studies is suggestive of greater efficacy for earlier treatment and might also translate into potentially significant cost savings from reduction in healthcare related expenses and earlier ability of the patients or their caregivers to return to work and avoid lost wages. In addition, very few patients in the phase I study presented more than 24h after ICH onset, indicating that only few additional patients are likely to be enrolled by extending the OTT beyond 24h at this stage.

Conversely, animal data do not strongly support limiting treatment to an earlier time window, such as within 12h. Although Okauchi et al [Okauchi 2010] reported that the optimal therapeutic window of DFO to reduce PHE formation was about 12h, the correlation between PHE and deficits on sensorimotor behavioral tests weeks-to-months after ICH was weak, which they attributed to the sensitivity of their assays. Previous studies have shown that PHE formation correlates with forelimb placing during the acute phase of ICH [Hua 2002]. A serial MRI study of the natural history of PHE in patients with ICH reported similar results; PHE correlated with worsening neurological status at 48h, but not 3-month functional outcome [Venkatasubramanian 2011]. Indeed, the influence of PHE on long-term recovery of ICH patients is debatable [Inaji 2003; McCarron 1999; Sansing 2011; Sykora 2009; Zazulia 1999]. Therefore, restricting the time-to-treatment to 12h or even less, for the sole purpose of its potential effect on PHE, seems unnecessary. In addition, very few patients presented within 12h in the phase-I study. Attempting to restrict the OTT window to less than 12h could limit recruitment into the study as well as the generalizability of the results to the wider ICH population. Therefore, OTT time is incorporated into the randomization algorithm in order to achieve an acceptable treatment balance. Similar to animal studies, this would also allow for further exploratory analysis to assess the effect of early vs. delayed treatment with DFO on PHE and outcome.

DURATION OF TREATMENT: Pre-clinical studies that examined the optimal duration of treatment with DFO following ICH produced variable results. In one study, treatment with DFO (HED ~ 16 mg/kg/day) for 2, 5, 7, or 14 days improved performance compared with placebo on forelimb placing test at days 28 and 56 [Okauchi 2010]. However, residual neurological deficit was present on corner turn test in animals treated for less than 7 days, and the 7-day treatment was associated with less adverse reactions than the 14 days, leading the investigators to conclude that the optimal duration of treatment in this model was 7 days. In other studies, treatment with DFO at HEDs of 16 and 32 mg/kg/day for 3 days resulted in significant improvement in rats' performance on both forelimb placing and corner turn tests and reduced brain atrophy at 56 weeks compared with placebo [Okauchi 2009]. In piglets, treatment with DFO for 3 or 7 days had similar protective effects on perihematomal reddish zone, white matter injury, iron accumulation, ferritin upregulation, and neuronal death within that zone [Gu 2009]. In other experiments, treatment with DFO at 200 mg/kg/day for 3 or 7 days after ICH also improved forelimb placing and corner turn scores and reduced brain edema [Nakamura 2003-2004]. Collectively, these results suggest that treatment with DFO for any duration ≥2 days results in improved functional performance, compared with vehicle treatment.

The phase I study assessed varying doses of DFO administered over a 3-day infusion period. The 3-day infusion duration was chosen for the following reasons: 1- Edema growth is fastest in the first 2-3 days after ICH onset and this initial growth (and not the later one) is associated with neurological deterioration [Venkatasubramanian 2011; Inaji 2003; Zazulia1999]; 2- The time course for hemoglobin hemolysis and release of its degradation products including iron is approximately 2-3 days [Macdonald 2004]; and 3- Iron in the perihematoma tissue peaks at day 3 after experimental ICH [Wu 2003]. Extending the duration of treatment to 5 days in HI-DEF was based on the above data in aged rats [Okauchi 2010]. The pulmonary toxicity of DFO is believed to be related to prolonged intravenous infusions of high doses of the drug, and a review of the 6 cases of ARDS in the DFO arm in HI-DEF revealed that the mean time from treatment to ARDS onset was ~ 78 hours, median ~ 76 hours. The longer duration of treatment might have contributed to increased pulmonary toxicity of the drug observed in HI-DEF, where 6/21 (28.6%) subjects in the treatment arm developed ARDS compared with 1/6 (16.7%) of patients who received the 62 mg/kg/day dose in phase I. Lowering the duration of treatment would decrease the total dose of the drug and might help to minimize the pulmonary toxicity of the drug without compromising the potential effectiveness of the drug. Therefore, we chose to decrease the duration of treatment to 3 days in this revised protocol.

Overall, a 3-day treatment provides the potential for improved drug safety and tolerability without significantly jeopardizing its efficacy. The 3-day treatment with DFO was superior to saline vehicle in improving functional outcome in rat models of ICH [Okauchi 2010]; although iron release from the hematoma continues for days-to-weeks, the time course of iron release from the hematoma may not directly correlate with the timing of iron toxicity. With time, there is an up-regulation in endogenous iron chelators after ICH which may limit iron toxicity and the need for more extended treatment with DFO; and the 32 mg/kg/day dose proposed in part 2 of this study exceeds the animal dose (100 mg/kg/day; HED 16 mg/kg/day) used in studies examining the optimal duration of DFO therapy after experimental ICH, and it is possible that the higher dosage and route of administration (IV as opposed to intramuscular in animal studies) might be as effective within a shorter treatment period.

STUDY DESIGN AND PLACEBO GROUP: The futility design directly addresses the question of whether or not DFO at a dose shown to be effective in animal models of ICH given over a clinically feasible duration of 3 days is of sufficient promise in improving functional outcome after ICH to consider a large-scale and costly phase-III trial. The proposed futility design is logically consistent with the aims of Phase II trials, which are to weed out ineffective interventions. It is not a substitute for phase-III and cannot by itself provide sufficient evidence to indicate that treatment with DFO is efficacious, since it is not designed or intended to test the efficacy hypothesis. Furthermore, non-futility in this phase-II study does not guarantee a positive phase-III result, which is important in preserving clinical equipoise for Phase III. Lastly, the futility hypothesis differs from hypotheses specified in traditional phase III efficacy trials and the probabilities of type-I and -II errors are interpreted differently. In futility analysis, we are less concerned about falsely concluding an ineffective treatment is possibly effective.

The advantage of the proposed two-arm design over a single-arm phase-II futility design is that it avoids the pitfalls associated with the use of historical data (temporal changes in other aspects of patient management, variations in data quality and protocol adherence, and differences in the eligibility criteria and specification of primary outcome measure between the various studies). These confounding variables can distort estimates of the historical reference proportion and are difficult to account for in a single arm study. Besides addressing these concerns, the inclusion of a placebo arm allows us to conduct secondary exploratory imaging analyses to determine the natural history of PHE progression and the effects of DFO on PHE as a surrogate marker of its biological activity on brain tissue. Furthermore, the proposed two-arm design allows us to configure and evaluate the logistics of randomization and blinding processes.

CHOICE OF FUTILITY THRESHOLD: The Minimum Clinically Important Difference (MCID) in ICH is to some extent arbitrary and is largely derived from Traumatic Brain Injury literature, where demonstration of effectiveness was set at a 10% increase in the percentage of patients with favorable outcome in many clinical trials of head injury. Indeed, previous and ongoing Phase III trials in ICH, such as ATACH-2, used MCID of 10% or greater in the absence of data supporting that lower magnitude of difference will change practice patterns. For example, in the GAIN International and GAIN America Studies of the glycine antagonist, Gavestinel, the rate of mRS 0-2 was approximately 4%-to-5% higher in Gavestinel-treated patients, compared with placebo, but this difference was not considered encouraging to further develop the drug as a therapy for ICH [Haley 2005]. We relied on data from previous ICH studies, the NINDS rt-PA trials in ischemic stroke, and outcome data from the phase-I study to derive a threshold for futility, based on mRS score of 0-2 at 3 months, in the current study. In phase-II study of factor VIIa in ICH, the proportion of treated patients with mRS 0-2 at 3 months was 12.8% to 17% (depending on the dose) greater than the placebo patients [Mayer 2005]. In the NINDS rt-PA trials, the proportion of rt-PA-treated patients with mRS scores of 0-2 at 3 months was 12% greater than their placebo-treated counterparts. Taking these numbers into consideration, the fact that no specific treatments exist to prevent disability after ICH, and the frequent observation of "winner's curse" in previous stroke trials (a phenomenon by which effect size tends to be overestimated in pre-phase III trials, only to become smaller in larger Phase III trials which involve more sites and greater heterogeneity), a 12% difference in the proportion of DFO-treated subjects who achieve

favorable outcome compared with placebo was chosen as the threshold for futility in the current study. Although setting the bar lower in this futility study may result in a more positive outcome favoring moving deferoxamine forward for Phase III evaluation, at the expense of a much larger sample size, the general consensus was that an effect size of 12% for the current proposal provides a balance between setting the bar too high (leading to rejection of a potentially effective therapy) or too low (leading to further testing of a marginally-effective mediocre therapy with its associated expense and resources, which could hinder the development of truly effective treatments for ICH).

CHOICE OF EFFICACY OUTCOME MEASURE: The mRS was chosen for the primary outcome assessment because of its high inter-rater reliability and to be consistent with previous ICH trials. The decision to use a dichotomous outcome aims to increase the sensitivity of detecting meaningful differences by reducing the rate of misclassification or score assignment. Favorable outcome, as opposed to poor outcome, was specified based on careful review of the putative beneficial mechanism(s) of DFO and expected lack of an effect from treatment on reducing hematoma growth, a major predictor of mortality and significant disability after ICH [Davis 2006], as well as the phase-I outcome data. However, it is possible that DFO might result in an increase in the proportion of patients with mRS 0-3 (and hence a decrease in the proportion of patients with mRS 4-6) instead of mRS 0-2. Although mRS 0-3 is less favorable than the primary outcome of mRS 0-2, it would still be a desirable effect in patients with ICH given that no treatments exist to reduce disability. Therefore, the proportion of DFO- and placebo-treated subjects with mRS 0-3 at 90 days will also be evaluated. The trial is adequately powered to assess the alternative futility hypothesis using mRS 0-3 as the outcome based on an absolute difference in treatment effect ≥13% in favor of DFO. Given increased acceptance of ordinal analysis of mRS in the stroke field and recognition that ICH patients may take longer to recover, we added ordinal analysis across all mRS scores and extended the follow up period to include assessment of mRS by phone at 6 months as secondary outcome measures.

SURROGATE MEASURES OF DFO BIOLOGICAL ACTIVITY: We plan to examine the effect of treatment with DFO on relative PHE volume and progression at days 3-4 as a surrogate marker of biological activity on brain tissue. Delayed brain edema formation following the first 24h after ICH is related to red blood cells' lysis and hemoglobin- and iron-mediated toxicity [Xi 1998/2002; Lee 1996; Qing 2009]. Treatment with DFO reduces brain edema, CSF free iron levels, iron deposition in the perihematoma region, and residual cavity volume after experimental ICH [Nakamura 2003-2004; Wan 2006-2009; Gu 2009; Okauchi 2009]. Human studies suggest that PHE continues to grow for weeks after ICH, and that edema progression is fastest during the first few days [Venkatasubramanian 2011]. Although the influence of PHE on long-term recovery after ICH is debatable [Hua 2002; Inaji 2003; Zazulia1999; McCarron 1999; Sykora 2009; Sansing 2011], there is evidence that early edema progression correlates with early neurological deterioration [Venkatasubramanian 2011; Inaji 2003]. Therefore, secondary analyses will examine the effects of treatment on PHE immediately following completion of the infusion and not weeks later, since PHE growth during the early time period seems to be more clinically relevant. Regardless of the clinical impact of PHE, demonstrating an effect of DFO on this variable would at least provide secondary evidence of the agent's biological activity under the chosen dosing regimen. The relative PHE volume (the absolute PHE volume divided by the hematoma volume) was chosen as it has been used previously to detect serial changes in edema volume while adjusting for subsequent hematoma expansion or retraction [Gebel 2002; Mehdiratta 2008].

4 SELECTION AND ENROLLMENT OF SUBJECTS

Study subjects will be recruited from the emergency departments or inpatient services at > 20 hospitals in North America under the responsibility of the site investigators. Patients with diagnosis of ICH, as confirmed by CT scan, in whom the first dose of the study drug can be administered within 24h from symptom-onset (determined from the time the patient was last known to be without presenting deficits), will be prospectively enrolled, according to the eligibility criteria. To minimize selection bias, consecutive patients who meet all eligibility criteria will be considered for enrollment.

4.1 Inclusion Criteria

1) Age ≥ 18 and ≤ 80 years
2) The diagnosis of ICH is confirmed by brain CT scan
3) NIHSS score ≥ 6 and GCS >6 upon presentation.
4) The first dose of the study drug is expected to be administered within 24h of ICH symptom onset (as described above).
5) Functional independence prior to ICH, defined as pre-ICH mRS ≤1.
6) Signed and dated informed consent is obtained.

4.2 Exclusion Criteria

1) Previous chelation therapy or known hypersensitivity to DFO products
2) Known severe iron deficiency anemia (defined as hemoglobin concentration < 7 g/dL or requiring blood transfusions
3) Abnormal renal functions, defined as serum creatinine greater than 2 mg/dl
4) Planned surgical evacuation of ICH prior to administration of study drug (placement of a catheter for ventricular drainage is not a contraindication to enrollment)
5) Suspected secondary ICH related to tumour, ruptured aneurysm or arteriovenous malformation, hemorrhagic transformation of an ischemic infarct, or venous sinus thrombosis
6) Infratentorial hemorrhage
7) Irreversibly impaired brainstem function (bilateral fixed and dilated pupils and extensor motor posturing)
8) Complete unconsciousness, defined as a score of 3 on item 1a of the NIHSS (Responds only with reflex motor or autonomic effects or totally unresponsive, and flaccid)
9) Pre-existing disability, defined as pre-ICH mRS ≥2
10) Coagulopathy - defined as elevated aPTT or INR >1.3 upon presentation; concurrent use of direct thrombin inhibitors (such as dabigatran), direct factor Xa inhibitors (such as rivaroxaban or abixapan), or low-molecular-weight heparin
11) Patients with confirmed aspiration, pneumonia, or evident bilateral pulmonary infiltrates on chest x-ray or CT scan prior to enrollment
12) Patients with significant respiratory disease such as chronic obstructive pulmonary disease, pulmonary fibrosis, or any use (chronic or intermittent) of inhaled O_2 at home
13) FiO_2 >0.35 (>4 L/min) prior to enrollment
14) Sepsis (present source of infection ± lactic acidosis defined as serum lactate >5 mmol/L and pH <7.35); Systemic Inflammatory Response Syndrome (defined as Temp >100.4F or <96.8F; Heart rate >90; Respiratory rate >20 or $PaCo_2$ <32 mmHg; WBC >12, <4 K/uL, or >10% bands); or shock (SBP <90 mmHg) at presentation
15) The presence of 4 or more of the following risk modifiers for ARDS prior to enrollment:
    a) Tachypnea (respiratory rate >30)
    b) SpO_2 <95%
    c) Obesity, defined as Body Mass Index (BMI) >30
    d) Acidosis (pH <7.35)
    e) Hypoalbuminemia (albumin <3.5 g/dL)
    f) Concurrent use of chemotherapy
16) Taking iron supplements containing ≥ 325 mg of ferrous iron, or prochlorperazine

17) Patients with heart failure taking > 500 mg of vitamin C daily
18) Known severe hearing loss
19) Known pregnancy, or positive pregnancy test, or breastfeeding
20) Positive drug screen for cocaine upon presentation
21) Patients known or suspected of not being able to comply with the study protocol due to alcoholism, drug dependency, noncompliance, living in another state or any other cause
22) Any condition which, in the judgement of the investigator, might increase the risk to the patient
23) Life expectancy of less than 90 days due to co-morbid conditions
24) Concurrent participation in another research protocol for investigation of another experimental therapy
25) Indication that a new DNR or Comfort Measures Only (CMO) order will be implemented within the first 72 hours of hospitalization.

4.3 STUDY ENROLLMENT PROCEDURES

4.3.1 SCREENING FOR POTENTIAL SUBJECTS

The majority of patients is expected to be recruited upon initial evaluation in the Emergency Department (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 potential eligible candidates will be examined and interviewed within 60-90 minutes of their arrival to the ED.

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 reason(s) for exclusion from the current study. The study coordinator at each site is required to enter the screening log data into the WebDCU™ study database on a monthly basis.

4.3.2 SCREENING EVALUATIONS

The following clinical, laboratory, and radiological assessments will be carried out upon screening of potential study subjects: 1) Demographic data; 2) Medical history; 3) Review of medications; 4) General physical examination and vital signs; 5) Neurological examination, including visual auditory assessment, NIHSS, and GCS; 6) Review of head CT scans and chest x-rays; 7) Review of all inclusion/exclusion criteria; 8) Determination of ICH score and pre-ICH mRS score; 9) Laboratory tests (hematology, serum chemistries, serum albumin, coagulation parameters, renal and hepatic function tests and urine analysis).

A baseline 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 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 Stroke Council of the American Heart Association [Morgenstern, 2010; please refer to appendix II].

A baseline chest x-ray is required before enrollment to exclude the presence of bilateral pulmonary infiltrates or pulmonary edema.

A negative serum pregnancy test is required for all women of childbearing potential prior to enrollment into the study.

4.3.3 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 witnessed, IRB-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 participant 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 subject's care in any way. Potential participants or their surrogates should be given ample opportunity 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 the subject's 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.

4.3.4 ENROLLMENT

Clinically and radiologically eligible patients for whom informed consent is obtained (from the subject or a legal representative or family member) will be randomized. Calculation of the ICH score [Hemphill 2001; please refer to appendix III] is required prior to randomization. Administration of the study drug to eligible candidates will only be permitted after completion of liver function tests and urine analysis, if not done upon presentation.

Participants should be reassessed immediately prior to the study drug administration to obtain a pre-treatment GCS and baseline NIHSS. Patients who exhibit significant clinical and neurological deterioration (i.e. develop fixed and 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 their participation in the study should be terminated.

To ensure that all eligible subjects presenting within 12h of ICH onset are enrolled in a timely fashion without delay: 1) enrollment and time from door (arrival-to-emergency room)-to-infusion will be monitored on an ongoing basis, and every attempt will be made to ensure that subjects are treated as soon as possible from symptom-onset; and 2) if enrollment into the early (≤12h) window is disproportionately low, we will implement a strategy of forced recruitment whereby each site will be required to enroll one subject into the early time window for each subject enrolled into the later (>12-24h) window (or maintain its overall ratio of ≤12h to >12-24h to at least 1:1) before subsequent enrollment into the later time window is permitted at this site.

4.3.5 DETERMINATION OF SUBJECT'S BODY WEIGHT

The subject's body weight will be obtained by self-report from the subject or his/her accompanying person to the ED, or estimated by the treating physician, if actual body weight cannot be determined during the acute phase of evaluation in order to prevent delays in administering the study drug. However, it is expected 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.

4.3.6 TREATMENT ALLOCATION AND RANDOMIZATION

Once it is determined that a patient meets all the eligibility criteria, the investigator(s) will log on to the secure, study-dedicated electronic database (WebDCU™) to enter demographics and required randomization data. The database will generate a randomization code. The investigator will then provide the site's pharmacy with the randomization code and subject weight. The pharmacist will retrieve the label with the corresponding randomization code from the Study Randomization Binder maintained separately in the pharmacy. The pharmacist will prepare the study drug for blinded administration. The pharmacists will be specifically instructed not to reveal treatment assignment to the investigators and not to break the blind. In the pilot phase I study, the reconstituted solution of DFO was colorless, and there were no specific treatment-related changes in laboratory tests including hematology, urine color, or adverse events to suggest that the active drug can be identified from placebo. The following additional measures will be taken to assure that the integrity of the blinding will remain intact: 1) An independent, unblinded statistician from the DCU, not involved in the operations of the study, will create the randomization algorithm; 2) Randomization codes will be numeric and will not contain any reference to the type or dose of treatment to be administered; and 3) The randomization binders will be kept in secured and locked cabinets in each pharmacy. There is no specific antidote to DFO. Therefore, unblinding is unnecessary in most cases. In cases of extreme emergency when the treating physicians request unblinding of treatment assignments for therapeutic purposes, the unblinding will only be revealed to the treating physicians but not the investigators. The treating physicians must be instructed not to reveal the blind to the subjects or study investigators. The study personnel (pharmacist) will be required to inform the Principal Investigator and the Project Manager within 24h in the event of unblinding. In cases where the treating physician is one of the study investigators, he/she also will be required not to reveal the identity of the study drug to other members of the study team, and not to perform subsequent study-related outcome assessments.

5 STUDY INTERVENTIONS

5.1 INTERVENTIONS, ADMINISTRATION, AND DURATION

The active study drug (DFO) will be supplied in vials containing 2 gm of sterile, lyophilized, powdered deferoxamine mesylate. The drug will be reconstituted for injection, by dissolving it in 20 ml of sterile water, then the volume of the reconstituted drug required for a dosing of 32mg/kg/day (up to a maximum of 6000 mg/day) will be calculated based on the subject's body weight and added to normal saline (0.9% sodium chloride) for administration by IV infusion. The drug will be reconstituted immediately prior to use to ensure microbiological safety. The matching placebo will be an isotonic saline solution (0.9% sodium chloride). Subjects will receive weight-adjusted intravenous infusions of the study drug. The maximum daily dose will not exceed 6000 mg per day regardless of subject's weight. 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 study drug must be administered daily during hospitalization for 3 consecutive days by IV infusion at a rate not to exceed 7.5 mg/kg/hour. The date and time of drug preparation and administration, as well as rate of infusion, will be recorded. Ideally, the 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 with an explanation as to why they occurred.

5.2 SAFETY MONITORING DURING STUDY DRUG ADMINISTRATION

All patients will be closely monitored for safety and neurological function during the administration of the study drug, and for at least 24 hours after completion of the infusions, in Neurological Intensive or Stroke Care Unit(s), staffed by stroke-trained neurologists and nursing staff. Patients will be monitored for all adverse events from the time of study drug initiation until day-7 or discharge, whichever occurs first; and, all new SAEs will be monitored until day-90 or resolution of the SAE. Continuing SAEs beyond day-90 will be monitored until day-180.
The patients will be closely observed during the initial 30 minutes of the infusion for possible adverse effects, such as an allergic/anaphylactic reaction, symptomatic bradycardia or hypotension. If there are no adverse effects, the infusion will continue. If a patient's neurological status deteriorates during the infusion, the NIHSS score and GCS will be reassessed by a member of the stroke team/study staff. Significant neurological worsening will be defined as an increase in NIHSS score of ≥ 4 points or a decrease of ≥ 2 points in GCS, compared to pre-treatment baseline values, that cannot be explained by other causes. A change of this nature lasting >4 hours could lead to premature discontinuation of the drug infusion based on the judgment of the local primary investigator(s). Vital signs (blood pressure and pulse) and neurological functions will be assessed at least once every 4h during intravenous drug infusion. Daily urinary output checks will be carried out every day until the day following the last infusion. An unexplained drop of >20% in mean arterial pressure will trigger review by the treating physician to determine its cause and if medical intervention is required. Fluid support will be used to prevent or treat hypotension. In more severe cases, use of inotropic agents may be required.

The skin at the infusion site will be examined at the same time points to assess for the presence and extent of local site reactions/irritation. If evidence of mild erythema/irritation or swelling emerges during the infusion, more frequent monitoring will be instituted depending on the severity and observed rate of change to ensure that the reaction does not progress further. The use of local anti-inflammatory agents may also be considered. In the event that local irritation continues to progress along with worsening edema, and development of pain or papular/vesicular eruption, the infusion will be terminated at that site and restarted in a different location. Close monitoring of the new infusion site, as well as the original site, will continue. If irritation develops at the new site or progresses at the original site, the infusion will be terminated and will not be re-started in this patient. In cases of an allergic reaction or anaphylaxis, the use of antihistamines and steroids is often sufficient; ACLS airway management may be required in severe cases. Appropriate treatment and monitoring will proceed according to the standard clinical practice at each institution until the reaction has resolved. Routine physical and neurological examinations will be carried out on a daily basis during the infusions, and the NIHSS and GCS scores will be determined. Safety laboratories (Hematology; Coagulation; Serum chemistry; Kidney and liver functions; and urine analysis) will be performed on the day following the last infusion of the study drug. Laboratory studies that are abnormal or worsen from baseline will be repeated. The frequency of subsequent evaluation of safety laboratories will be determined by the treating physician on a patient-by-patient case.

All patients must be closely monitored for any signs or symptoms of respiratory compromise, including ARDS (based on Berlin criteria – see appendix VII). A diagnosis of ARDS will lead to premature discontinuation of the drug infusion. Any evidence of respiratory compromise should trigger the investigators to complete the AE CRF on Web-DCU™ within 24 hours of onset for immediate safety review by the Independent MSMs. In addition, the following data must be checked at least once daily for all intubated patients (or more frequently in patients with changes in respiratory status requiring changes in ventilator settings and increased oxygen requirement) throughout day-7 or discharge and entered into Web-DCU™: 1) PaO_2/FiO_2 ratio; 2) Plateau and peak pressures; and 3) Chest X-ray results (when available). A CHEST X-RAY IS REQUIRED IF THE PAO_2/FIO_2 RATIO IS <300.

In order to minimize the potential pulmonary complications of the study drug, the investigators MUST follow the guidelines by ARDSNet for management of intubated patients [http://www.ardsnet.org/system/files/Ventilator%20Protocol%20Card.pdf] – please refer to appendix VI and section 7.3 for more details.

5.3 HANDLING OF STUDY INTERVENTIONS

5.3.1 SUPPLY, STORAGE, PREPARATION, AND DISPOSITION OF STUDY DRUG

The active drug (DFO) will be purchased by the Department of Health and Human Services (DHHS) from the manufacturer and shipped to the Program Support Center, Supply Service Center, Department of Health and Human Services (DHHS-SSC), in Perry Point, MD. The DHHS-SSC will serve as the drug distribution center, purchase the study drug periodically during the trial, and resupply the sites as recruitment progresses. The research pharmacist at each clinical site will receive the study drug in shipments.

The active study drug (DFO) will be supplied in vials containing 2 gm of sterile, lyophilized, powdered deferoxamine mesylate. The drug will be reconstituted for injection by dissolving it in 20 ml of sterile water, then the volume of the reconstituted drug required for a dosing of 32 mg/kg/day (up to a maximum of 6000 mg/day) will be calculated based on the subject's body weight and added to normal saline (0.9% sodium chloride) in an IV bag to achieve a final concentration of 7.5 mg per ml for IV administration. The infusion rate will not exceed 7.5 mg/kg/hour. The matching placebo will be an isotonic saline solution (0.9% sodium chloride). The drug will be reconstituted immediately prior to use to ensure microbiological safety. However, the reconstituted solution may be stored at room temperature for approximately 24h before use. In the phase I study, the reconstituted solution of DFO was colorless, and there were no specific treatment-related changes in laboratory tests including iron, hematology, urine color, or adverse events to suggest that the active drug can be identified from placebo.

The shelf half-life of the drug is 2 years, when stored in a cool place (15°C-25°C) away from direct light and heat. The drug should be stored in a secured and locked location. The storage room temperature should be recorded at least daily, and a temperature log should be maintained. Deviations from the recommended storage conditions should be immediately communicated to the Project Manager and the PI. The study drug affected by the deviations should not be administered to subjects until the monitoring team has assessed the impact of the deviation and determined whether the study drug can be used. Any materials remaining after each infusion should be discarded by the site in accordance with standard clinical practices.

5.3.2 STUDY DRUG TRACKING AND ACCOUNTABILITY

The PI at each site has the overall responsibility for drug accountability at his/her site, which will be carried out in accordance with ICH/GCP and individual clinical site's Standard Operating Procedures. Upon receipt of the study drug, the research pharmacist will inspect and count the study drug supply and confirm receipt of the study drug in the Web-DCU™ study database. The pharmacy at each clinical site also must maintain records of the amount of study drug received, dispensed to study subjects, and destroyed or returned at the end of the study. Drug accountability records and storage temperature logs will be inspected by the study monitor and may be subjected to inspection by relevant authorities as well. Study drug supplies will be counted and reconciled at each site during monitoring visits and at the end of the study.

5.4 CONCOMITANT MEDICATIONS AND PRECAUTIONS

Concomitant medications will be recorded during the study period from the time of study drug initiation until day-7 or discharge (whichever is earlier). There are few restrictions on the use of concomitant medications for study

participants. The use of prochloroperazine (compazine), a phenothiazine derivative, is not allowed before treatment, during treatment, or up to 72 hours after completion of the study drug infusion, since the combination of DFO and compazine can lead to impairment of consciousness [Blake, 1985]. Concurrent use of other experimental therapy is not allowed. Vitamin C supplements will not be allowed in patients with heart failure during treatment with DFO.

All standard therapies used in the management of ICH patients will be allowed under close monitoring and supervision. These include volume expansion with normal saline or crystalloids, vasopressors, antiedema agents such as steroids or mannitol, anti-hypertensives including diuretics, anti-convulsants, anti-arrhythmic agents and anti-emetics, except for phenothiazine derivatives.

In order to minimize the variability in care and to assure consistency in management across sites, the general care of ICH patients should conform to the guidelines from the Stroke Council of the American Heart Association [Morgenstern, 2010], and the European Stroke Initiative Guidelines [Steiner, 2006]. Pertinent issues are detailed in Appendix II and III.

6 CLINICAL AND LABORATORY EVALUATIONS

6.1 PATIENT EVALUATION AND DATA COLLECTION SCHEDULE

All study data will be collected using Case Report Forms (CRFs) designed specifically for the study. Patient confidentiality will be maintained throughout, as participants will only be identified on the CRFs by a unique study ID number. Patients' identifying information and source documents for the CRF data should be kept by the primary investigator at each participating site. The data obtained will include: 1) Demographics; 2) Previous medical history; 3) Concomitant medications; 4) Vital signs; 5) Results of laboratory tests; 6) NIHSS and GCS scores; 7) ICH score; 8) mRS, SIS-16, and MoCA scores; 9) Adverse events; 10) Surgical and non-surgical treatments; and 11) Imaging findings, including chest x-rays, and CT and MRI scans identifying the location of ICH, presence of IVH or hydrocephalus, and etiology of ICH (after completing diagnostic work-up).

6.1.1 CLINICAL AND LABORATORY ASSESSMENTS

The following assessments will be carried out throughout the 90-day study period:

Upon <u>screening</u> of potential study subjects: 1) Review of head CT and determination of the time of ICH onset or the time the patient was last known to be without presenting deficits; 2) Demographic data; 3) Medical history; 4) Review of medications; 5) General physical examination; 6) Neurological examination, including NIHSS and GCS; 7) Visual and auditory assessment (which includes assessments for cataracts, visual loss or field cut, disturbed color vision, hearing loss, and presence of tinnitus), whenever possible in awake patients; 8) Determination of pre-morbid mRS; 9); Review of admission laboratory tests - Hematology [hemoglobin, hematocrit, red blood cell count and platelet count]; Coagulation [partial thromboplastin time and international normalized ratio]; and serum albumin; and 10) Review of all inclusion/exclusion criteria. A baseline chest x-ray is required to rule out the presence of bilateral pulmonary infiltrates or pulmonary edema. A pregnancy test is required for all women of childbearing potential prior to enrollment into the study. Subjects in whom all eligibility criteria are met should be considered for enrollment, and those who agree to participate via signed and dated informed consent should be enrolled.

Participants should be reassessed immediately prior to the study drug administration to obtain a pre-treatment baseline. **<u>The Pre-treatment baseline reassessments include</u>:** 1) Vital signs, including blood pressure and heart rate; 2)

Neurological examination, including NIHSS and GCS to confirm stability of their neurological status and to obtain pre-treatment baseline scores; and 3) Assessment for new adverse events since screening. 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 their participation will be terminated.

Administration of the study drug should only be permitted after obtaining pre-treatment blood sample for serum chemistry and glucose, hepatic function tests, and urine analysis (if not already done upon arrival to the ED).

Subjects who receive the study drug(s) will be evaluated daily for the first 3 days (during study drug infusion while in hospital) and on day-7 or discharge from the hospital, whichever occurs first. Clinic visits will take place on days 30±7 and 90±7. Telephone interviews will be conducted on day 60±7 and 180±7.

The following assessments should be performed **after each daily infusion** (every 24±6h) and through the day following completion of the last infusion: 1) General physical examination; 2) Visual and auditory assessments; 3) Neurological examination, including NIHSS and GCS; and 4) Vital signs, including blood pressure and heart rate. A repeat head CT scan and blood samples for hematology, serum chemistry, renal and hepatic function tests, coagulation studies, and urine analysis should be obtained within 24±6h following the last infusion of the study drug. Vital signs (blood pressure and pulse) and neurological functions should be assessed at least once every 4h during intravenous drug infusions. Daily urinary output checks should be carried out every day until the day following the last infusion. In addition, the following data must be checked at least once daily for all intubated patients (or more frequently in patients with changes in respiratory status requiring changes in ventilator settings and increased oxygen requirement) throughout day-7 or discharge and entered into Web-DCU™: 1) PaO_2/FiO_2 ratio; 2) Plateau and peak pressures; and 3) Chest X-ray results (when available). ***A chest x-ray is required if the PaO_2/FiO_2 ratio is <300.***

On day-7 or Discharge (whichever comes first), the following assessments are done: mRS, NIHSS, GCS, MoCA and visual and auditory assessments.

During hospitalization, the NIHSS and GCS should be done any time a subject's neurological status deteriorates, or whenever the investigator believes it is prudent to do an assessment. Laboratory assessments beyond those required for the study should be done whenever clinically indicated.

The **Day-30 (±7)** will be an in-person visit comprised of a general physical examination, visual and auditory assessments, review of SAEs, and assessments of NIHSS, SIS-16, MoCA and mRS.

The **Day-60 (±7)** assessments, which will be completed via telephone, will be comprised of a functional assessment to obtain a score on mRS and query for SAEs.

The **Day-90 (±7)** visit will be an in-person visit comprised of a general physical examination, visual and auditory assessments, and assessments of NIHSS, MoCA, SIS-16, and mRS. However, a telephone interview to obtain a score on mRS (the primary outcome measure) may be allowed on a case-by-case basis, after consultation with the PI, if the subject is unable to return for an in-person evaluation.

The **Day-180 (±7)** assessments, which will be completed via telephone, will be comprised of a functional assessment to obtain a score on mRS.

A study staff member certified in NIHSS and mRS and experienced in administering GCS, SIS-16, and MoCA should perform the assessments at all time points. We require that all assessments at all time points be performed by the same blinded

investigator, whenever possible, to minimize inter-rater variability. Data on the subject's functional status (mRS and SIS-16) can be obtained from a proxy if the subject is unable to provide the information. Please refer to Appendix V for details of NIHSS, GCS, SIS-16, and MoCA scales.

Concomitant medications and non-drug therapies should be assessed at all points of contact with the subject after study drug initiation. All adverse events (serious and non-serious) should be assessed until day-7 or discharge, whichever occurs first. All new SAEs will be monitored until day-90, resolution of the SAE, or withdrawal of consent, whichever is earlier. Continuing SAEs beyond day-90 will be monitored until day-180.

6.1.2 RADIOLOGICAL ASSESSMENTS

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 ASA [Morgenstern 2010; refer to Appendix II]. The volume of ICH on admission scan must be determined by the local investigators using the ABC/2 method (*please refer to Appendix IV for instructions)* before randomizing the subject in WebDCU™. 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.*

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 PaO_2/FiO_2 ratio is <300.

6.2 Schedule of Evaluations

Table 6.2 below summarizes the timing and type of assessments/evaluations throughout the study.

Schedule of Assessments and Data Collection

	Screening	Baseline	oh	24h	48 h	72h	24h post-last infusion (± 6h) and as needed	Day 7 or Discharge*	Day 30	Day 60 - Phone	Day 90	Day 180 - Phone	End of Study
		Prior to study drug start		± 6h	± 6h	± 6h		± 6h	± 7 days	± 7 days	± 7 days	± 7 days	
Screen Failure Log	X												
Inclusion/Exclusion Criteria	X												
Demographics & Medical History	X												
Informed Consent	X												
Subject Enrolment / Randomization		X											
Study Drug Administration			X	X	X	X							
Physical Examination	X			X	X	X	XX		X		X		
Visual & Auditory Assessment€	X			X	X	X	XX	X	X				
NIHSS	X	X		X	X	X	XX	X	X		X		

GCS	X	X		X	X	X	XX	X					
ICH Score	X												
mRS	X							X	X	X	X[¥]	X	
MoCA								X	X		X		
SIS-16									X		X		
Vital Signs (BP & pulse)[$]		X		X	X	X	XX	X					
Safety Monitoring			X	X	X	X							
Urinary Output				X	X	X							
Hematology	X						XX						
Serum Chemistry	X						XX						
Coagulation Parameters	X						XX						
Urine Analysis	X						XX						
Liver Function Tests	X						XX						
Kidney Function Tests	X						XX						
Serum albumin	X												
Pregnancy Test (women of childbearing potential)	X												
Blood sample for future research[×]		X					XX						
CT scan	X						XX						
Chest x-ray[%]	X						X						
Prior Medications	X												
Concomitant Medications			X	X	X	X		X	X	X	X		
Concomitant Non-Drug Therapies			X	X	X	X		X	X	X	X		
Adverse Events			X	X	X	X	X	X	X	X	X		
End of Study													X

[€] Includes assessments for cataracts, visual loss or field cut, disturbed color of tinnitus – Should be performed, whenever possible in awake patients

* Day 7 or Discharge– whichever comes first

[$] Vital signs (blood pressure and pulse) and neurological functions will be assessed at least once every 4h during intravenous drug infusion Laboratory tests may be performed outside the ±6h window, if it is a standard site procedure to perform laboratory tests[6] at a specific time each day.

XX These assessments must be performed within 24±6h following completion of the last infusion of the study drug

[×] We plan to collect (bank) additional blood samples at baseline and after the last infusion to be stored and analyzed in the future from subjects providing informed consent.

● Post-treatment scan should be performed within 24±6 hours of the last infusion even if it is terminated before day-5 of treatment

¥ A telephone interview to obtain a score on mRS (the primary outcome measure) may be allowed on a case-by-case basis if the subject is unable to return for an in-person evaluation on day 90.

[%] **Chest x-ray must be performed in any intubated patient if PaO_2/FiO_2 ratio is <300.**

6.3 Blood Banking Repository Sub-Study

The main study provides an opportunity to "bank" blood samples from the participants for future innovative ICH research, particularly if the efforts to develop DFO as a therapy for ICH are successful. Future pharmacogenetic studies may be considered to help define other therapeutic targets and responders vs. non-responders to DFO therapy. We, therefore, plan to collect additional blood samples at baseline and after the last DFO infusion (approximately 30 ml) to be stored and analyzed in the future. Subjects' participation in this blood-banking repository will be optional; they do not have to participate in the repository sub-study in order to participate initially or to continue their participation in the main study. The blood samples from all participating sites will be sent to the Beth Israel Deaconess Medical Center (The Coordinating Center) by overnight mail. All samples will be stripped of identifiers and randomly assigned a unique code number. The key linking code numbers and identifying information will be kept in a secure location accessible only to the principal investigator of the study or his designee, on a password protected network drive. All samples will be

stored at -80 degrees Celsius low-temperature, locked, freezer until final planned analyses are formulated and carried out. The samples will be stored indefinitely or until no more remains for genomic and protein research that can be performed at future dates.

The exact questions to be asked and tests to be done in the future are not fully identified at this stage. We tentatively plan to investigate the relationship between polymorphisms from a panel of genes encoding iron-handling proteins (which includes genes involved in both intra- and extra-cellular iron metabolism, such as ceruloplasmin, haptoglobin, hemopexin, transferrin receptor, ferritin heavy- and light-chain, and heme-oxygenase 1 and 2 genes) and PHE, outcome, and response to DFO therapy. Genotyping will be performed using high-throughput genome-wide SNP genotyping methods. Genotype results from DFO- and placebo-treated subjects will be examined for differences in allele frequency that may be associated with risk of malignant PHE progression or response to DFO therapy. Extracted DNA samples will be genotyped without knowledge of the treatment arm by chip-based methods utilizing mass spectrometry. The exact location of genotyping is undetermined at this point in time, although it is likely to be performed at the Broad Institute, given our ongoing collaboration in ICH Genome Wide Association Studies.

We plan to seek ancillary funding to support these additional analyses. Once funding is secured and the final analyses are formulated, we plan to seek an IRB approval for the specified analyses and use of the blood banking repository data.

7 ADVERSE EVENTS

7.1 DEFINITION OF ADVERSE EVENTS

Adverse events are any *untoward* medical occurrence 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. When evaluating possible adverse events, an assessment should be made regarding its seriousness, severity and temporal relationship to the administration of the study drug. An adverse event is considered serious if it is life-threatening, prolongs hospitalization, requires re-hospitalization, results in significant disability, leads to death, or requires medical or surgical intervention to prevent one of the other listed outcomes. An assessment should be made regarding the seriousness, severity and relationship to the administration of the study medication as well as to the ICH. The following factors should be considered when evaluating possible adverse events: 1) the temporal sequence from drug administration; 2) patient's response after drug discontinuation or re-introduction; and 3) severity of the event. The investigators, on the basis of their clinical judgment and guided by the following definitions, should determine the relationship of an adverse event to the study drug(s) as: definitely related, i.e. following in a reasonable temporal sequence, known to be a complication of DFO, and having no other explanation; probably related, i.e. following in a reasonable temporal sequence and not reasonably explained by the patient's clinical state or other therapies; possibly related, i.e. could have been explained by other therapies or patient's clinical state; or unlikely or not related. The severity of adverse events should be graded as mild, moderate, severe, life-threatening, or fatal.

All adverse events or complications will be entered into WebDCU™ and assigned to a system-organ class and preferred term using the MedDRA coding dictionary. Each subject must be monitored closely throughout his/her hospitalization for serious adverse events (SAEs). All adverse events (serious and non-serious) should be assessed until day-7 or discharge, whichever occurs earlier, and serious adverse events until day-90 or withdrawal of consent, whichever is earlier.

7.2 POTENTIAL COMPLICATIONS OF THE STUDY INTERVENTION

Aspects of the study that have potential for risks are blood withdrawals, CT scan imaging studies, and injections of the study medication(s). There are no additional risks for any of these procedures other than those present in any routine clinical situation, especially for blood draws and CT scans. Patients may experience some temporary discomfort, bruising, or, rarely, infection or the formation of a small clot or swelling at the site of the needle puncture in the process of drawing blood or starting the intravenous drip. The condition of ICH, in itself, carries a high risk for secondary complications including serious life-threatening adverse events, and even death, whether or not the active study drug (DFO) is used. Recent studies indicate that approximately 40% of patients with ICH have a serious adverse event during hospitalization, of which approximately 26% can be fatal [Haley, 2005; Mayer 2005; Mayer 2006; Lyden 2007].

DFO has been extensively used in clinical practice for more than 40 years, and is approved by the Federal Drug Administration for the treatment of acute iron intoxication and of chronic iron overload due to transfusion-dependent anemia. Safety studies indicate that it is relatively well tolerated. The adverse reactions observed with DFO have been previously detailed in section 2.2.2.

The most observed adverse events in our Phase I study in ICH patients were injection site reaction (irritation, pain, erythema, infiltration) and a modest decrease in blood pressure, which did not require any medical intervention. One subject developed visual hallucination during IV infusion of DFO. Almost all of these adverse events were mild, self-limited, did not require specific treatment, and resolved spontaneously. There were no deaths or serious adverse events related to DFO use. There were 2 cases of respiratory failure, both of which occurred in the 62mg/kg/day dose-tier. They were thought to be related to aspiration pneumonia, and unrelated to the study drug. However, a recent expert review found that one of these cases was an undiagnosed case of ARDS, and concurred that aspiration was a plausible explanation for it.

In the first part of phase II investigation of DFO in ICH (HI-DEF trial, where subjects were treated with a continuous infusion of DFO at 62 mg/kg/day for 5 consecutive days), 5 cases of ARDS were reported among the first 42 participants. A detailed expert review of reported cases of respiratory failure and pulmonary edema revealed 2 more cases of undiagnosed ARDS. Overall, 6/7 of the ARDS cases in HI-DEF were in the DFO treatment arm; 3 were fatal and the cause of death was ARDS-related in 2/3 cases. The expert who was blinded to treatment assignment identified a plausible cause for ARDS, other than the study drug or ICH itself, in 4/7 ARDS cases, while no other explanation, other than the study drug or ICH, was apparent for the remaining 3 cases. Although the overall rate of ARDS was in line with published reports in ICH patients [Elmer 2013], the imbalance in the frequency of ARDS between the DFO- and placebo-treated groups raised concerns that the pulmonary toxicity of the drug was likely. There were no other safety concerns. A MedWatch report was filed with the FDA and Health Canada for an AE of hypophosphatemia that was judged to be serious (potentially life-threatening), unexpected, and possibly related to the study drug. Overall, hypophosphatemia of varying severity was reported in 3 subjects in HI-DEF; 2 in DFO- and 1 in placebo-treated patients.

The effects of DFO on the fetus are unknown. It is also not known if DFO is excreted in human milk. Therefore, women who are pregnant and those who are breast-feeding will be excluded from this study. Those with child-bearing potential must have a negative pregnancy test before participating in the study.

7.3 PREVENTION AND MANAGEMENT OF ADVERSE EVENTS

Aseptic and sterile techniques should be used during blood draws, which should be performed by experienced phlebotomists. Application of warm compresses to the site of IV infusion throughout the infusion period is advised to minimize the potential for injection site irritation. In order to maximize safety during this study, we are using a slow infusion rate of < 7.5 mg/kg/hour and are limiting the maximal dose that any subject can receive to 6000 mg per day. The subjects must be carefully monitored throughout their participation in the study as detailed above. Any medical complications

should be managed as appropriate, according to the standard clinical practice at participating institutions. There is no specific antidote to DFO. General symptomatic and supportive measures should be applied.

Subjects should be admitted to the Neurological Intensive Care or Stroke Unit, undergo repeated clinical (neurological and general physical examinations) and laboratory evaluations at regular intervals throughout their participation in the study for safety monitoring, and receive standard medical management for ICH based on the American Stroke Association Guidelines [Morgenstern 2010]. Pertinent issues, including blood pressure management, are detailed in the appendix II and III. Laboratory studies that are abnormal or worsen from baseline should be repeated.

It is important that investigators ensure maintenance of intravascular volume prior to administration of the drug infusions, especially in hypovolemic patients, to minimize DFO-induced hypotension; and to carefully observe the subjects during the initial 30 minutes of the intravenous infusion for possible adverse effects, such as an allergic/anaphylactic reaction, arrhythmias, or hypotension. If there are no adverse effects, the infusion should continue. All patients should be kept hydrated and, if necessary, fluid support should be used to prevent or treat hypotension. In more severe cases, use of inotropic agents may be required.

The skin at the site of IV infusion must be carefully inspected periodically for signs of irritation, induration, or inflammation during physical examinations, coincident with the times of all assessments of vital signs, during the infusion of the drug and for 24 hours afterwards. Section 5.2 above details appropriate measures for management of local injection site reactions.

In order to minimize the potential pulmonary complications of the study drug, the investigators MUST follow the following guidelines by ARDSNet for management of intubated patients [http://www.ardsnet.org/system/files/Ventilator%20Protocol%20Card.pdf]– please refer to appendix VI: **Ventilator settings –** 1) Tidal volume (V_T)= ≤8 cc/kg PBW (predicted body weight); 2) Plateau Pressure (P_{plat}) <30 cm H_2O; 3) Peak Pressure (P_{peak}) <50 cm H_2O; and 4) Positive End-Expiratory Pressure (PEEP): at least 5 cm H2O. Investigators MUST also implement a **Ventilator Associated Pneumonia prevention protocol** – 1) Head of bed elevation at least 30 degrees or greater; and 2) Regular clorhexidine mouth wash and oral care. In addition, a conservative fluid management strategy that aims to minimize or eliminate positive fluid balance and cautions against indiscriminate use of blood transfusion unless hemoglobin concentration drops below 7 g/dL is recommended. All patients must be closely monitored for any signs or symptoms of respiratory compromise, including ARDS (based on Berlin criteria – see appendix VII). A confirmed diagnosis of ARDS should lead to premature discontinuation of the drug infusion. Appropriate treatment and monitoring, including the use of invasive mechanical ventilation, low tidal volume, permissive hypercapnea, or high PEEP, should proceed according to the standard clinical practice at each institution. In patients with respiratory failure, strategies that decrease oxygen utilization, such as antipyretics to control fever and sedatives to control agitation; and appropriate use of neuromuscular blockade when asynchrony with the ventilator persists despite adequate sedation are recommended.

Infections with Yersinia enterocolitica and Y. pseudotubeculosis have been reported in DFO-treated patients. Although these are unlikely to occur in patients without significant systemic iron overload, appropriate bacteriological tests should be performed, and suitable antibiotic coverage for Yersinia should be instituted if a patient in the study develops fever accompanied by acute enteritis, abdominal pain, or pharyngitis. Appropriate treatment and monitoring should proceed according to the standard clinical practice at each institution.

7.4 CRITERIA FOR INTERVENTION DISCONTINUATION

The investigators may terminate the study drug infusion if, in their judgment, its continued administration poses harm to the patient's medical condition. The only pre-established criteria for premature discontinuation of the study drug are: 1) severe allergic reaction or anaphylaxis; 2) worsening of renal functions, defined as serum creatinine >2 mg/dl on 2 repeated measures 8 hours apart; 3) development of ARDS based on Berlin criteria/definition (see appendix VII); or 4) if the patient or his proxy voluntarily withdraws consent. Subjects whose study drug is discontinued but who do not withdraw consent should still be followed for 180 days.

7.5 REPORTING OF ADVERSE EVENTS

In order to ensure prompt reporting of adverse events, all adverse events (as well as all related study data) must be entered into the WebDCU™ within five working days following the completion of the Baseline, Treatment, and Day-7 or discharge (whichever occurs first) trial phases. All serious adverse events (SAEs) must be reported on the WebDCU™ within 24 hours of the study site staff first being made aware of its occurrence. The 24-hour reporting requirement for SAEs applies to all study phases. The investigators are required to provide relevant information, including description of the adverse event, date/time of onset and resolution, severity and seriousness, action taken, and suspected relationship to the study drug. Similarly, all adverse events of respiratory compromise, whether serious or not, must be reported in WebDCU™ and the relevant CRF completed within 24 hours of the study site staff first being made aware of its occurrence.

Reporting of respiratory compromise, as well as any serious or life-threatening adverse event, will trigger notification of the event to the Project Manager (PM), the independent MSMs, and appropriate members of the Executive Committee (EC). The MSMs will conduct an independent review of each of these events to determine its relatedness to the study drug along with other elements, and to confirm or exclude the diagnosis of ARDS in cases of respiratory compromise. Within 72 hours of receipt of these events for review, the MSMs will enter into the trial's database their opinion regarding whether the adverse event is, in fact, serious, and if it is unexpected and related to the study drug. If the MSMs believe all three elements are present in the SAE, 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 (21 CFR 312.32(c)(1)). If the study site investigator(s) and the MSMs are not in agreement on these issues and fail to resolve their disagreement after direct 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 database) 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 instructions for accessing the report. It is the responsibility of each clinical site PI to file these reports with his/her IRB 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™.

7.6 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. For the closed report only, the statistics will also be provided by partially blinded treatment group (A vs. B). If the DSMB wishes to be completely unblinded for these reports, a sealed identification envelope will be provided to the NINDS DSMB liaison; this envelope can be opened at the discretion of the DSMB. An annual report will be submitted to the FDA and Health Canada.

7.7 STOPPING RULE

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 NINDS-appointed DSMB recommended that recruitment be stopped if the difference in the number of confirmed ARDS cases between the groups is 5 at any time during the recruitment of the first 40 subjects; 10 at any time during the recruitment of subjects 41-80; 12 at any time during the recruitment of patients 81-120; or if the difference in the number of confirmed ARDS cases between the groups is statistically significant after 40, 80, or 120 subjects have completed the in-hospital phase based on a Pocock-adjusted, one-sided, 0.05 alpha level. This one-sided hypothesis is consistent with our concern for patient safety, wherein early termination is considered only if ARDS incidence is higher on the DFO arm than on the control arm.

These analyses will be based on the occurrence of confirmed ARDS cases (according to the Berlin criteria) thought to be at least possibly related to study drug. 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.

8 STATISTICAL CONSIDERATIONS

8.1 RANDOMIZATION PROCEDURES

A combination of minimization and biased coin methodologies will be used to randomize participants to either DFO or placebo [Pocock 1975; Taves 1974]. The minimization method aims to control imbalance in the treatment groups with respect to pre-specified baseline characteristics; the biased coin approach is adopted to avoid deterministic assignment. Throughout the trial, the probability of treatment assignment will take into account the imbalance associated

with clinical site, baseline ICH score, OTT, baseline ICH volume, baseline NIHSS score, and concurrent use of anticoagulants at the time of ICH onset.

8.2 STUDY ENDPOINTS AND DATA ANALYSIS

8.2.1 CLINICAL ENDPOINTS

The primary efficacy outcome measure is the mRS, dichotomized to define good functional outcome as mRS score of 0-2 at 90 days. At the conclusion of the study, the proportion of DFO-treated subjects with a good outcome will be compared to the placebo proportion in a futility analysis. The primary futility hypothesis is tested via generalized linear model relating the probability of a good outcome to the treatment. Adjustment for OTT, ICH score, baseline ICH volume, NIHSS score, and anticoagulant use are included in the model to obtain proper significance due to the inclusion of these variables in the randomization scheme. The binomial distribution for Y, with the identity link, is used to derive an estimate of the adjusted risk difference for good outcome. The primary futility hypothesis, H_0: (π_{DFO}-$\pi_{placebo}$) ≥0.12, will be tested at one-sided alpha (the probability that an effective intervention will be called ineffective, or futile) 0.10. The corresponding alternative hypothesis, H_A: (π_{DFO}-$\pi_{placebo}$) <0.12, defines futility as a treatment effect less than absolute 12% in favor of DFO. The futility analysis will be conducted using a one-sided 90% upper confidence bound on the risk difference, which is consistent with the one-sided alternative hypothesis and stated level of significance. To declare futility, the entire interval must lie below the value 0.12, indicating that the true difference in risk of good outcome is less than 0.12 with 90% confidence. Under this design, a significant result would suggest that it would be futile to move DFO forward to Phase III testing.

As secondary analyses of the primary outcome, the presence of a differential treatment effect in the OTT windows will be explored. The generalized linear model described above for the primary analysis will be expanded to include an interaction between treatment and OTT window. While the Trial will be underpowered to definitively address this question, the magnitude of the treatment effect, and corresponding confidence interval, will be estimated for each time window. A dichotomized analysis considering the proportion of DFO- and placebo-treated subjects with mRS 0-3 will also be performed. Although mRS 0-3 is less favorable than the primary outcome of mRS 0-2, it would still be a desirable effect in patients with ICH given that no treatments exist to reduce disability. The trial is adequately powered to assess the futility hypothesis using mRS 0-3 as the outcome based on an absolute difference in treatment effect <13% in favor of DFO. We will also perform similar analyses at 180 days and ordinal analysis across all mRS scores as secondary outcome measures.

8.2.2 SAFETY ENDPOINTS:

All adverse events will be assessed until day-7 or discharge (whichever is earlier), and SAEs until day-90. Mortality (all causes and ICH-related) will be assessed until the end of the study (day-180). Safety endpoints of particular interest include all DFO-related adverse events until day-7 or discharge (whichever is earlier), all SAEs through day-90, and deaths (all causes and ICH-related) through day-180.

The following events will be defined as **ADVERSE EVENTS OF SPECIAL INTEREST** (AEOSI) for safety surveillance during this study: 1) Anaphylaxis (at any time point during study drug infusion); 2) Hypotension (defined as a decrease in blood pressure requiring medical intervention at any time point during drug infusion that cannot be explained by other causes); 3) Respiratory compromise of any cause during the in-hospital phase (day-7 or discharge, whichever is earlier); and 4) Development of new and unexplained visual or auditory changes after initiating treatment with the study drug.

All adverse events or complications will be submitted electronically via the WebDCU™ system and assigned to a system-organ class and preferred term using MedDRA coding dictionary. The number and percent of all adverse events will be summarized for each treatment arm by event type. Tables will be generated to detect any clinically significant laboratory abnormalities in change of values from baseline to end of the last infusion. We anticipate no missing safety data regarding adverse events, since patients will remain hospitalized and closely monitored until day-7 or discharge (whichever is earlier). The cumulative incidences of each AEOSI, as well as mortality, will be compared via 95% confidence intervals. Mortality will also be assessed via the log rank test for comparing survival curves.

Analysis of the safety data regarding the occurrence of ARDS will be carried out continuously throughout the trial by the unblinded study statistician, who will notify the EC and DSMB if recruitment must be stopped. The DSMB will be notified of each individual ARDS occurrence upon confirmation by the MSMs, per their request. Analysis of other safety data by the DSMB will occur semiannually (or more frequently if requested by the DSMB). If any of these analyses reveal serious emerging concerns, the EC, in consultation with the DSMB, may implement modifications to assure safety as necessary. Apparent, consistent and persistent evidence of net harm that tends to overwhelm any benefit may allow for premature termination of the study.

8.3 STUDY SAMPLES

ALL analyses will involve data from two samples:

1- Modified Intent-to-Treat (mITT): Outcome data from all subjects who are randomized and in whom the study infusion begins, even if it is discontinued prematurely, will be analyzed. Classically, ITT analysis is used in Phase III trials and includes all subjects randomized, regardless of whether they receive the treatment or not. However, in order to evaluate the efficacy of DFO as administered, randomized subjects in whom the study infusion is never initiated will be excluded from the primary analysis. As a sensitivity analysis, the futility hypothesis will also be assessed according to the ITT principle. All subjects randomized will be included and considered in the treatment group to which he/she was randomized, regardless of the treatment actually received. The outcomes for subjects in whom treatment is never initiated will be imputed based on available baseline data.

Safety analysis will involve data from all patients in whom study infusion begins, even if it is discontinued prematurely (i.e. the mITT sample).

2- Per-protocol sample, i.e. all subjects who have at least one post-treatment assessment and no major protocol violations that affect the analysis. The Executive Committee (EC) will adjudicate major protocol violations and patients' inclusion in the per-protocol population before unblinding. Analyses based on the per-protocol sample will be supportive in nature.

8.4 SAMPLE SIZE CALCULATION

The sample size is calculated to achieve 80% power for the futility analysis described above using a one-sided alpha level of 0.10. It is anticipated that approximately 28% of control subjects will have mRS 0-2 at 3 months; this is based on the weighted average of the good outcome proportions reported in the placebo-treated subjects of the Factor VII, FAST, GAIN, and CHANT trials [Haley 2005; Lyden 2007; Mayer 2005-2008]. If the true good outcome proportions in the DFO and placebo arms are identical (π_{tx}=0.28, π_{ctrl}=0.28, a truly futile situation), 254 subjects (127 in each arm) are required to test the futility hypothesis with 80% power. This calculation takes into account the 0.12 null value specified in the futility hypothesis [Chow, 2003]. The primary analysis will be conducted according to a modified Intent-to-Treat (ITT) principle, wherein subjects in whom the study drug infusion is not initiated will be excluded from the analysis. Therefore, the final sample size was inflated by a factor of 1.11 (Friedman, Furberg, and DeMets) to account for dilution of the treatment effect associated with a conservative drop-out rate of 5% (due to loss-to-follow-up (LTFU) and

withdrawal of consent), and an additional factor of 1.04 to account for randomized subjects in whom the study drug is not initiated. Therefore, the final sample size is 294 subjects.

8.5 LOSS-TO-FOLLOW-UP AND MISSING DATA

Extensive efforts will be made to keep missing data, particularly the primary outcome (mRS at 90 days), to a minimum, and to ensure near complete follow-up. Missing primary outcome data will be imputed via standard multiple imputation (MI) methods (i.e. via logistic regression model predicting outcome based on pertinent baseline and treatment data). As a sensitivity assessment, we will use the Last Observation Carried Forward (LOCF) approach, wherein the last available score will be carried forward for missing day 90 assessments. If the treatment effect is robust, we expect to reach similar conclusions via these imputation methods, particularly for minimal missing data (<5%).

9 STUDY MONITORING

9.1 MONITORING FOR STUDY PROGRESS AND RECRUITMENT

The Executive Committee will monitor recruitment progress at each site on a monthly basis to address individual site issues and concerns. To minimize unnecessary delays in enrolling eligible subjects into the early time window (≤12h from ICH onset), we will monitor the time-from-door-to-infusion on an ongoing basis and make every effort to ensure eligible subjects are enrolled as quickly as possible after ED arrival. If we observe that enrollment into the early (≤12h) time window is disproportionately low compared to the >12-24h window, we will implement a strategy of forced recruitment whereby each site will be required to enroll one subject into the early time window for each subject enrolled into the later (>12-24h) window (or maintain its overall ratio of ≤12h to >12-24h to at least 1:1) before subsequent enrollment into the later time window is permitted by the site. If frequent delays are observed at a particular site, the Principal Investigator will be asked to take the necessary corrective steps. The Executive Committee additionally may require that the infusion of the study drug must be started within a certain time window following the subject's arrival to the emergency room, at a particular site or across all sites, if necessary.

The Executive Committee will also monitor accrual of subjects on an ongoing basis throughout the study, and will conduct formal reviews of the overall recruitment across all sites and site-by-site on a yearly basis (or at more frequent intervals, if needed). For sites whose recruitment is less than 75% of their expected rate (approximately 4-6 subjects per year), the local principal investigator will be asked to submit his/her own analysis of the barriers to recruitment at his/her site and corrective actions and plans. The "low" enrolling sites will be monitored closely at 3-month intervals to determine if further corrective actions or dismissal from the trial are warranted.

9.2 QUALITY MANAGEMENT AND DATA CONTROL

The Data Coordination Unit (DCU) in the Department of Public Health Sciences at the Medical University of South Carolina (MUSC) serves as the Statistics and Data Management Center (SDMC) for the trial, coordinating all statistical, data and project management responsibilities. The study data will be managed (including data queries) by the SDMC using the WebDCU™ system. This user-friendly web-based database system, developed and validated by the SDMC, will be used for regulatory document management, subject randomization, data entry, data validation, project progress monitoring, subject tracking, user customizable report generation and secure data transfer. In addition to the study database, the SDMC will provide the clinical site staff access (via password) to a standard set of web-enabled tools, including subject visit calendar, subject accrual status, case report form completion status, and outstanding DCR status pertaining to their respective clinical sites. Furthermore, all approved study materials, such as the protocol, informed consent template and manual of procedures, will be housed on the website to ensure that the clinical sites always have access to the most current trial documents.

Data should be independently entered by the designated personnel at each clinical site into WebDCU within five working days following the completion of any trial phase – Baseline, Treatment, day-7 or discharge (whichever occurs first), Month 1, Month 2, Month 3, and Month 6. Enrollment data, however, must be entered into the WebDCU database before the subject can be randomized. The SAE and adverse events of respiratory compromise data must be entered into the WebDCU within 24 hours of the site staff's first awareness of the event. It is critically important to the effective and efficient conduct of the study that ALL data be entered in a timely manner. An electronic copy of the CRFs will be made available to the clinical sites prior to initiation of the study to be used as worksheets to capture the required data for the study. The SDMC staff will perform range verification, consistency checks, and quality assurance on the data. The staff at the SDMC will contact the sites regarding missing data or queries on CRF data. They will maintain direct contact with the staff at the participating sites to ensure the study is conducted according to the Good Clinical Practice Guidelines and FDA and all applicable regulations.

Experienced clinical research monitors will be contracted through the SDMC to perform on site source data verification (SDV) during the study. The first visit will take place after enrollment of the first subject by the site and will involve source document verification of 100% of the data. For subsequent subjects, a checklist of key outcome and safety data variables requiring SDV will be developed based on the trial's endpoints. The checklist ensures that a target of no less than 40% of the clinical data submitted to the Hi-Def database are verified against source documents at the performance sites prior to finalization of the database. Of the data on the checklist, the safety and efficacy variables represent approximately half of the data to be verified. The remaining half of source monitored data include: 100% of deaths and 100% of serious adverse events and source data reviews based on the per-patient evaluation of safety parameters defined in the protocol. All informed consent and HIPAA documents will be verified by the clinical research monitor. Subsequent visits to each site will depend on the number of patients recruited at the site as well as other issues. Monitoring will also involve, as appropriate, correspondence and telephone contacts. In addition to data verification, the monitor will evaluate drug accountability, site facilities, and regulatory documents. 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 any queries. The close out monitoring visit will take place after the study is completed.

The SDMC will prepare, at selected intervals, a summary report of screened and enrolled patients, completeness and quality of CRF data, status of enrolled patients, a listing of SAEs, and a table of event-specific cumulative rates. The Executive Committee and the independent Medical Safety Monitors will review these reports and monitor the study performance (recruitment, compliance, protocol violations, and follow up) and safety data on an ongoing basis. The study statistician will also generate a comprehensive statistical report bi-annually to the DSMB, unless requested at more frequent intervals.

9.3 ONGOING SAFETY MONITORING DURING THE STUDY

Two independent Medical Safety Monitors (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. As mentioned above in section 7.6, the MSMs will review all SAEs and cases of respiratory compromise and determine whether they are related to study drug administration, and 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, 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. an 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.

Analysis of the safety data regarding the occurrence of ARDS will carried out continuously throughout the trial by the unblinded study statistician, who will notify the EC and DSMB if recruitment must be stopped (please refer to section 7.7 for the stopping rule). The DSMB will be notified of each individual ARDS occurrence upon confirmation by the MSMs, per their request.Analysis of the overall safety data by the DSMB will take place periodically throughout the trial. The first analysis is planned after the first 40 subjects have completed the in-hospital phase of the study. The number and timing of subsequent analyses will be determined in consultation with the DSMB as the study progresses.

Safety analyses will be carried out at least semiannually (unless requested at more frequent intervals by the DSMB or MSMs). Two statistical reports will be generated – an open report to be distributed to the Executive Committee and MSM, 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 due to adverse events, whether or not study drug-related), and data management/quality information. The statistics will be provided for the overall study. For the closed report only, the statistics will also be provided by partially blinded treatment group (A vs. B). If the DSMB wishes to be completely unblinded for these reports, a sealed identification envelope will be provided to the NINDS DSMB liaison; this envelope can be opened at the discretion of the DSMB. An annual report will be submitted to the FDA.

10 HUMAN SUBJECTS

10.1 ETHICAL CONDUCT OF THE STUDY

This study will be conducted in accordance with Declaration of Helsinki, and in compliance with the protocol, applicable regulatory requirements, and GCP/ICH guidelines (please refer to appendix VIII). The PI at each site is responsible for the care and medical follow-up of the patients throughout their participation in the study. If the PI is not present in the clinical site, he/she will leave instructions for other members of the study staff and a telephone number where he/she can be reached, if needed.

10.2 INSTITUTIONAL REVIEW BOARD (IRB) REVIEW AND INFORMED CONSENT

This protocol, the ICF, and any subsequent modifications must be reviewed and approved by the local IRB at each of the participating institutions. A signed and dated ICF must be obtained from the subject, his/her legal representative, or family member as defined in 21CFR50.3(m). The ICF must also be signed and dated by a member of the study staff qualified to be delegated the authority to obtain informed consent, and a witness (if required by the local IRB). A copy of the ICF must be given to the subject, his/her legal representative or family member and the consent process must be documented in the subject's medical record. The PI or delegated sub-Investigator is responsible for ensuring that informed consent is obtained from each patient, his/her legal representative, or family member prior to conducting any study-related activities.

No deviations from or changes to the study protocol should be initiated except when necessary to eliminate immediate hazard to the patient. However, the IRB and PI must be informed of this as soon as possible thereafter. It is the study site PI's responsibility to report SAEs occurring during the study and MedWatch/Safety Report to their IRB, as required and as soon as possible.

10.3 SUBJECT CONFIDENTIALITY

All participating study investigators must ensure that the confidentiality of personal identity and all personal medical information of study participants will be maintained at all times. Additionally, the clinical sites are to follow privacy obligations to study participants under the Health Insurance Portability and Accountability Act (HIPAA). All records re

garding this study must be securely stored in a locked cabinet. Subject confidentiality will be strictly maintained by the use of a subject ID number. The study database and any study documents submitted to the SDMC will only identify study subjects by this unique study identification code. All data will be stored in a manner that is HIPAA compliant, without the ability to track the information back to a specific subject except through a password protected system. Personal medical information may be reviewed for the purpose of verifying data recorded in the CRF by site monitors. Other properly authorized persons, such as the regulatory authorities, also may have access to these records. Personal medical information, however, always will be treated as strictly confidential. All SDMC personnel are certified by the NIH Office of Human Subjects Research in the Protection (OHRP) of Human Research Subjects course, or other training courses acceptable to the NIH OHRP.

In order to maintain the confidentiality of subjects who elect to participate in the blood bank repository, as well: 1) the results of any genetic analyses performed on samples collected from this repository will not appear in the medical records and will not be released to the subjects or their healthcare providers; 2) the samples will be coded and the key will be kept in a separate locked file; and 3) in the event of future second or third party use of the samples, all codes will be removed so that there will be no method by which the sample can be tracked back to the subject.

10.4 DATA AND SAFETY MONITORING PLAN

The DSMB, appointed by the NINDS and managed by the NINDS Clinical Trials group, will be responsible for the oversight of safety of trial participants, review of the safety reports, requesting additional data/information (if necessary), and advising the NINDS regarding continuation/ discontinuation of the study. The study may be modified or discontinued at any time by the NINDS, the FDA, or the Executive Committee to ensure that research subjects are protected. All ARDS cases will monitored continuously throughout the trial by the unblinded study statistician, who will notify the EC and DSMB if recruitment must be stopped (please refer to section 7.7 for the stopping rule). The DSMB will be notified of each individual ARDS occurrence upon confirmation by the MSMs, per their request. Analysis of the overall safety data by the DSMB will take place periodically throughout the trial. The first analysis is planned after the first 40 subjects have completed the in-hospital phase of the study (day-7 or discharge, whichever is earlier). The DSMB will meet to review the accumulated safety data, with particular attention to mortality, SAEs, and adverse events of special interest (AEOSI) including ARDS, from initiation of treatment to day-7 or discharge (whichever occurs first) to ensure that there are no emerging safety concerns. Unblinding of treatment assignments will only be allowed by the Chair of the DSMB, if felt necessary, but the unblinded data will be confidentially maintained within the DSMB. Enrollment will continue with the recommendation of the DSMB, including necessary modifications, if needed, to address any safety concerns early on.

After this meeting, the DSMB will regularly meet at least once approximately every 6 months or at more frequent intervals if needed to review recruitment and safety data. Analyses of the safety data will be carried out on an ongoing basis throughout the trial, as mentioned above. All AEOSIs, all SAEs, deaths, and adverse events will be reviewed by the DSMB during their meetings. There will be no limit on the number and timing of analyses aimed at guaranteeing the safety of the patients. An apparent, consistent and persistent evidence of net harm that tends to overwhelm any benefit may allow for premature termination of the study. Please refer to section 7.7 from the pre-specified stopping rule based on the frequency of ARDS cases.

10.5 STUDY MODIFICATION/DISCONTINUATION

The study may be modified or discontinued at any time by the NINDS, the OHRP, the FDA, or a study site IRB (but only for that individual study site) as part of their duties to ensure that research subjects are protected.

11 PUBLICATION OF RESEARCH FINDINGS

Publication and presentations of the results of this trial will be governed by the policies and procedures developed by the Executive Committee in conjunction with the NINDS. The Publication Policy will be fully compliant with the voluntary NIH Public Access Policy mandated by the Consolidated Appropriations Act of 2008 (Division G, Title II, Section 218 of PL 110-161). The Executive Committee will follow NIH policies on data sharing (as described at the site: [http://grants2.nih.gov/grants/policy/data_sharing/data_sharing_ guidance.htm] and any updates thereto). Any manuscript(s) will be made available for review by the sponsor and the NINDS prior to submission.

A Publications Subcommittee of the Executive Committee, consisting of Drs. Magdy Selim, Sharon Yeatts, Yuko Palesch, and Claudia Moy will establish a writing group headed by the Study Chair to oversee the writing of the main study-related manuscripts. Any of the Trial's investigators (clinicians as well as study coordinators) wishing to write a manuscript must first submit to the Publications Subcommittee a brief description/proposal of the manuscript content. The Subcommittee will review the proposal in a timely manner, and if the proposal is approved, it will be disseminated to all study investigators to encourage those who have similar interests in the topic to participate in the writing group. The Publications Subcommittee will appoint the writing group members. The Publication Subcommittee must review and approve all writing and presentation activities of the study prior to submission to a journal or a meeting for scientific presentation.

12 ANCILLARY STUDIES POLICY

Any of the study investigator(s) wishing to conduct ancillary studies must submit in writing to the Executive Committee a 2-3 page outline of the proposal. The Executive Committee will discuss the proposal, and each member of the Executive Committee will vote to approve or disapprove the proposal. The key criteria for evaluation are scientific merit, relevance to the major goals of the main study, and the ancillary study's impact on the conduct and feasibility of the main trial. If the proposal is approved by the Executive Committee, it will be forwarded to the DSMB members and the NINDS Administrative Officer who will also vote for approval or disapproval. Upon approval by the Executive Committee, the DSMB and the NINDS, the investigator(s) may then submit the proposal to potential funding source(s), if needed.

13 RESOURCE- AND DATA-SHARING PLAN

The Executive Committee will follow the NIH policies on data sharing [http://grants2.nih.gov/grants/policy/ data_sharing/data_sharing_guidance.htm], and any updates thereto. Sharing of the data generated by this study will be carried out in several different ways to make our results available to the scientific community interested in stroke and ICH and to avoid unintentional duplication of research. Our plan for data sharing will include: 1) Presentations at national and international scientific meetings, such as the International Stroke Conference, the Annual meeting of the American Academy of Neurology, the European Stroke Conference, and the International Cerebral Hemorrhage conference; 2) Posting information about stroke and ICH written primarily for a general audience on the study's website; 3) Making a description of this clinical trial and summary of the results available on www.ClinicalTrials.gov.

We would also welcome collaboration with others who could make use of the data generated by the study. Upon completion of the study, the public use database will be prepared by stripping any and all personal identifiers. The public use database, consisting of several data files, will contain: (1) baseline and demographic characteristics; (2) outcomes assessments; (3) CT data; (4) concomitant medications and procedures; and (5) adverse events. Each data file will be made available as a formatted SAS dataset or other electronic format. The data files will be distributed along with the data dictionary and a brief instruction file. Anyone wishing to access the data may do so by completing a data-sharing agreement and data request form and submitting those forms to the SDMC or subsequently to an external data archiving unit chosen by the NINDS.

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15 APPENDIX

I. DFO in ICH (Phase I) Manuscript
II. RECOMMENDED PROTOCOL FOR MANAGEMENT OF PATIENTS WITH ICH
III. ASA/AHA ICH MANAGEMENT GUIDELINES
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VIII. DECLARATION OF HELSINKI

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Background and Purpose—Treatment with the iron chelator, deferoxamine mesylate (DFO), improves neurological recovery in animal models of intracerebral hemorrhage (ICH). We aimed to evaluate the feasibility, safety, and tolerability of varying dose-tiers of DFO in patients with spontaneous ICH, and to determine the maximum tolerated dose to be adopted in future efficacy studies.

Methods—This was a multicenter, phase-I, dose-finding study using the Continual Reassessment Method. DFO was administered by intravenous infusion for 3 consecutive days, starting within 18 hours of ICH onset. Subjects underwent repeated clinical assessments through 90 days, and computed tomography neuroimaging pre- and post-drug-administration.

Results—Twenty subjects were enrolled onto 5 dose tiers, starting with 7 mg/kg per day and ending with 62 mg/kg per day as the maximum tolerated dose. Median age was 68 years (range, 50–90); 60% were men; and median Glasgow Coma Scale and National Institutes of Health Stroke Scale scores on admission were 15 (5–15) and 9 (0–39), respectively. ICH location was lobar in 40%, deep in 50%, and brain stem in 10%; intraventricular hemorrhage was present in 15%. DFO was discontinued because of adverse events in 2 subjects (10%). Six subjects (30%) experienced 12 serious adverse events, none of which were drug-related. DFO infusions were associated with mild blood-pressure-lowering effects. Fifty percent of patients had modified Rankin scale scores ≤2, and 39% had modified Rankin scale scores of 4 to 6 on day 90; 15% died.

Conclusions—Consecutive daily infusions of DFO after ICH are feasible, well-tolerated, and not associated with excessive serious adverse events or mortality. Our findings lay the groundwork for future studies to evaluate the efficacy of DFO in ICH. **(*Stroke*. 2011;42:00-00.)**

Key Words: deferoxamine mesylate ■ iron ■ ICH

At present, there is no treatment for intracerebral hemorrhage (ICH) beyond supportive and aggressive medical care. The iron chelator, deferoxamine mesylate (DFO), is a potentially promising therapeutic intervention to target secondary effects of ICH to limit brain injury, facilitate neuronal repair, and improve outcome.

Hemoglobin and its degradation products, particularly iron, released from hemolyzed red blood cells after ICH are implicated in neuronal injury via several mechanisms; these include exacerbation of excitotoxicity, autophagy, hydroxyl radical formation, and oxidative stress.[1–8] DFO has diverse neuroprotective effects independent of its iron-chelating properties[9]; these include antiapoptosis, antioxidative stress, antiphagocytosis, and anti-inflammatory effects[10–12]; it also blocks hemoglobin-mediated accentuation of glutamate excitotoxicity.[5] Animal studies have shown that DFO reduces hemoglobin-induced neurotoxicity in vitro and in animal models of hemorrhage, and it improves neurological function after experimental ICH in several species.[13–15]

To translate these preclinical data, we undertook the current study to assess the tolerability and safety of DFO in patients with ICH, and to determine the maximum tolerated dose (MTD) to be investigated in future studies to determine

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whether treatment with DFO would improve overall outcome after ICH.

Methods

Subjects and Overall Study Design

This was a multicenter, Phase I, dose-finding study using the Continual Reassessment Method (CRM).[16] Subjects with spontaneous ICH, presenting to the emergency department within 18 hours of symptom onset, were enrolled from July 2008 to January 2010 at 4 sites: Beth Israel Deaconess Medical Center (n=6), Massachusetts General Hospital (n=5), Medical College of Wisconsin (n=5), and Hartford Hospital (n=4). The Data Coordination Unit, housed in the Division of Biostatistics and Epidemiology at the Medical University of South Carolina, served as the statistical and data management center for the study. The study was approved by the local Institutional Review Boards, and all subjects (or their legal representatives) were required to sign written informed consent before enrollment. Supplemental Table S1, http://stroke.ahajournals.org, lists inclusion and exclusion criteria.

The study was supported by the National Institute of Neurological Disorders and Stroke (NINDS), and registered with clinicaltrials.gov as NCT00598572. An Investigational New Drug (IND) was granted from the US Food and Drug Administration to conduct the study (IND #77306).

Study Procedures

All patients with ICH were screened on presentation. A pretreatment baseline plain computed tomography scan establishing the presence of ICH was required to confirm the diagnosis. Neurological examination included assessments of National Institute of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS) scores, as well as study-specific visual and auditory tests (whenever possible in awake patients), which included assessments for cataracts, hearing loss, color blindness, and tinnitus. Consecutive eligible patients were approached for consent and underwent baseline examination (repeated NIHSS, GCS, and physical examination including vital signs) 3 to 6 hours later to assure neurological stability. Stable subjects received the first dose of the study drug within 45 minutes of baseline assessments and 18 hours of ICH-symptom onset. All subjects were admitted to neurological intensive care or stroke units; the general care of subjects conformed to guidelines from the Stroke Council of the American Heart Association.[17] Supplemental Table S2 summarizes the timing and type of various assessments throughout the study. Subjects were monitored for safety and vital signs recorded every 30 minutes during each infusion and hourly afterward. The subjects were contacted by phone on day 90 (±7 days) to assess modified Rankin scale (mRS), Barthel Index (BI), and Extended Glasgow Outcome Scale (GOS-E) scores and mortality. All AEs were assessed until day 7 or discharge (whichever was earlier), and serious adverse events (SAE) until the completion of the study on day 90. Administration of DFO can result in a vin rosé discoloration of urine in patients with systemic iron overload, which raised concerns regarding the potential for unblinding in future controlled trials of DFO. Therefore, we performed urine analyses at multiple points during treatment with DFO.

Weight-adjusted intravenous infusions of DFO were administered at a rate of 7.5 mg/kg per hour and repeated daily for 3 consecutive days. The first cohort received a dose of 7 mg/kg per day, with subsequent cohorts treated at dose-tiers determined according to the Piantadosi modified CRM.[16] Regardless of subject weight or assigned dose, the maximum daily dose was restricted to 6000 mg/d, in accordance with the manufacturer's brochure and U.S. Food and Drug Administration recommendations, to minimize risk of toxicity. A minimum cohort size of 3 subjects was prespecified for each dose. The safety information guiding the transition from 1 dose to the next was based on number of subjects in a cohort who experienced prespecified dose-limiting toxicities (DLT). To guard against rapid dose escalation, we prespecified incremental increases of ≤25 mg/kg per day until DLT was observed, at which time the CRM was implemented to determine the dose for each of the subsequent cohorts.

To assure safety, we conservatively defined DLTs as any of the following AEs occurring within 7 days of initiation of treatment with DFO or until discharge (whichever was earlier): anaphylaxis at any time point during DFO infusion; hypotension, defined as a decrease in systolic blood pressure >20 mm Hg or diastolic blood pressure >10 mm Hg, or systolic blood pressure <85 mm Hg, confirmed by 3 consecutive readings, and requiring medical treatment at any time point during DFO infusion, that cannot be explained by other causes; worsening neurological status, defined as an increase ≥4 points on NIHSS or a decrease of ≥2 points on GCS, that cannot be explained by other causes, occurring at any time point during DFO infusion; mortality, regardless of relationship to DFO; and any AE prolonging hospital stay, resulting in emergent medical therapy, or resulting in death, regardless of relationship to DFO.

An independent Medical Safety Monitor reviewed all SAEs and DLTs on an ongoing basis. The Medical Safety Monitor communicated his decisions directly to the Chair of the NINDS-appointed Data and Safety Monitoring Board. As a safety precaution, we planned to suspend enrollment if 2 of 3 subjects in a cohort experienced DLTs to allow the Data and Safety Monitoring Board to review the accumulated data and make a recommendation for early termination versus resumption of the study.

Outcome Measures

The primary outcome measure was safety, defined as the occurrence of DLTs as defined above. There was no lost-to-follow up with regard to safety outcomes, because the CRM was based on safety assessments conducted during hospitalization through day 7 or discharge (whichever was earlier).

Because this study was envisioned as a prelude to future efficacy studies, we assessed various neurological and functional outcome scales (mRS, BI, and GOS-E) on day 90. We also explored effects of treatment on the progression of hematoma and relative perihematoma edema (PHE) volumes on serial computed tomography scans, primarily for safety purposes, to ensure that DFO does not aggravate hematoma or PHE growth. We used relative PHE, as opposed to absolute PHE volume, to adjust for underlying ICH volume.[18] Computerized radiological volumetric measurements were performed by a single investigator, blinded to the assigned dose and clinical data, as previously described.[19] The blinded investigator examined ICH and PHE volumes in 10 randomly selected, deidentified scans twice at an interval of several months apart. The test-retest intraclass correlation coefficients for intraobserver agreements were 1.0 for both ICH and PHE volume measurements. The concordance correlation coefficient was 0.996 (95% CI, 0.990–0.999) for ICH and 0.998 (95% CI, 0.993–0.999) for PHE volumes.

Statistical Analysis

The CRM was used to identify the maximum tolerated DFO dose, defined a priori as the dose associated with a 0.40 DLT probability. The maximum acceptable DLT probability of 0.40 was prespecified based on the weighted average of all SAEs reported in placebo-treated patients who participated in recent ICH trials (FAST, CHANT, GAIN).[20–22] Under the CRM, when the third subject in each cohort completed the 7-day or discharge period, the dose-toxicity curve was updated based on DLTs observed in all previously enrolled subjects, and the estimated MTD obtained from the updated curve. Subjects enrolled onto the following cohort were then treated at the re-estimated MTD. This reassessment process was repeated until the stopping convergence criterion was reached. The CRM algorithm was considered to have converged when the re-estimated MTD following completion of the current cohort was within 5% of the current dose. Analysis of CRM data was performed on an ongoing basis throughout the study. The DLT data were available to the study statistician (S.Y.), who implemented the CRM algorithm and updated the dose for subsequent cohorts.

Table 1. Demographic and Clinical Characteristics of Patients per Dose Tier

Characteristics	Dose					Total
	7 mg/kg	32 mg/kg	47 mg/kg	57 mg/kg	62 mg/kg	
Patients, n	4	3	3	4	6	20
Age, y, median (range)	50 (50–69)	66 (53–76)	67 (54–85)	76 (65–90)	70 (55–80)	68 (50–90)
Male sex, %	2	2	1	2	5	12 (60.0)
Race/ethnicity						
White, %	3	2	3	3	6	17 (85.0)
African American, %	1	1	0	1	0	3 (15.0)
Hispanic or Latino, %	1	0	0	1	0	2 (10.0)
Medical History						
Other stroke	1	1	0	1	2	5 (25.0)
Hypertension	4	3	2	4	5	18 (90.0)
Hyperlipidemia	2	2	2	2	3	11 (55.0)
Diabetes mellitus	1	0	1	1	1	4 (20.0)
Baseline vitals						
SBP (mm Hg), median (range)	145 (132–168)	130 (110–144)	158 (157–177)	154 (136–164)	134 (125–146)	143 (110–177)
DBP (mm Hg), median (range)	76 (50–88)	67 (66–101)	77 (66–86)	66 (58–75)	68 (52–75)	69 (50–101)
MAP, median (range)	97 (80–115)	93 (81–111)	104 (96–116)	99 (84–100)	88 (81–97)	96 (80–116)
Screening glucose, median (range)	136 (110–163)	109 (88–137)	210 (109–379)	140 (113–258)	131 (100–166)	131 (88–379)
Baseline NIHSS, median (range)	15 (7–28)	0 (0–1)	8 (5–9)	12 (1–22)	13 (1–35)	9 (0–35)
Baseline GCS, median (range)	13 (7–15)	15 (15–15)	15 (14–15)	13 (11–15)	13 (5–15)	15 (5–15)
Screening CT						
Hematoma volume, mL, median (range)	10 (3–40)	2 (1–6)	29 (3–39)	23 (4–41)	18 (1–45)	12 (1–45)
Location	1	0	0	0	1	2 (10.0)
Infratentorial						
Supratentorial, %	3	3	3	4	5	18 (90.0)
Lobar, %	0	1	1	3	3	8 (40.0)
Deep,	3	2	2	1	2	10 (50.0)
IVH present	2	0	1	0	0	3 (15.0)
Time from onset to treatment, h, median (range)	11 (8–12)	17 (14–22)†	13 (13–18)	17 (15–18)	13 (8–18)	14 (8–22)

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; MAP, median mean Blood pressure; NIHSS, National Institutes of Health Stroke Scale; GCS, Glascow Coma Scale; CT, computed tomography; IVH, intraventricular hemorrhage.

†One patient was enrolled 22 h after symptom onset. At the time of enrollment, symptom onset was thought to be 23:00. After enrollment, additional information became available, which indicated that symptom onset was actually 15:00, 8 h earlier.

AEs were assigned to a system-organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Exploratory descriptive statistics (median, range, percentages) of additional safety parameters and clinical and radiological data were computed by dose group. The effect of DFO on laboratory parameters and vital signs is summarized by the median change in the corresponding parameter and 95% CI.

Results

Subjects Baseline and Clinical Characteristics

A total of 20 subjects were enrolled onto 6 cohorts during the course of the study. Two subjects (10%) withdrew consent following the treatment period; neither withdrawal was because of an AE. No other subjects were lost to follow-up.

The first cohort (n=4) was treated at 7 mg/kg per day, the prespecified starting dose, with subsequent cohorts treated at doses identified by the CRM algorithm as follows: 32 mg/kg (n=3), 47 mg/kg (n=3), 57 mg/kg (n=4), and 62 mg/kg (n=3). On completion of the fifth cohort, the updated dose-toxicity curve indicated that the next cohort should maintain the 62 mg/kg per day dose. As this met our prespecified convergence criterion, the final estimated MTD is 62 mg/kg per day. Thereafter, following consultation with the Data and Safety Monitoring Board, we enrolled 3 additional subjects at the MTD to collect additional safety data at this dose. Table 1 summarizes the demographic, baseline, and clinical characteristics of trial subjects by assigned dose.

Safety Data

Adverse Events

The infusions of DFO were, overall, well-tolerated. Seventeen subjects (85%) completed the 3-day study drug infusions. In 2 subjects (10%), infusions were prematurely discontinued because of AEs. These were shoulder pain, initially thought to be infusion-related, which was later

Table 2. Serious Adverse Events and Dose-Limiting Toxicities

	Dose					
Events	7 mg/kg	32 mg/kg	47 mg/kg	57 mg/kg	62 mg/kg	Total n, (%)
Cases, n	4	3	3	4	6	20
Dose-limiting toxicities*						
Anaphylaxis during infusions, n	0	0	0	0	0	0
Unexplained hypotension requiring treatment during infusions, n	0	0	0	0	0	0
Unexplained worsening of neurological status during infusions, n	0	0	0	0	0	0
Mortality within 7 d of initiation, n	1	0	0	0	0	1 (5.0)
Any adverse event prolonging hospital stay, resulting in emergent therapy, or resulting in death within 7 d of initiation, n	1	0	0	0	2	3 (15.0)
Total, n	1	0	0	0	2	3 (15.0)
Serious adverse events*						
Neurological decompensation, n	1	0	0	0	1†	2
Pulmonary embolism, n	0	0	1	0	0	1
Recurrent intracerebral hemorrhage, n	0	0	0	1†	2	3
Aspiration leading to respiratory failure and intubation, n	0	0	0	0	2	2
Hypotension requiring vasopressor therapy, n	0	0	0	0	1	1
Renal failure, n	0	0	0	0	1	1
Total, n	1	0	1	1	3	6 (30.0)

*Each subject may have multiple events reported.
†One subject may have experienced the same serious adverse events twice.

determined to be unrelated, and visual hallucinations, thought to be possibly study-drug-related. One subject only received the first infusion, without experiencing AEs, but subsequent infusions were not continued because his family declined additional treatment.

A total of 94 AEs (12 serious [13%], 82 nonserious), were reported during the study. The 12 SAEs occurred in 6 subjects (30%). Six of these 12 SAEs occurred in 3 subjects during the first 7 days of hospitalization. One subject (in the 62 mg/kg dose-tier) experienced 5 SAEs. Three subjects (15%) experienced 4 DLTs; of these, 2 subjects, both treated at the 62 mg/kg dose, developed aspiration pneumonia and required intubation. These were considered DLTs, because intubation prolonged their hospital stay. Because the rate of DLTs in this cohort (0.33) was less than was our prespecified acceptable probability of 0.40, the 62 mg/kg per day dose still met our predefined criteria for the MTD. Table 2 summarizes the occurrence of DLTs and SAEs by dose tier.

Three subjects (15%) died during the 90-day follow-up period; 1 subject (5%) died in hospital within 7 days of ICH onset, and 2 subjects died between 7 and 30 days after ICH onset. None of the SAEs, DLTs, or mortalities were adjudicated to be related to the study drug.

Sixteen nonserious AEs (20%) were possibly or probably related to the study drug. They were mild, self-limited, and did not require specific treatment. These included: injection site irritation (15%) and intravenous infiltration (20%), itching or rash (10%), visual hallucinations (5%), blurred vision (5%), decrease in blood pressure (20%), and arm pain (10%). Supplemental Table S3 summarizes all AEs by Medical Dictionary for Regulatory Activities body system and by dose-tier.

Vital Signs and Laboratory Studies

Administration of DFO did not result in important alterations in heart rate, respiratory rate, oxygen saturation, or temperature. Overall, median mean blood pressure (MAP) at baseline was 95.8 mm Hg (95% CI, 84–100.3) versus 93.2 mm Hg (95% CI, 87.6–98.1) during the infusions. A total of 8 patients (40%) experienced a maximal drop in MAP >20% (median, 29%; 95% CI, 27–39) at some point during the infusions compared with baseline values. One subject, in the 62 mg/kg dose-tier, required vasopressors; his hypotension was thought to be related to intubation and anesthesia. None of the remaining 7 subjects required any medical treatment. In the 62 mg/kg dose-tier cohorts, 4 of 6 subjects (67%) experienced a maximal drop in MAP >20% during the infusions (median, 29%; 95% CI, 25–39; mean absolute change, 22.4 mm Hg; standard error, 0.49); median MAP at baseline was 87.7 mm Hg (95% CI, 80.7–96.7) versus 87.4 mm Hg (95% CI, 79.5–96.0) during the infusions. However, the blood pressure drop was not clinically significant, did not meet our definition for a DLT, and did not require treatment, except in the subject mentioned above.

Analyses of laboratory data indicated no safety concerns. There were no differences in routine laboratory values and in the incidence of abnormalities and change from baseline in electrocardiogram parameters. Serum hemoglobin and hematologic parameters, renal and hepatic functions, and electrolytes were stable over time. We observed no

Table 3. Summary of Radiological and Clinical Outcome Data

	Dose					
	7 mg/kg	32 mg/kg	47 mg/kg	57 mg/kg	62 mg/kg	Total
Cases, n	4	3	3	4	6	20
Hematoma volumes						
Screening, median (range)	9.92 (3.05–40.21)	2.27 (0.98–5.92)	28.82 (3.39–39.08)	23.43 (3.65–40.84)	17.69 (0.36–45.36)	11.97 (0.36–45.36)
Hour 72, median (range)	9.08 (3.69–44.67)	1.05 (0.93–6.10)	31.19 (3.40–33.91)	25.86 (2.83–49.29)	21.95 (0.31–45.40)	11.51 (0.31–49.29)
Day 7 or discharge, median (range)	4.31 (3.65–4.96)	3.11 (3.11–3.11)	25.66 (23.11–28.22)	19.94 (2.74–47.26)	24.74 (9.65–44.64)	21.44 (2.74–47.26)
PHE volume						
Screening, median (range)	6.89 (0.92–45.31)	13.57 (1.43–14.8)	33.2 (8.98–52.69)	23.15 (8.38–86.17)	24.38 (0–55.14)	13.87 (0–86.17)
Hour 72, median (range)	12.94 (1.94–101.65)	14.58 (2.16–15.29)	47.35 (9.32–52.31)	39.02 (9.12–86.46)	33.21 (0–84.94)	14.93 (0–101.65)
Day 7 or discharge, median (range)	7.75 (2.78–12.73)	13.96 (13.96–13.96)	58.42 (49.18–67.65)	26.64 (9.34–100.49)	53.65 (13.05–99.42)	37.91 (2.78–100.49)
Relative PHE volume						
Screening, median (range)	0.69 (0.3–1.13)	2.29 (1.46–6.52)	1.83 (0.85–2.65)	1.82 (0.55–2.30)	1.12 (0–1.65)	1.21 (0–6.52)
Hour 72, median (range)	1.50 (0.53–2.28)	2.39 (2.32–14.56)	1.54 (1.52–2.74)	1.86 (0.91–3.22)	1.66 (0–1.97)	1.77 (0–14.56)
Day 7 or discharge, median (range)	1.66 (0.76–2.57)	4.49 (4.49–4.49)	2.26 (2.13–2.40)	2.13 (1.34–3.41)	2.10 (1.35–2.39)	2.18 (0.76–4.49)
GCS on Day 7 or discharge, median (range)	15 (10–15)	15 (15–15)	15 (15–15)	15 (12–15)	15 (7–15)	15 (7–15)
NIHSS on Day 30, median (range)	2 (2–6)	0 (0–0)	3 (2–4)	3 (0–9)	1 (0–11)	2 (0–11)
mRS on Day 90, median (range)	2.5 (1–6)	0 (0–0)	4.5 (3–6)	4 (0–5)	3 (0–6)	2.5 (0–6)
BI on Day 90, median (range)	100 (75–100)	100 (95–100)	80 (80–80)	5 (0–100)	100 (0–100)	100 (0–100)
Mortality, n						
During study Period	1	0	1	0	1	3 (15.0)
During first 7 d	1	0	0	0	0	1 (5.0)
After 7 d	0	0	1	0	1	2 (10.0)

BI indicates Barthel Index; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PHE, perihematoma edema; GCS, Glasgow Coma Scale.

changes in urine output or color over the 3-day course of DFO infusions in any subject. Treatment with DFO did not result in iron deficiency or anemia. We found no relationship between DFO dose-tier and changes in serum iron studies. Supplemental Table S4 summarizes laboratory values at baseline, 72 hours, and day 30.

Radiological Studies

Analysis of volumetric measurements of ICH and relative PHE volumes over time indicated no safety concerns at any of the tested dose-tiers. These data are summarized in Table 3. Overall, treatment with DFO was not associated with increase in hematoma or PHE growth. Median change in ICH volume from baseline to after the third DFO infusion was -0.05 cm^3 (95% CI, -0.87–0.64). Overall median change in relative PHE volume from screening to post-third DFO infusion was 0.48 (95% CI, 0.10–0.76) and from screening to day 7 or discharge (whichever occurred first) was 0.87 (95% CI, 0.51–1.28).

Functional Outcome Data

We collected data on mRS, BI, and GOS-E at day 90. These data are summarized in Table 3. Two subjects (10%) withdrew consent, 1 after the 7-day visit (mRS=5), and 1 after the 30-day visit (mRS=1). Among the remaining 18 subjects, 9 subjects (50%) had mRS scores of 0 to 2; 2 subjects (11%) had a score of 3; and 7 subjects (39%) had scores of 4 to 6. Three subjects died before completing the 90-day assessments. Among the 15 survivors, 9 subjects (60%) had a BI score ≥95; 2 subjects (13%) had scores of 60 to 80 and 4 subjects (27%) had scores of 0 to 50; 6 subjects achieved upper good recovery on GOS-E at day 90, 1 subject achieved lower good recovery, and 8 subjects achieved moderate-to-severe disability.

Animal studies have shown that human-equivalent doses of DFO ≥16 mg/kg are associated with improved outcome after experimental ICH.[15] Therefore, we explored trends in functional outcome data among 14 subjects who completed the study in the 32 mg/kg to 62 mg/kg dose-tier cohorts. Seven subjects (50%) had mRS of 0 to 2 and 6 subjects (43%) had mRS of 4 to 6 at day 90. The baseline characteristics for this subgroup were as follows: median age, 71 years; admission ICH volume, 16.5 mL; baseline NIHSS, 7; baseline GCS, 14.

Discussion

The primary objectives of this phase-I study were to investigate the feasibility, tolerability, and safety of repeated infusions of DFO in patients with acute spontaneous ICH, and to determine its MTD to be used in future Phase II and Phase III studies. We found that repeated daily infusions of DFO for 3 consecutive days after ICH onset are feasible and well-tolerated; are not associated with an increase in SAEs or mortality, when compared with placebo-treated patients in recent ICH trials[20–22]; and do not result in substantial biochemical, hematologic, or radiological AEs. DFO has been used in clinical practice for over 40 years, mostly for the treatment of acute iron intoxication and chronic iron overload in patients requiring repeated blood transfusions. The safety profile of DFO in this study is in line with previous clinical experience of DFO use in nonstroke patients.[23] In rat models of ICH, DFO doses of 100 mg/kg per day and 200 mg/kg per day were both effective in improving neurological and functional recovery[15]; based on mass constant conversion factors, the calculated human equivalent doses are approximately 16 mg/kg per day and 32 mg/kg per day. We identified 62 mg/kg per day (up to a maximum daily dose of 6000 mg/d, irrespective of body weight) as the MTD for DFO infusions.

There is growing experimental and clinical evidence linking iron-mediated toxicity to secondary neuronal injury after ICH.[1–7] Animal studies demonstrate an increase in iron-positive cells, heme oxygenase protein, and markers of DNA damage in the perihematoma area within the first day after ICH, which peak by day 3.[3,10] In ICH patients, serum ferritin on admission correlates with relative PHE on day 3 (which coincides with the timing for hemoglobin hemolysis[24])[19] and with functional outcome at 3 months[25]; iron content within the hematoma, estimated by magnetic resonance imaging, correlates with the relative PHE volume.[26] There is also extensive preclinical evidence that the iron chelator, DFO, confers substantial neuroprotection and reduces hemoglobin-induced neurotoxicity after ICH in different species and by different investigators.[6,10,13–15] These studies have shown that the benefit of DFO in ameliorating secondary neuronal injury after ICH is mediated via several diverse mechanisms and may be at least partly independent of its iron-chelating effects.[5,10–12] Our findings that the MAP decreases by approximately 2 mm Hg during DFO infusions indicates that DFO also exerts a mild blood-pressure-lowering effect, which may be of some potential benefit in ICH.[27] Therefore, DFO is a rational choice for additional investigation as a potential therapeutic intervention to improve the outcome of patients with ICH.

This study represents the first translational attempt in this regard. Most attention in ICH research has been focused on targeting hematoma and its expansion, utilizing various approaches such as surgical evacuation, endoscopic aspiration with or without lysis, ultrahemostatic therapy, or intensive blood-pressure-lowering. In contrast, treatment with DFO aims to target the pathophysiological mechanisms that contribute to secondary neuronal injury, which continues for days after ICH onset, and if successful can provide a complementary therapy to ongoing efforts targeting hematoma and its expansion.

Treatment with DFO at all tested dose-tiers did not result in significant alterations in hematologic or serum iron studies. Serum ferritin, however, showed a trend toward increase following treatment (Supplemental Table S4). This may be related to a paradoxical increase in serum ferritin following ICH as part of an acute stress response.[28] Our study did not include a placebo arm to address adequately this possibility and to assess whether treatment with DFO in our study might have blunted an otherwise greater rise in serum ferritin. The lack of significant reduction in serum iron studies after 3-day treatment with DFO may be similarly explained, and does not necessarily imply lack of its potential efficacy in ICH. Again, the benefit of DFO may be, at least partly, independent of its iron-chelating effects.[5,10–12] Previous animal studies have shown that DFO decreases ferritin-positive cells in the brain following ICH.[14] However, they did not examine the effects of DFO on serum ferritin levels. Future studies should examine levels of serum ferritin and iron following experimental ICH and the effects of DFO on these measures; they should also carefully probe temporal changes in these serum measures during the days following ICH in DFO- and non-DFO treated patients, ideally in a randomized, placebo-controlled, trial setting.

Animal studies show that: PHE volume increases rapidly between day 1 and 3 after ICH onset, at which point it reaches its peak,[28–29] delayed brain edema formation is largely related to hemoglobin- and iron-mediated toxicity,[2,30] and treatment with DFO attenuates the development of brain edema after ICH.[10,14–15] Human studies, however, suggest that the peak in PHE is delayed beyond 3 days.[31–32] Our radiological data regarding relative PHE volume, where it increased by 0.48 from admission to day 3 and 0.87 to day 7 or discharge, are consistent with these reports. They also compare favorably with previous studies evaluating the natural progression of PHE, which showed that relative PHE volume almost doubles within the first 24 to 72 hours.[18–19] Although debatable, relative PHE might influence recovery after ICH.[33] Animal studies have shown that DFO decreases PHE in a dose-dependent manner.[13] We did not observe a clear dose-dependent effect on PHE progression in our study. This may be because of the small number of subjects treated at each dose cohort. Future studies will need to include larger number of subjects and non-DFO-treated subjects to clarify conclusively the effect of DFO on PHE. It is important, however, to point out that our study was focused on safety and dose finding. It was not designed to assess efficacy, mechanisms of action of DFO, or surrogate measures of its biological activity. It was also not powered or blinded to address

properly clinical outcomes. Therefore, the above findings are purely exploratory at this stage.

We started DFO infusions within 18 hours of ICH onset. Recent animal studies indicate that the beneficial effects of DFO are maintained when it is administered up to 48 hours after ICH induction, and that the optimal therapeutic time window is up to 24 hours.[15]

Our study utilized the modified CRM statistical design, which represents a novel approach to conducting phase-I safety and dose-finding studies in stroke. The CRM provides greater responsiveness to the occurrence of AEs, minimizes exposing additional subjects unnecessarily to doses below the MTD, and allows for determination of the MTD with a small sample size.

In conclusion, the current study provides data demonstrating the feasibility, tolerability, and safety of DFO in doses up to 62 mg/kg per day, up to a maximal daily dose of 6000 mg/d, in patients with ICH. These results support continued development of DFO as a potential therapy for ICH. Development of a multicenter, Phase II trial of DFO in ICH is currently underway.

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SUPPLEMENTAL MATERIAL

Table 1 (online): Inclusion and Exclusion Criteria

INCLUSION CRITERIA

1. Age ≥ 18 years
2. The diagnosis of ICH is confirmed by brain CT scan.
3. The first dose of the study drug can be administered within 18 hours of ICH symptom onset.
4. Informed consent is obtained
5. Stable clinical and neurological status. Patients whose clinical or neurological status significantly deteriorated compared to presentation prior to administration of the study drug were excluded

EXCLUSION CRITERIA

1. Previous chelation therapy or known hypersensitivity to DFO products
2. Abnormal renal function (serum creatinine > 2 mg/dl)
3. Known iron deficiency anemia, defined as hemoglobin concentration <7g/L or requiring blood transfusions
4. Planned surgical evacuation of ICH prior to administration of the study drug
5. Patients with suspected secondary ICH related to tumor, coagulopathy (defined as INR ≥ 1.7), ruptured aneurysm or arteriovenous malformation, or venous sinus thrombosis
6. Evidence of significant shift of midline brain structure (> 10 mm) or herniation on imaging studies.
7. Deep coma (Glasgow Coma Score ≤5) upon presentation
8. Taking iron supplements (≥ 325 mg of ferrous iron) or prochlorperazine
9. Patients with heart failure taking > 500 mg of vitamin C daily

10. Known hearing impairment
11. Systolic blood pressure < 100 mmHg or diastolic blood pressure < 60 mmHg, confirmed by 3 consecutive readings
12. Patients whose clinical or neurological status significantly deteriorates (defined as an increase in NIHSS ≥ 4 points or a decrease in GCS ≥2 points compared to presentation) prior to administration of the study drug
13. Significant chronic respiratory insufficiency requiring frequent hospitalization or oxygen dependency
14. Known pregnancy (or positive pregnancy test), or breast-feeding
15. Patients known or suspected of not being able to comply with the study protocol due to alcoholism, drug dependency, incompliance, or any other cause
16. Any condition which, in the judgment of the investigator, might increase the risk to the patient
17. Life expectancy of less than 90 days due to co-morbid conditions
18. Concurrent participation in another research protocol for investigation of another experimental therapy
19. Pre-existing Do Not Resuscitate (DNR) order, or indication that a new DNR order will be implemented within the first 48 hours of hospitalization

Table 2 (online): Schedule of assessments

Data Collection Schedule											
	Screening	Baseline	0 Hr	24 hour	48 hour	72 hour	Day 7 or Discharge*	As needed	Day 30	Day 90 (phone)	End of Study
		30-45 min prior to study drug start		+/- 6h	+/- 6h	+/- 6h	+/- 6h	Whenever felt necessary by the investigators	+/- 7d	+/- 7d	
Study Procedures:											
Inclusion Exclusion Criteria	X										
Medical History	X										
Informed consent	← X →										
Subject Enrollment			X								
Study Drug Administration			X	X	X						
Clinical Exams:											
Physical Examination	X	X		X	X	X	X		X		
Visual and Auditory Assessment	X			X	X	X	X		X		
NIH Stroke Scale (NIHSS)	X	X		X	X	X	X	X	X		
Glasgow Coma Scale (GCS)	X	X		X	X	X	X	X			
Extended Glasgow Outcome Scale (GOS-E)							X		X	X	
Modified Rankin Scale (mRS)							X		X	X	
Barthel Index (BI)							X		X	X	
Vital Signs	X	X				X	X		X		
Safety Monitoring			X	X	X						
Urine Output				X	X	X					
Laboratory Assessments:											
Electrocardiogram	X			X		X		X			
Hematology (CBC)[§]	X			X	X	X		X	X		

Serum Chemistry	X			X	X	X		X	X		
Coagulation Parameters	X			X		X		X			
Urine Analysis	X			X	X	X		X	X		
Liver Function Test	X					X		X			
Kidney Function Test	X			X	X	X		X	X		
Serum Iron Studies[×]		X		X		X	X	X	X		
Serum Pregnancy Test	X										
Brain Imaging:											
Plain CT Scan	X					X	X	X			
Miscellaneous:											
Prior Medications	X										
Concomitant Medications			X	X	X	X	X		X		
Concomitant Non-Drug Therapies			X	X	X	X	X		X	X	
Adverse Events			X	X	X	X	X	X	X	X	
Dose Limiting Toxicities			X	X	X	X	X				
End of Study											X

* Day 7 or Discharge– whichever occurred first
[§] CBC = Complete Blood Counts
[×] Total serum iron, Iron Binding Capacity, Serum Ferritin, and Serum Transferrin

Table 3 (Online): All reported adverse events during the 90-day follow up period by body system.

MedDRA Body System	MedDRA Preferred Term	Dose					Total
		7 mg/kg	32 mg/kg	47 mg/kg	57 mg/kg	62 mg/kg	
		N=4	N=3	N=3	N=4	N=6	N=20
Blood and lymphatic system disorders	Anaemia	0	1	0	0	0	1
	Leukocytosis	1	0	1	0	0	2
Endocrine disorders	Diabetes mellitus	0	0	1	0	0	1
	Hyperglycaemia	0	0	1	1	1	3
Eye disorders	Eye pruritus	1	0	0	0	0	1
	Vision blurred	1	0	0	0	0	1
Gastrointestinal disorders	Abdominal pain	0	0	1	0	0	1
	Diarrhoea	0	0	1	0	0	1
	Vomiting	0	0	0	0	1	1
General disorders and administration site conditions	Application site erythema	0	1	0	0	0	1
	Fatigue	0	0	0	0	1	1
	Injection site extravasation	0	1	2	1	0	4
	Injection site haematoma	0	0	0	1	0	1
	Injection site phlebitis	0	0	0	0	1	1
	Pyrexia	2	0	1	0	0	3
Infections and infestations	Infection	0	0	0	0	1	1
	Urinary tract infection	1	0	1	2	2	6
Injury, poisoning and procedural complications	Fall	1	0	0	1	0	2
Investigations	Blood creatinine increased	0	0	0	1	0	1
	Blood pressure decreased	0	1	0	0	1	2
Metabolism and nutrition disorders	Hypokalaemia	0	0	1	0	0	1

	Hyponatraemia	0	0	0	0	1	1
	Hypophosphataemia	0	0	0	1	0	1
Musculoskeletal and connective tissue disorders	**Arthralgia**	1	0	0	1	0	2
	Musculoskeletal pain	1	0	0	0	0	1
Nervous system disorders	**Agitation**	0	0	0	0	1	1
	Cerebral haemorrhage	0	0	0	1	2	3
	Convulsion	0	0	0	0	1	1
	Diplopia	1	0	0	0	0	1
	Dizziness	1	0	0	0	0	1
	Headache	0	1	1	0	1	3
	Hydrocephalus	1	0	0	0	0	1
	Lethargy	0	0	0	1	1	2
	Neurological decompensation	1	0	0	1	1	3
Psychiatric disorders	**Delirium**	0	0	0	2	1	3
	Delirium tremens	0	1	0	0	0	1
	Depression	0	0	1	0	1	2
	Hallucination, visual	1	0	0	1	0	2
Renal and urinary disorders	**Haematuria**	0	0	0	1	1	2
	Ketonuria	1	0	0	0	0	1
Respiratory, thoracic and mediastinal disorders	**Pneumonia aspiration**	2	0	0	0	1	3
	Pulmonary oedema	0	0	0	1	0	1
	Respiratory failure	0	0	0	0	2	2
Skin and subcutaneous tissue disorders	**Erythema**	0	0	2	0	0	2
	Pruritus	1	0	0	0	0	1

	Rash	0	0	0	1	1	2
	Rash erythematous	0	0	1	0	0	1
	Skin irritation	0	0	0	0	1	1
Vascular disorders	**Contusion**	0	0	0	1	0	1
	Deep vein thrombosis	0	0	0	0	1	1
	Haematoma	0	0	1	0	0	1
	Hypertension	0	0	1	0	0	1
	Hypotension	0	0	0	1	1	2
	Pulmonary embolism	0	0	1	0	0	1
Total number of subjects with AEs		4	3	3	4	6	20
Total number of AEs*		21	6	19	22	26	94

*Each subject may have multiple AEs reported

Table 4 (Online): Summary of laboratory test results.

			Dose-tier Cohorts					Total
			7 mg/kg	32 mg/kg	47 mg/kg	57 mg/kg	62 mg/kg	
Hematology	**White Blood Cell Count (THOU/uL)**	**Screening**	9.2 (4.6-16.0)	6.4 (5.8-8.7)	11.9 (9.4-14.3)	10.3 (6.0-12.8)	9.3 (5.0-14.9)	9.3 (4.6-16.0)
		72 hours	11.6 (5.3-14.9)	4.3 (4.3-6.7)	12.9 (11.0-14.9)	10.0 (6.1-13.6)	5.9 (3.9-10.5)	8.5 (3.9-14.9)
		Day 30	6.4 (3.1-6.9)	4.9 (4.7-5.8)	5.9 (5.9-5.9)	6.9 (3.3-7.8)	7.6 (5.5-12.9)	6.4 (3.1-12.9)
	Red Blood Cell Count (MIL/uL)	**Screening**	4.14 (3.95-4.88)	3.77 (3.33-4.00)	4.70 (4.31-4.80)	4.46 (3.97-5.01)	4.63 (4.23-5.44)	4.38 (3.33-5.44)
		72 hours	4.26 (3.37-5.00)	3.58 (3.49-4.40)	4.56 (4.30-4.90)	4.28 (3.70-4.37)	4.46 (4.10-5.10)	4.35 (3.37-5.10)
		Day 30	5.10 (3.75-5.13)	3.77 (3.57-4.50)	4.20 (4.20-4.20)	4.45 (4.42-4.83)	4.60 (3.88-5.42)	4.45 (3.57-5.42)
	Hemoglobin (g/dL)	**Screening**	13.9 (12.5-14.7)	11.6 (10.6-12.5)	14.0 (13.8-14.4)	13.6 (12.5-13.7)	14.0 (13.3-16.4)	13.7 (10.6-16.4)
		72 hours	12.8 (11.0-14.8)	11.1 (10.8-13.4)	13.9 (13.6-14.8)	12.0 (11.4-13.4)	13.7 (11.8-16.6)	13.4 (10.8-16.6)
		Day 30	14.6 (11.0-14.7)	11.5 (11.3-13.4)	12.6 (12.6-12.6)	12.8 (12.7-14.0)	14.0 (11.6-16.6)	13.4 (11.0-16.6)
	Hematocrit (%)	**Screening**	38.5 (36.0-41.0)	33.0 (30.6-35.0)	40.0 (39.9-41.0)	39.8 (35.0-41.0)	41.4 (38.0-48.0)	40.0 (30.6-48.0)
		72 hours	36.5 (31.8-41.0)	31.0 (29.5-39.0)	39.1 (39.0-44.0)	36.0 (34.0-38.5)	39.3 (36.0-48.0)	38.5 (29.5-48.0)

		Day 30	44.0 (32.5-45.0)	33.0 (30.8-40.0)	39.0 (39.0-39.0)	41.0 (38.6-41.0)	40.0 (35.3-48.4)	40.0 (30.8-48.4)
	Platelet Count (x10^3/mm^3)	**Screening**	255 (222-305)	272 (193-330)	344 (187-383)	184 (156-244)	253 (183-300)	248 (156-383)
		72 hours	228 (189-360)	272 (217-310)	304 (166-374)	173 (137-223)	249 (168-306)	227 (137-374)
		Day 30	291 (174-302)	343 (213-364)	392 (392-392)	208 (168-243)	318 (222-461)	291 (168-461)
Electrolytes	**Sodium (mmol/L)**	**Screening**	138 (135-141)	142 (137-142)	138 (136-145)	136 (131-140)	138 (130-143)	138 (130-145)
		72 hours	137 (135-142)	135 (130-142)	141 (138-144)	138 (127-139)	137 (132-141)	138 (127-144)
		Day 30	138 (138-141)	138 (121-141)	142 (142-142)	137 (128-147)	138 (137-139)	138 (121-147)
	Potassium (mmol/L)	**Screening**	4.0 (3.5-5.3)	4.1 (3.5-4.9)	3.6 (3.5-4.0)	3.9 (3.5-4.3)	3.9 (3.4-4.0)	3.9 (3.4-5.3)
		72 hours	3.5 (3.2-3.9)	4.4 (3.7-4.9)	3.4 (3.2-4.2)	3.5 (3.3-3.9)	3.7 (3.1-3.8)	3.6 (3.1-4.9)
		Day 30	4.1 (3.9-4.4)	4.4 (3.5-5.0)	4.8 (4.8-4.8)	4.5 (4.3-4.7)	4.0 (3.7-4.5)	4.3 (3.5-5.0)
	Serum Glucose (mg/dL)	**Screening**	136 (110-163)	109 (88-137)	210 (109-379)	140 (113-258)	130.5 (100-166)	131 (88-379)
		72 hours	139.5 (98-208)	91 (89-94)	135 (132-211)	154 (108-170)	122.5 (92-146)	131.5 (89-211)
		Day 30	104 (81-136)	82 (77-112)	91 (91-91)	95 (87-110)	101 (85-131)	95 (77-136)
Renal Functions	**Blood Urea Nitrogen (mg/dL)**	**Screening**	16 (14-21)	11 (10-23)	16 (15-22)	15 (11-29)	16 (8-23)	16 (8-29)

		72 hours	16 (13-18)	15 (7-17)	19 (8-21)	13 (7-23)	14 (9-16)	15 (7-23)
		Day 30	22 (14-23)	13 (9-22)	12 (12-12)	11 (10-48)	21 (15-42)	17 (9-48)
	Serum Creatinine (mg/dL)	**Screening**	0.99 (0.50-1.30)	1.10 (0.92-1.65)	0.80 (0.70-1.00)	0.88 (0.60-1.26)	0.77 (0.70-1.20)	0.90 (0.50-1.65)
		72 hours	0.95 (0.80-1.17)	0.90 (0.80-1.79)	0.80 (0.66-0.90)	0.69 (0.60-1.77)	0.81 (0.70-1.01)	0.80 (0.60-1.79)
		Day 30	0.90 (0.80-1.16)	0.97 (0.70-1.79)	0.62 (0.62-0.62)	0.90 (0.80-1.60)	0.80 (0.70-1.70)	0.89 (0.62-1.79)
Hepatic Functions	**ALT (IU/L)**	**Screening**	34 (23-56)	20 (11-23)	20 (10-30)	16 (8-16)	29 (8-40)	20 (8-56)
		72 hours	27 (17-57)	15 (12-22)	33 (16-76)	15 (10-30)	23 (11-30)	19 (10-76)
	AST (IU/L)	**Screening**	25 (24-74)	25 (19-34)	19 (17-21)	17 (15-25)	22 (15-34)	21 (15-74)
		72 hours	21 (14-27)	22 (20-29)	44 (29-51)	25 (17-48)	19 (17-66)	24 (14-66)
	Alkaline Phosphatase (IU/L)	**Screening**	84 (64-95)	65 (57-78)	86 (75-202)	62 (46-69)	79 (64-100)	72 (46-202)
		72 hours	67 (58-74)	65 (58-68)	99 (81-188)	66 (50-77)	81 (66-95)	74 (50-188)
	Total Bilirubin (mg/dL)	**Screening**	0.8 (0.4-0.9)	0.3 (0.2-0.6)	0.4 (0.3-0.4)	0.5 (0.3-0.7)	0.6 (0.4-1.3)	0.5 (0.2-1.3)
		72 hours	0.6 (0.2-1.1)	0.3 (0.3-0.6)	0.5 (0.3-0.5)	0.5 (0.3-0.9)	0.7 (0.4-1.1)	0.5 (0.2-1.1)
Serum Iron Studies	**Total Iron (µg/dL)**	**Baseline**	116 (67-144)	52 (30-133)	56 (52-77)	59 (44-82)	68 (34-116)	67 (30-144)
		72 hours	22 (19-64)	81 (68-109)	71 (36-96)	55 (53-101)	94 (30-163)	68 (19-163)
		Day 30	120 (73-212)	84 (82-102)	56 (56-56)	87 (39-99)	71 (44-92)	82 (39-212)
	Ferritin (ng/mL)	**Baseline**	183 (116-462)	148 (28-261)	115 (32-387)	115 (84-150)	229 (15-381)	148 (15-462)

		72 hours	464 (347-641)	286 (64-421)	98 (38-461)	152 (93-195)	270 (16-385)	201 (16-641)
		Day 30	293 (209-597)	208 (18-595)	144 (144-144)	196 (102-249)	163 (49-842)	208 (18-842)
	Transferrin (ng/mL)	**Baseline**	227 (210-299)	197 (159-203)	267 (223-272)	220 (188-270)	264 (201-311)	225 (159-311)
		72 hours	223 (176-246)	209 (180-235)	216 (187-270)	169 (165-240)	235 (158-316)	210 (158-316)
		Day 30	223 (206-245)	223 (216-274)	132 (132-132)	194 (184-211)	240 (198-325)	223 (132-325)
	Total Iron Binding Capacity (µg/dL)	**Baseline**	290 (273-389)	207 (133-237)	317 (290-338)	287 (219-308)	355 (228-590)	307 (133-590)
		72 hours	288 (229-290)	272 (204-318)	248 (243-350)	305 (227-398)	349 (267-390)	290 (204-398)
		Day 30	274 (257-309)	286 (281-291)	156 (156-156)	222 (217-243)	312 (250-398)	278 (156-398)
	Calculated Transferrin Saturation (%)	**Baseline**	37 (23-42)	25 (13-100)	17 (16-27)	20 (14-37)	21 (8-32)	23 (8-100)
		72 hours	8 (8-22)	33 (25-40)	20 (15-40)	22 (16-25)	31 (8-43)	25 (8-43)
		Day 30	39 (27-82)	29 (28-29)	36 (36-36)	36 (18-46)	20 (18-29)	29 (18-83)

APPENDIX II

RECOMMENDED PROTOCOL FOR MANAGEMENT OF PATIENTS WITH ICH

RECOMMENDED PROTOCOL FOR MANAGEMENT OF PATIENTS WITH ICH
"Futility Study of Deferoxamine Mesylate in ICH"

GENERAL PRINCIPLES:

- Patients with ICH are frequently medically and neurologically unstable, particularly within the first few days after onset.
    - Initial monitoring and management of ICH patients should take place in an intensive care unit with physician and nursing neuroscience intensive care expertise.
    - Frequent vital sign checks, neurologic assessments, and continuous cardiopulmonary monitoring including a cycled automated BP cuff, EKG telemetry, and O_2 saturation should be standard.
    - Continuous intra-arterial BP monitoring should be considered in patients receiving intravenous vasoactive medications.
    - Surveillance and monitoring of ICP, cerebral perfusion pressure (CPP) and hemodynamic function should be implemented when indicated.
    - Patients with a GCS score of 8 or less, those with clinical evidence of transtentorial herniation, or those with significant IVH or hydrocephalus might be considered for ICP monitoring and treatment. A CPP of 50-70 mmHg may be reasonable to maintain depending on the status of cerebral autoregulation.

- CT angiography, CT venography, contrast-enhanced CT, contrast-enhanced MRI, MRA and MRV can be useful to evaluate for underlying structural lesions including vascular malformations and tumors when there is clinical or radiological suspicion.

- GENERAL MEDICAL MANAGEMENT:
    - The incidence of fever after ICH is high. Fever worsens outcome in experimental models of brain injury, and the duration of fever is related to outcome in ICH patients.
        - Fever should be aggressively treated to maintain normothermia.
        - Use Tylenol (650 mg every 4-6 hours), indomethacin (25 mg every 6 hours), or a cooling blanket (if needed)

    - Glucose should be monitored and normoglycemia is recommended.
        - Treat blood glucose abnormalities, if present
            - One amp of D50, if blood sugar < 50 mg/dL
            - Insulin sliding scale, if blood sugar > 150 mg/dL
            - Insulin drip, if blood sugar remains poorly controlled with Insulin Sliding Scale

    - Prevent complications of immobility through positioning and mobilization.
        - Patients with ICH should have intermittent pneumatic compression for prevention of venous thromboembolism in addition to elastic stockings for the first 48-96 hours.
        - After documentation of cessation of bleeding, low-dose subcutaneous low-molecular-weight heparin or unfractionated heparin may be considered for prevention of venous thromboembolism in patients with lack of mobility after 1 to 4 days from onset.

    - Aspiration precautions

- Patients who are given DNR status at any point should receive all other appropriate medical interventions unless otherwise explicitly indicated.

- Where possible, multi-disciplinary rehabilitation should begin as early as possible and continued as part of a well-coordinated ('seamless') program of accelerated hospital discharge and home-based re-settlement to promote ongoing recovery.

SPECIFIC MANAGEMENT ISSUES:

- MANAGEMENT OF BLOOD PRESSURE
    - Target BP should be based on mean arterial pressure (MAP)
        - Keep MAP < 130 mmHg to maintain CPP of 60-70 mm Hg
        - In patients with history of hypertension (Target BP ~ 170/100; ~ MAP 125)
        - In patients without known HTN (target BP ~ 150/90; ~ MAP 110)
        - Avoid rapid reduction of MAP by > 20%. Recent trials suggest that acute lowering of systolic BP to 140 mmHg is safe and probably effective.
        - Keep MAP < 100 mmHg post-op (if surgical evacuation is carried out)
    - Recommended treatment of elevated blood pressure is as follows:
        - If SBP is >200 mmHg or MAP is >150 mm Hg, consider aggressive reduction of blood pressure with continuous intravenous infusion, with frequent blood pressure monitoring every 5 minutes.
        - If SBP is >180 mmHg or MAP is >130 mm Hg, use intermittent or continuous intravenous medications to decrease the BP to a target of 160/90 mm Hg or a MAP of 110 mm Hg. Reevaluate BP in 15 minutes.
        - Consider monitoring ICP, if high ICP is suspected, and maintain a cerebral perfusion pressure $\geq$ 60 mmHg.
        - IV drugs, with short half-life, should be used as first-line treatment**.** Use any of the following:
            - Labetalol (10-100 mg bolus every 10 min, up to 300 mg; 0.5-2 mg/min infusion – Avoid in patients with asthma and bradycardia)
            - Nicardipine (5-15 mg/h infusion)
            - Celviprex (1-2 mg/h infusion)
            - Enalapril (1.25-5 mg every 6h)
            - Hydralazine (10-20 mg bolus)
            - Nitroprusside (0.2-10 µg/kg/min), If SBP > 230 or DBP > 140, and is refractory to treatment with other drugs.

- MANAGEMENT OF SEIZURES
    - Clinical seizures should be treated with anti-epileptic drugs.
    - Patients with a change in mental status who are found to have electrographic seizures on EEG should be treated with anti-epileptic drugs.
        - For ongoing seizures, use lorazepam (0.1 mg/kg)
        - Preferably use levetiracetam for maintenance therapy, starting at a daily dose of 500 mg BID and titrating up to 1500 mg BID.
        - If rapid loading is needed, use IV phenytoin (18-20 mg/kg) or fosphenytoin (15-20 mg/kg) as a slow IV infusion (maintenance dose of phenytoin is approximately, 300 mg daily), then taper off while titrating up levetiracetam.
    - The use of prophylactic anti-seizure medications is not routinely required and could be harmful.
        - Prophylactic treatment, if initiated, should not exceed 4 weeks
        - Prophylactic use of phenytoin is associated with worse functional outcome in patients with ICH, and should be avoided.

- MANAGEMENT OF COAGULOPATHY
  - Patients with a severe coagulation factor deficiency or severe thrombocytopenia (platelet count < 100,000) should receive appropriate factor replacement therapy or platelets, respectively.
  - Patients with ICH whose INR is elevated due to warfarin therapy should have their warfarin withheld, receive therapy to replace vitamin K dependent factors and correct the INR, and receive intravenous vitamin K (10 mg).
  - Patients with ICH due to elevated PTT due to heparin therapy should receive protamine.
  - Always consult with your blood bank or a hematologist regarding the choice and dose of coagulation factor(s) replacement. Available products are:
    - Fresh Frozen plasma (FFP) (10-15 ml/kg, approximately 2 units)
    - Cryoprecipitate (1-2 units/10 kg)
    - Prothrombin Complex Concentrates (PCC) such as Profilnine (30 IU/kg)
      - The use of factor VII for spontaneous ICH is not indicated and currently available clinical anticoagulants act downstream of factor VII, therefore, it is difficult to understand a role for rVIIa alone in reversing these medications.

- MANAGEMENT OF CEREBRAL EDEMA AND INCREASED ICP
  - Take measures to avoid aggravation of ICP
    - Keep HOB at 30° - Avoid flat position - Keep head at midline
    - Avoid hypotonic fluids
    - Keep the patient euvolemic – dry
    - Treat high BP (as above)
    - Treat fever
    -
  - Use osmotherapy (if needed)
    - Mannitol 20% (0.75-1 g/kg as bolus, then 0.25-0.5 g/kg q4-6h) - Target serum osmolarity ~ 310-320 mOsm/L
    - Hypertonic saline (NaCl 7.5%; 150 ml bolus – maintain serum sodium < 155 mmol/L)
    - There is no evidence to support the use of steroids in ICH

  - Sedation and neuromuscular paralysis
    - Propofol (5 µg/kg/min) IV infusion for 5 min then titrate in 5 to10 µg/kg/min increments to achieve desired level of sedation; allow minimum of 5 min between dose adjustments; usual maintenance rates 5 to 50 µg/kg/min
    - Vecuronium Bromide (1 µg/kg/min continuous IV infusion, then titrate to effect; range 0.8-1.2 µg/kg/min)

  - Hyperventilation (tidal volume 12-14 ml/kg; pco_2 30-35)
    - Should be used only as a temporary measure if herniation is present
    - Avoid prolonged hyperventilation as it can cause cerebral ischemia

  - If ICP remains elevated (> 20 mm Hg) despite the above measures, consider:
    - Ventricular drain placement
    - Hypothermia
    - Pentobarbital sodium (5-20 mg/kg loading dose, then 1-3 mg/kg/hour as acontinuous infusion adjusted to burst suppression pattern on EEG)
      - IV pressors, such as dopamine or phenylephrine, should be ready at the bed side to maintain BP should hypotension develops.

- SURGICAL ISSUES
  - For most patients with supratentorial ICH, the usefulness of surgery is uncertain.
  - For patients presenting with lobar clots >30 cc and within 1 cm of the surface, evacuation of supratentorial ICH might be considered.
  - Ventricular drainage as treatment for hydrocephalus is reasonable in patients with decreased level of consciousness.

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Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Lewis B. Morgenstern, J. Claude Hemphill, III, Craig Anderson, Kyra Becker, Joseph P. Broderick, E. Sander Connolly, Jr, Steven M. Greenberg, James N. Huang, R. Loch Macdonald, Steven R. Messé, Pamela H. Mitchell, Magdy Selim, Rafael J. Tamargo and on behalf of the American Heart Association Stroke Council and Council on Cardiovascular Nursing

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Guidelines for the Management of Spontaneous Intracerebral Hemorrhage

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

The American Association of Neurological Surgeons and the Congress of Neurological Surgeons have reviewed this document and affirm its educational content.

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Magdy Selim, MD, PhD, FAHA; Rafael J. Tamargo, MD; on behalf of the American Heart Association Stroke Council and Council on Cardiovascular Nursing

Purpose—The aim of this guideline is to present current and comprehensive recommendations for the diagnosis and treatment of acute spontaneous intracerebral hemorrhage.

Methods—A formal literature search of MEDLINE was performed. Data were synthesized with the use of evidence tables. Writing committee members met by teleconference to discuss data-derived recommendations. The American Heart Association Stroke Council's Levels of Evidence grading algorithm was used to grade each recommendation. Prerelease review of the draft guideline was performed by 6 expert peer reviewers and by the members of the Stroke Council Scientific Statements Oversight Committee and Stroke Council Leadership Committee. It is intended that this guideline be fully updated in 3 years' time.

Results—Evidence-based guidelines are presented for the care of patients presenting with intracerebral hemorrhage. The focus was subdivided into diagnosis, hemostasis, blood pressure management, inpatient and nursing management, preventing medical comorbidities, surgical treatment, outcome prediction, rehabilitation, prevention of recurrence, and future considerations.

Conclusions—Intracerebral hemorrhage is a serious medical condition for which outcome can be impacted by early, aggressive care. The guidelines offer a framework for goal-directed treatment of the patient with intracerebral hemorrhage. **(*Stroke*. 2010;41:2108-2129.)**

Key Words: AHA Scientific Statements ■ intracerebral hemorrhage ■ treatment ■ diagnosis ■ intracranial pressure ■ hydrocephalus ■ surgery

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Spontaneous, nontraumatic intracerebral hemorrhage (ICH) is a significant cause of morbidity and mortality throughout the world. Although much has been made of the lack of a specific targeted therapy, much less is written about the success and goals of aggressive medical and surgical care for this disease. Recent population-based studies suggest that most patients present with small ICHs that are readily survivable with good medical care.[1] This suggests that excellent medical care likely has a potent, direct impact on ICH morbidity and mortality now, even before a specific therapy is found. Indeed, as discussed later, the overall aggressiveness of ICH care is directly related to mortality from this disease.[2] One of the purposes of this guideline, therefore, is to remind clinicians of the importance of their care in determining ICH outcome and to provide an evidence-based framework for that care.

In order to make this review brief and readily useful to practicing clinicians, the reader is referred elsewhere for the details of ICH epidemiology.[1,3,4] Similarly, there are many ongoing clinical studies throughout the world related to this disease. The reader is encouraged to consider referring patients to these important efforts, which can be found at http://www.strokecenter.org/trials/. We will not discuss ongoing studies because we cannot cover them all; the focus of this statement is on currently available therapies. Finally, a recent guideline on pediatric stroke was published[5] that obviates the need to repeat the issues of pediatric ICH here.

The last ICH Guidelines were published in 2007,[6] and this current article serves to update those guidelines. As such, differences from former recommendations are specified in the current work. The writing group met by phone to determine subcategories to evaluate. These included emergency diagnosis and assessment of ICH and its causes; hemostasis, blood pressure (BP); intracranial pressure (ICP)/fever/glucose/seizures/hydrocephalus; iron; ICP monitors/tissue oxygenation; clot removal; intraventricular hemorrhage (IVH); withdrawal of technological support; prevention of recurrent ICH; nursing care; rehab/recovery; future considerations. Each subcategory was led by an author with 1 or 2 additional authors making contributions. Full MEDLINE searches were done of all English-language articles regarding relevant human disease treatment. Drafts of summaries and recommendations were circulated to the whole writing group for feedback. A conference call was held to discuss controversial issues. Sections were revised and merged by the Chair. The resulting draft was sent to the whole writing group for comment. Comments were incorporated by the Vice Chair and Chair, and the entire committee was asked to approve the final draft. Changes to the document were made by the Chair and Vice Chair in response to peer review, and the document was again sent to the entire writing group for suggested changes and approval. Recommendations follow the American Heart Association Stroke Council's methods of classifying the level of certainty of the treatment effect and the class of evidence (Tables 1 and 2). All Class I recommendations are listed in Table 3.

Emergency Diagnosis and Assessment of ICH and Its Causes

ICH is a medical emergency. Rapid diagnosis and attentive management of patients with ICH is crucial because early deterioration is common in the first few hours after ICH onset. More than 20% of patients will experience a decrease in the Glasgow Coma Scale (GCS) score of ≥2 points between the prehospital emergency medical services assessment and the initial evaluation in the emergency department (ED).[7] Among those patients with prehospital neurological decline, the GCS score decreases by an average of 6 points and the mortality rate is >75%. Further, within the first hour of presentation to a hospital, 15% of patients demonstrate a decrease in the GCS score of ≥2 points.[8] The risk for early neurological deterioration and the high rate of poor long-term outcomes underscores the need for aggressive early management.

Prehospital Management

The primary objective in the prehospital setting is to provide ventilatory and cardiovascular support and to transport the patient to the closest facility prepared to care for patients with acute stroke (see ED Management section that follows). Secondary priorities for emergency medical services providers include obtaining a focused history regarding the timing of symptom onset (or the time the patient was last normal) and information about medical history, medication, and drug use. Finally, emergency medical services providers should provide advance notice to the ED of the impending arrival of a potential stroke patient so that critical pathways can be initiated and consulting services can be alerted. Advance notice by emergency medical services has been demonstrated to significantly shorten time to computed tomography (CT) scanning in the ED.[9]

ED Management

It is of the utmost importance that every ED be prepared to treat patients with ICH or have a plan for rapid transfer to a tertiary care center. The crucial resources necessary to manage patients with ICH include neurology, neuroradiology, neurosurgery, and critical care facilities including adequately trained nurses and physicians. In the ED, appropriate consultative services should be contacted as quickly as possible and the clinical evaluation should be performed efficiently, with physicians and nurses working in parallel. Table 4 describes the integral components of the history, physical examination, and diagnostic studies that should be obtained in the ED.

For patients with ICH, emergency management may include neurosurgical interventions for hematoma evacuation, external ventricular drainage or invasive monitoring and treatment of ICP, BP management, intubation, and reversal of coagulopathy. Although many centers have critical pathways developed for the treatment of acute ischemic stroke, few have protocols for the management of ICH.[18] Such pathways may allow for more efficient, standardized, and integrated management of critically ill patients with ICH.

Neuroimaging

The abrupt onset of focal neurological symptoms is presumed to be vascular in origin until proven otherwise. However, it is impossible to know whether symptoms are due to ischemia or hemorrhage based on clinical characteristics alone. Vomiting, systolic BP >220 mm Hg, severe headache, coma or decreased level of consciousness, and progression over minutes or hours all suggest ICH, although none of these findings are specific;

Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT ↓ / SIZE OF TREATMENT EFFECT →	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *Risk ≥ Benefit* Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations†	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†In 2003, the ACCF/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All guideline recommendations have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines and will allow queries at the individual recommendation level.

neuroimaging is thus mandatory.[19] CT and magnetic resonance imaging (MRI) are both reasonable for initial evaluation. CT is very sensitive for identifying acute hemorrhage and is considered the gold standard; gradient echo and T2*susceptibility-weighted MRI are as sensitive as CT for detection of acute blood and are more sensitive for identification of prior hemorrhage.[20,21] Time, cost, proximity to the ED, patient tolerance, clinical status, and MRI availability may, however, preclude emergent MRI in a sizeable proportion of cases.[22]

The high rate of early neurological deterioration after ICH is in part related to active bleeding that may proceed for hours after symptom onset. The earlier time from symptom onset to first neuroimage, the more likely subsequent neuroimages will demonstrate hematoma expansion.[15,23,24] Among patients undergoing head CT within 3 hours of ICH onset, 28% to 38% have hematoma expansion of greater than one third on follow-up CT.[8,25] Hematoma expansion is predictive of clinical deterioration and increased morbidity and mortality.[8,10,15,25] As such, identifying patients at risk for hematoma expansion is an active area of research. CT angiography and contrast-enhanced CT may identify patients at high risk of ICH expansion based on the presence of contrast extravasation within the hematoma.[26–30] MRI/angiogram/venogram and CT angiogram/venogram are reasonably sensitive at identifying secondary causes of hemorrhage, including arteriovenous malformations, tumors, moyamoya, and cerebral vein thrombosis.[31–33] A catheter angiogram may be considered if clinical suspicion is high or noninvasive studies are suggestive of an underlying vascular cause. Clinical suspicion of a secondary cause of ICH may include a prodrome of headache, neurological, or constitutional symptoms. Radiological suspicions of secondary causes of ICH should be

Table 2. Definition of Classes and Levels of Evidence Used in American Heart Association Stroke Council Recommendations

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
Class IIa	The weight of evidence or opinion is in favor of the procedure or treatment
Class IIb	Usefulness/efficacy is less well established by evidence or opinion
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful
Therapeutic recommendations	
Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts, case studies, or standard of care
Diagnostic recommendations	
Level of Evidence A	Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
Level of Evidence B	Data derived from a single grade A study, or one or more case-control studies, or studies using a reference standard applied by an unmasked evaluator
Level of Evidence C	Consensus opinion of experts

invoked by the presence of subarachnoid hemorrhage, unusual (noncircular) hematoma shape, the presence of edema out of proportion to the early time an ICH is first imaged, an unusual location for hemorrhage, and the presence of other abnormal structures in the brain like a mass. An MR or CT venogram should be performed if hemorrhage location, relative edema volume, or abnormal signal in the cerebral sinuses on routine neuroimaging suggest cerebral vein thrombosis.

In summary, ICH is a medical emergency, characterized by high morbidity and mortality, which should be promptly diagnosed and aggressively managed. Hematoma expansion and early deterioration are common within the first few hours after onset.

Recommendations

1. **Rapid neuroimaging with CT or MRI is recommended to distinguish ischemic stroke from ICH *(Class I; Level of Evidence: A)*.** (Unchanged from the previous guideline)
2. **CT angiography and contrast-enhanced CT may be considered to help identify patients at risk for hematoma expansion *(Class IIb; Level of Evidence: B)*, and CT angiography, CT venography, contrast-enhanced CT, contrast-enhanced MRI, magnetic resonance angiography, and magnetic resonance venography can be useful to evaluate for underlying structural lesions, including vascular malformations and tumors when there is clinical or radiological suspicion *(Class IIa; Level of Evidence: B)*.** (New recommendation)

Medical Treatment for ICH

Hemostasis/Antiplatelets/Deep Vein Thrombosis Prophylaxis

Underlying hemostatic abnormalities can contribute to ICH. Patients at risk include those on oral anticoagulants (OACs), those with acquired or congenital coagulation factor deficiencies, and those with qualitative or quantitative platelet abnormalities. Patients undergoing treatment with OACs constitute 12% to 14% of patients with ICH,[34,35] and with increased use of warfarin, the proportion appears to be increasing.[36] Recognition of an underlying coagulopathy thus provides an opportunity to target correction in the treatment strategy. For patients with a coagulation factor deficiency and thrombocytopenia, replacement of the appropriate factor or platelets is indicated.

For patients being treated with OACs who have life-threatening bleeding, such as intracranial hemorrhage, the general recommendation is to correct the international normalized ratio (INR) as rapidly as possible.[37,38] Infusions of vitamin K and fresh-frozen plasma (FFP) have historically been recommended, but more recently, prothrombin complex concentrates (PCCs) and recombinant factor VIIa (rFVIIa) have emerged as potential therapies. Vitamin K remains an adjunct to more rapidly acting initial therapy for life-threatening OAC-associated hemorrhage because even when given intravenously, it requires hours to correct the INR.[39–41] The efficacy of FFP is limited by risk of allergic and infectious transfusion reactions, processing time, and the volume required for correction. Likelihood of INR correction at 24 hours was linked to time to FFP administration in 1 study, although 17% of patients still did not have an INR $\leq$1.4 at this time, suggesting that FFP administered in this manner may be insufficient for rapid correction of coagulopathy.[42]

PCCs are plasma-derived factor concentrates primarily used to treat factor IX deficiency. Because PCCs also contain factors II, VII, and X in addition to IX, they are increasingly recommended for warfarin reversal. PCCs have the advantages of rapid reconstitution and administration, having high concentrations of coagulation factors in small volumes, and processing to inactivate infectious agents. Though different PCC preparations differ in relative amounts of factors (with VII the most likely to be low), several studies have shown that PCCs can rapidly normalize INR (within minutes) in patients taking OACs (reviewed in[43–45]). Nonrandomized retrospective reviews and a small case-control study have shown more rapid correction of INR with vitamin K and PCC than vitamin K and FFP, but have not revealed a difference in clinical outcome.[46–48] One randomized trial compared the use of a PCC (Konyne) to supplement FFP versus FFP alone in patients with OAC-related ICH, finding that those who received PCC had significantly shorter time to INR correction and received less volume of FFP. Although there was no difference in outcome, those who received FFP also had more adverse events, primarily attributable to fluid overload.[49] Although PCCs may theoretically increase the risk of thrombotic complications, this risk appears relatively low.[43] De-

Table 3. Class I Recommendations

	Recommendations	Class/Level of Evidence
Emergency diagnosis and assessment of ICH and its causes	Rapid neuroimaging with CT or MRI is recommended to distinguish ischemic stroke from ICH. *(Unchanged from the previous guideline)*	Class I, Level A
Medical treatment for ICH	Patients with a severe coagulation factor deficiency or severe thrombocytopenia should receive appropriate factor replacement therapy or platelets, respectively. *(New recommendation)*	Class I, Level C
Hemostasis/antiplatelets/DVT prophylaxis	Patients with ICH whose INR is elevated due to OAC should have their warfarin withheld, receive therapy to replace vitamin K–dependent factors and correct the INR, and receive intravenous vitamin K. *(Revised from the previous guideline)*	Class I, Level C
	Patients with ICH should have intermittent pneumatic compression for prevention of venous thromboembolism in addition to elastic stockings. *(Unchanged from the previous guideline)*	Class I, Level B
Inpatient management and prevention of secondary brain injury		
General monitoring	Initial monitoring and management of ICH patients should take place in an intensive care unit, preferably one with physician and nursing neuroscience intensive care expertise. *(Unchanged from the previous guideline)*	Class I, Level B
Management of glucose	Glucose should be monitored and normoglycemia is recommended	Class I, Level C
Seizures and antiepileptic drugs	Patients with clinical seizures should be treated with antiepileptic drugs. *(Revised from previous guideline)*	Class I, Level A
	Patients with a change in mental status who are found to have electrographic seizures on EEG should be treated with antiepileptic drugs	Class I, Level C
Procedures/surgery—clot removal	Patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible. *(Revised from the previous guideline)*	Class I, Level B
Prevention of recurrent ICH	After the acute ICH, absent medical contraindications, BP should be well controlled, particularly for patients with ICH location typical of hypertensive vasculopathy. *(New recommendation)*	Class I, Level A

CT indicates computed tomography; MRI, magnetic resonance imaging; DVT, deep vein thrombosis; INR, international normalized ratio; OAC, oral anticoagulants; and EEG, electroencephalogram.

spite the lack of large, well-controlled, randomized trials, PCCs are being increasingly recommended as an option in guidelines promulgated for warfarin reversal in the setting of OAC-associated life-threatening or intracranial hemorrhages.[37,38,50–52] Table 5 provides a list of several products for factor replacement in warfarin reversal that are commercially available in the United States at the present time.

rFVIIa, licensed to treat hemophilia patients with high titer inhibitors or congenital factor VII deficiency, has garnered attention as a potential treatment for spontaneous and OAC-associated ICH. Although rFVIIa can rapidly normalize INR in the setting of OAC-associated ICH,[53–57] it does not replenish all of the vitamin K–dependent factors and therefore may not restore thrombin generation as well as PCCs.[58] In light of the limited data, a recent American Society of Hematology evidence-based review recommended against routine use of rFVIIa for warfarin reversal.[59]

rFVIIa has also been tested in patients with non-OAC ICH. A phase 2 randomized trial showed that treatment with rFVIIa within 4 hours after ICH onset limited hematoma growth and improved clinical outcomes relative to placebo, though with increased frequency of thromboembolic events (7% versus 2%).[60] A subsequent phase 3 study comparing placebo with 20 μg/kg and 80 μg/kg of rFVIIa failed to show differences in clinical outcome, despite confirming the ability of both doses to diminish hematoma enlargement.[61] Although overall serious thromboembolic adverse events were similar, the higher rFVIIa (80 μg/kg) group had significantly more arterial events than the placebo group. The authors noted imbalances in the treatment groups, particularly the greater number of patients with IVH in the higher-dose rFVIIa group.[60] It remains to be determined whether rFVIIa will benefit a particular subset of patients with ICH, but currently its benefits in ICH patients, whether or not they are undergoing treatment with OACs, remain unproven.

Studies of the effect of prior antiplatelet agent use or platelet dysfunction on ICH hematoma growth and outcome have found conflicting results. Reported antiplatelet agent use was not associated with hematoma expansion or clinical outcome in the placebo group of an ICH neuroprotective study.[62] However, others have suggested that platelet dysfunction as measured by platelet function assays may be associated with hematoma expansion and clinical outcome.[63,64] The utility and safety of platelet transfusion or

Table 4. Integral Components of the History, Physical Examination, and Work-Up of the Patient With ICH in the ED

	Comments
History	
Time of symptom onset (or time the patient was last normal)	
Initial symptoms and progression of symptoms	
Vascular risk factors	Hypertension, diabetes, hypercholesterolemia, and smoking
Medications	Anticoagulants, antiplatelet agents, decongestants, antihypertensive medications, stimulants (including diet pills), sympathomimetics
Recent trauma or surgery	Carotid endarterectomy or carotid stenting in particular, as ICH may be related to hyperperfusion after such procedures
Dementia	Associated with amyloid angiopathy
Alcohol or illicit drug use	Cocaine and other sympathomimetic drugs are associated with ICH, stimulants
Seizures	
Liver disease	May be associated with coagulopathy
Cancer and hematologic disorders	May be associated with coagulopathy
Physical examination	
Vital signs	Fever is associated with early neurologic deterioration[10]
	Higher initial blood pressure is associated with early neurologic deterioration and increased mortality[11]
A general physical examination focusing on the head, heart, lungs, abdomen, and extremities	
A thorough but time-urgent neurologic examination	A structured examination such as the National Institutes of Health Stroke Scale can be completed in minutes and provides a quantification that allows easy communication of the severity of the event to other caregivers. GCS score is similarly well known and easily computed, and the initial GCS score is a strong predictor of long-term outcome.[12,13] These can be supplemented as needed
Serum and urine tests	
Complete blood count, electrolytes, blood urea nitrogen and creatinine, and glucose	Higher creatinine is associated with hematoma expansion. Higher serum glucose is associated with hematoma expansion and worse outcome (although there are no data to suggest that normalization improves outcome)[11,14]
Prothrombin time or INR and an activated partial thromboplastin time	Warfarin-related hemorrhages are associated with an increased hematoma volume, greater risk of expansion, and increased morbidity and mortality[15–17]
Toxicology screen in young or middle-aged patients to detect cocaine and other sympathomimetic drugs of abuse	Cocaine and other sympathomimetic drugs are associated with ICH
Urinalysis and urine culture and a pregnancy test in a woman of childbearing age	
Other routine tests	
ECG	To assess for active coronary ischemia or prior cardiac injury that may indicate poor cardiac function and to obtain a baseline in the event of cardiopulmonary issues during hospitalization
Chest radiograph	
Neuroimaging	As described in the text

GCS indicates Glasgow Coma Scale; ECG, electrocardiogram.

other agents in patients with a normal platelet count, but use of antiplatelet agents or platelet dysfunction, is not known.

Patients with ICH have a high risk of thromboembolic disease.[65] Women and African Americans appear to be at greater risk.[65–67] Intermittent pneumatic compression combined with elastic stockings has been shown by a randomized trial to be superior to elastic stockings alone in reducing occurrence of asymptomatic deep vein thrombosis after ICH (4.7% versus 15.9%).[68] Graduated compression stockings alone are ineffective in preventing deep vein thrombosis.[69] Less clear, however, is the role of adding anticoagulation to pneumatic compression. Two small randomized studies found no difference in deep vein thrombosis incidence, and no increase in bleeding, in patients given low-dose subcutaneous heparin initiated at day 4 or at day 10 after ICH.[70,71] An uncontrolled study of treatment initiated on day 2 found a reduction in thromboembolic disease without increased rebleeding.[70]

Recommendations

1. **Patients with a severe coagulation factor deficiency or severe thrombocytopenia should receive appropriate factor replacement therapy or platelets, respectively *(Class I; Level of Evidence: C)*.** (New recommendation)
2. **Patients with ICH whose INR is elevated due to OACs should have their warfarin withheld, receive therapy to replace vitamin K–dependent factors and correct the INR, and receive intravenous vitamin K *(Class I; Level of Evidence: C)*. PCCs have not shown improved outcome compared with FFP but may have fewer complications compared with FFP and are reasonable to consider as an alternative to FFP *(Class IIa; Level of Evidence: B)*. rFVIIa does not replace all clotting factors, and although the INR may be lowered, clotting may not be restored in vivo; therefore, rFVIIa is not routinely recommended as a sole agent for OAC reversal in ICH *(Class III; Level of Evidence: C)*.** (Revised from the previous guideline).
3. **Although rFVIIa can limit the extent of hematoma expansion in noncoagulopathic ICH patients, there**

Table 5. Products Commercially Available in the United States for Coagulation Factor Replacement

Product	Factor(s)	Dose (Consultation With a Hematologist Is Recommended for Specific Dosing)	Uses
Fresh-frozen plasma	I (fibrinogen), II, V, VII, IX, X, XI, XIII, antithrombin	10–15 mL/kg with ideal recovery would raise factor levels 15%–20%	OAC reversal Consumptive coagulopathy Hepatic dysfunction
Cryoprecipitate	I, VIII, XIII, vWF	1–2 U/10 kg	Hypo/a-fibrinogenemia Lack of factor-specific products for factor VIII deficiency or vWD Factor XIII deficiency
Prothrombin complex concentrates	II, IX, X (small amounts of VII)	Assayed in factor IX activity	Factor IX deficiency (hemophilia B)
Bebulin VH (Baxter), Profilnine SD (Grifols)		Both Bebulin and Profilnine are 3-factor PCCs that have approximately 1/10th the factor VII activity relative to factor IX activity. The amounts of factor II and X relative to IX is variable, but for Bebulin X>II>IX and for Profilnine II>X~IX Dosing for factor IX deficiency—1 U/kg raises activity by 1% Dosing for OAC reversal has not been well established	OAC reversal (not FDA-approved)
NovoSeven RT (Novo Nordisk)	Recombinant activated VII	Higher risk of thromboembolic complications with higher doses For hemophilia A or B patients with inhibitors, 90 μg/kg every 2 h For factor VII–deficient patients, 15–30 μg/kg every 4–6 h	Factor VIII or IX deficiency with inhibitors to factor VIII or IX Congenital factor VII deficiency Not recommended for spontaneous ICH or OAC reversal
Factor VIII concentrates Plasma-derived Alphanate (Grifols)*† Humate-P (CSL-Behring)*† Koate-DVI (Bayer)* Wilate (Octapharma)*† Immunoaffinity purified Hemofil-M (Baxter) Monarc-M (Baxter) Monoclate-P (CSL-Behring) Recombinant Advate (Baxter) Helixate FS (CSL-Behring) Kogenate FS (Bayer) Recombinate (Baxter) Xyntha (Wyeth)	VIII	Each factor VIII unit/kg raises the serum factor VIII level by 2% (typically, a 50-U/kg dose is used to raise the factor VIII level to 100%)	Factor VIII deficiency (hemophilia A) Wilate is not indicated for hemophilia A.
Factor IX concentrates Plasma-derived AlphaNine SD (Grifols) Mononine (Baxter) Recombinant BeneFix (Wyeth)	IX	Each Factor IX unit/kg raises the serum level by 1% (typically, a 100-U/kg dose is used to raise the level to 100%)	Factor IX deficiency (hemophilia B) One unit of BeneFix raises the serum level by ≈0.83%, so 120 U/kg raises the activity to 100%.

vWD indicates von Willebrand disease; FDA, US Food and Drug Administration; and PCCs, prothrombin complex concentrates.
*Also contains von Willebrand factor.
†Indicated for von Willebrand disease (dose by ristocetin cofactor units; ratio of fVIII to ristocetin cofactor unit varies by product).

is an increase in thromboembolic risk with rFVIIa and no clear clinical benefit in unselected patients. Thus rFVIIa is not recommended in unselected patients. ***(Class III; Level of Evidence: A).*** (New recommendation) ***Further research to determine whether any selected group of patients may benefit from this therapy is needed before any recommendation for its use can be made.***

4. **The usefulness of platelet transfusions in ICH patients with a history of antiplatelet use is unclear and is considered investigational** ***(Class IIb; Level of Evidence: B).*** (New recommendation)

5. **Patients with ICH should have intermittent pneumatic compression for prevention of venous thromboembolism in addition to elastic stockings *(Class I; Level of Evidence: B)*.** (Unchanged from the previous guideline)
6. **After documentation of cessation of bleeding, low-dose subcutaneous low-molecular-weight heparin or unfractionated heparin may be considered for prevention of venous thromboembolism in patients with lack of mobility after 1 to 4 days from onset *(Class IIb; Level of Evidence: B)*.** (Revised from the previous guideline)

Blood Pressure

Blood Pressure and Outcome in ICH

Blood pressure (BP) is frequently, and often markedly, elevated in patients with acute ICH; these elevations in BP are greater than that seen in patients with ischemic stroke.[72,73] Although BP generally falls spontaneously within several days after ICH, high BP persists in a substantial proportion of patients.[72,73] Potential pathophysiologic mechanisms include stress activation of the neuroendocrine system (sympathetic nervous system, renin-angiotensin axis, or glucocorticoid system) and increased intracranial pressure. Hypertension theoretically could contribute to hydrostatic expansion of the hematoma, peri-hematoma edema, and rebleeding, all of which may contribute to adverse outcomes in ICH, although a clear association between hypertension within the first few hours after ICH and the risk of hematoma expansion (or eventual hematoma volume) has not been clearly demonstrated.[25,74]

A systematic review[75] and a recent large multisite study in China[73] show that a measurement of systolic BP above 140 to 150 mm Hg within 12 hours of ICH is associated with more than double the risk of subsequent death or dependency. Compared with ischemic stroke, where consistent U- or J-shaped associations between BP levels and poor outcome have been shown,[76] only 1 study of ICH has shown a poor outcome at very low systolic BP levels (<140 mm Hg).[77] For both ischemic stroke and possibly ICH, a likely explanation for such association is reverse causation, whereby very low BP levels occur disproportionately in more severe cases, so that although low BP levels may be associated with a high case fatality, it may not in itself be causal.

Effects of BP-Lowering Treatments

The strong observational data cited previously and sophisticated neuroimaging studies that fail to identify an ischemic penumbra in ICH[78] formed the basis for the INTensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) pilot study, published in 2008.[79] INTERACT was an open-label, randomized, controlled trial undertaken in 404 mainly Chinese patients who could be assessed, treated, and monitored within 6 hours of the onset of ICH; 203 were randomized to a treatment with locally available intravenous BP-lowering agents to target a low systolic BP goal of 140 mm Hg within 1 hour and maintained for at least the next 24 hours, and 201 were randomized to a more modest systolic BP target of 180 mm Hg, as recommended in an earlier AHA guideline.[80] The study showed a trend toward lower relative and absolute growth in hematoma volumes from baseline to 24 hours in the intensive treatment group compared with the control group. In addition, there was no excess of neurological deterioration or other adverse events related to intensive BP lowering, nor were there any differences across several measures of clinical outcome, including disability and quality of life between groups, although the trial was not powered to detect such outcomes. The study provides an important proof of concept for early BP lowering in patients with ICH, but the data are insufficient to recommend a definitive policy. Another study, the Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH) trial,[81] also confirms the feasibility and safety of early rapid BP lowering in ICH.[82] This study used a 4-tier, dose escalation of intravenous nicardipine-based BP lowering in 80 patients with ICH.

Thus, advances have been made in our knowledge of the mechanisms of ICH and the safety of early BP lowering since the publication of the 2007 American Heart Association ICH guidelines. INTERACT and ATACH now represent the best available evidence to help guide decisions about BP lowering in ICH. Although these studies have shown that intensive BP lowering is clinically feasible and potentially safe, the BP pressure target, duration of therapy, and whether such treatment improves clinical outcomes remain unclear.

Table 6. Suggested Recommended Guidelines for Treating Elevated BP in Spontaneous ICH

1. If SBP is >200 mm Hg or MAP is >150 mm Hg, then consider aggressive reduction of BP with continuous intravenous infusion, with frequent BP monitoring every 5 min.
2. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is the possibility of elevated ICP, then consider monitoring ICP and reducing BP using intermittent or continuous intravenous medications while maintaining a cerebral perfusion pressure ≥60 mm Hg.
3. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is not evidence of elevated ICP, then consider a modest reduction of BP (eg, MAP of 110 mm Hg or target BP of 160/90 mm Hg) using intermittent or continuous intravenous medications to control BP and clinically reexamine the patient every 15 min.

Note that these recommendations are Class C. SBP indicates systolic blood pressure; MAP, mean arterial pressure.

Recommendations

1. **Until ongoing clinical trials of BP intervention for ICH are completed, physicians must manage BP on the basis of the present incomplete efficacy evidence. Current suggested recommendations for target BP in various situations are listed in Table 6 and may be considered *(Class IIb; Level of Evidence: C)*.** (Unchanged from the previous guideline)
2. **In patients presenting with a systolic BP of 150 to 220 mm Hg, acute lowering of systolic BP to 140 mm Hg is probably safe *(Class IIa; Level of Evidence: B)*.** (New recommendation)

Inpatient Management and Prevention of Secondary Brain Injury

General Monitoring

Patients with ICH are frequently medically and neurologically unstable, particularly within the first few days after

onset. Care of ICH patients in a dedicated neuroscience intensive care unit is associated with a lower mortality rate.[83] Frequent vital sign checks, neurological assessments, and continuous cardiopulmonary monitoring including a cycled automated BP cuff, electrocardiographic telemetry, and O_2 saturation probe should be standard. Continuous intra-arterial BP monitoring should be considered in patients receiving intravenous vasoactive medications.

Nursing Care

The specific nursing care required for ICH patients in intensive care units may include (1) surveillance and monitoring of ICP, cerebral perfusion pressure and hemodynamic function; (2) titration and implementation of protocols for management of ICP, BP, mechanical ventilation, fever, and serum glucose; and (3) prevention of complications of immobility through positioning, airway maintenance, and mobilization within physiological tolerance. The consensus document from the Brain Attack Coalition on comprehensive stroke centers delineates these as specific areas of monitoring and complication prevention in which nurses should be trained. This document also recommends that nurses be trained in detailed assessment of neurological function including standardized scales such as the National Institutes of Health Stroke Scale, GCS, and the Glasgow Outcome Scale.

In a Canadian study of 49 hospitals that included ICH patients, a higher proportion of registered nurses and better nurse–physician communications were independently associated with lower 30-day mortality even after adjusting for disease severity, comorbidities, and hospital characteristics.[84]

Recommendation

1. **Initial monitoring and management of ICH patients should take place in an intensive care unit with physician and nursing neuroscience intensive care expertise *(Class I; Level of Evidence: B)*.** (Unchanged from the previous guideline)

Management of Glucose

High blood glucose on admission predicts an increased risk of mortality and poor outcome in patients with and without diabetes and ICH.[85–87] A randomized trial showing improved outcomes with tight glucose control (range 80 to 110 mg/dL) using insulin infusions in mainly surgical critical care patients[88] has increased the use of this therapy. However, more recent studies have demonstrated increased incidence of systemic and cerebral hypoglycemic events and possibly even increased risk of mortality in patients treated with this regimen.[89–92] At present the optimal management of hyperglycemia in ICH and the target glucose remains to be clarified. Hypoglycemia should be avoided.

Temperature Management

Fever worsens outcome in experimental models of brain injury.[93,94] The incidence of fever after basal ganglionic and lobar ICH is high, especially in patients with IVH. In patients surviving the first 72 hours after hospital admission, the duration of fever is related to outcome and appears to be an independent prognostic factor in these patients.[95] These data provide a rationale for aggressive treatment to maintain normothermia in patients with ICH; however, there are no data linking fever treatment with outcome. Similarly, therapeutic cooling has not been systematically investigated in ICH patients.

Seizures and Antiepileptic Drugs

The incidence of clinical seizures within the first 2 weeks after ICH has been reported to range from 2.7% to 17%, with the majority occurring at or near onset.[96–100] Studies of continuous electroencephalography (EEG) have reported electrographic seizures in 28% to 31% of select cohorts of ICH patients, despite most having received prophylactic anticonvulsants.[101,102] In a large, single-center study, prophylactic antiepileptic drugs did significantly reduce the number of clinical seizures after lobar ICH.[98] However, in prospective and population-based studies, clinical seizures have not been associated with worsened neurological outcome or mortality.[97,103,104] The clinical impact of subclinical seizures detected on EEG is also not clear. A recent analysis from the placebo arm of an ICH neuroprotectant study found that patients who received antiepileptic drugs (primarily phenytoin) without a documented seizure were significantly more likely to be dead or disabled at 90 days, after adjusting for other established predictors of ICH outcome.[105] Another recent single-center observational study had similar findings, specifically for phenytoin.[106] Thus only clinical seizures or electrographic seizures in patients with a change in mental status should be treated with antiepileptic drugs. Continuous EEG monitoring should be considered in ICH patients with depressed mental status out of proportion to the degree of brain injury. The utility of prophylactic anticonvulsant medication remains uncertain.

Recommendations

Management of Glucose

1. **Glucose should be monitored and normoglycemia is recommended *(Class I: Level of Evidence: C)*.** (New recommendation)

Seizures and Antiepileptic Drugs

1. **Clinical seizures should be treated with antiepileptic drugs *(Class I; Level of Evidence: A)*.** (Revised from the previous guideline) **Continuous EEG monitoring is probably indicated in ICH patients with depressed mental status out of proportion to the degree of brain injury *(Class IIa; Level of Evidence: B)*. Patients with a change in mental status who are found to have electrographic seizures on EEG should be treated with antiepileptic drugs *(Class I; Level of Evidence: C)*. Prophylactic anticonvulsant medication should not be used *(Class III; Level of Evidence: B)*.** (New recommendation)

Iron

Systemic treatment with the iron chelator deferoxamine ameliorates ICH-induced changes in markers of DNA damage, attenuates brain edema, and improves functional recovery in rat models of ICH.[107–111] A few studies have examined the role of iron in ICH patients and reported that high serum ferritin levels are associated with poor outcome after ICH[112] and correlate with the perihematoma edema volume.[113,114]

Limiting iron-mediated toxicity is a promising therapeutic target in ICH. Besides chelating iron, deferoxamine exhibits other neuroprotective properties.[115] It induces transcription of

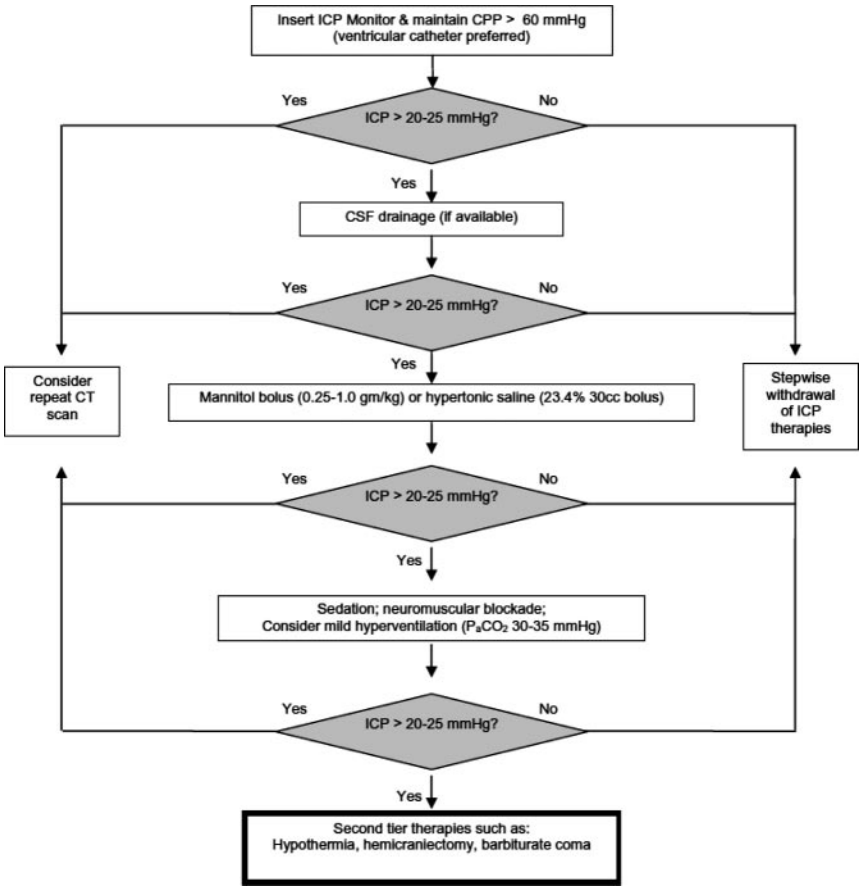

Figure. Intracranial pressure treatment algorithm. CPP indicates cerebral perfusion pressure; CSF, cerebrospinal fluid. Adapted from Brain Trauma Foundation Head Injury Guidelines.[126] Copyright 2000, Brain Trauma Foundation.

heme oxygenase-1 and inhibits hemoglobin-mediated glutamate excitotoxicity and hypoxia inducible factor prolyl hydroxylases.[116–119] Further studies in this area are warranted, but no current therapeutic recommendation can be made at present.

Procedures/Surgery

ICP Monitoring and Treatment

ICP monitoring is often performed in patients with ICH. However, only very limited published data exist regarding the frequency of elevated ICP and its management in patients with ICH.[120,121] There is evidence for differential pressure gradients in at least some cases so that ICP may be elevated in and around the hematoma but not distant from it.[122] Because the usual causes of elevated ICP are hydrocephalus from IVH or mass effect from the hematoma (or surrounding edema), patients with small hematomas and limited IVH usually will not require treatment to lower ICP.

ICP is measured using devices inserted into the brain parenchyma, typically at the bedside. Fiberoptic technology can be used in both types of devices. A ventricular catheter (VC) inserted into the lateral ventricle allows for drainage of cerebrospinal fluid, which can help reduce ICP in patients with hydrocephalus. A parenchymal catheter ICP device is inserted into the brain parenchyma and allows for monitoring of ICP, but not cerebrospinal fluid drainage. The absence of published studies showing that management of elevated ICP impacts on ICH outcome makes the decision whether to monitor and treat elevated ICP unclear. Risks associated with ICP monitor insertion and use include infection and intracranial hemorrhage. In general, the risk of hemorrhage or infection is thought to be higher with VC than with parenchymal catheters, although data on these rates are not derived from patients with ICH, but rather principally from those with traumatic brain injury or aneurysmal subarachnoid hemorrhage. In a 1997 series of 108 intraparenchymal devices, the rate of infection was 2.9% and the rate of intracranial hemorrhage was 2.1% (15.3% in patients with coagulopathies).[123] A direct comparison of the complications associated with each type of monitoring device was reported in a 1993 to 1997 series of 536 intracerebral monitoring devices (274 VCs, 229 intraparenchymal parenchymal catheters, and 33 other types of devices) in which the overall rate of infection was 4% and the overall rate of intracranial hemorrhage was 3%.[124] Before insertion of a monitoring device, the patient's coagulation status should be evaluated. Prior use of antiplatelet agents may justify platelet transfusion before the procedure, and the use of warfarin may require reversal of coagulopathy before placement. The decision to use a VC or a parenchymal catheter device should be based on the specific need to drain cerebrospinal fluid in patients with hydrocephalus or trapped ventricle and the balance of monitoring risks with the unknown utility of ICP management in patients with ICH.

ICP treatment should be directed at the underlying cause, especially if due to hydrocephalus or mass effect from the hematoma. Because of limited data regarding ICP in ICH, management principles for elevated ICP are borrowed from

traumatic brain injury guidelines, which emphasize maintaining a cerebral perfusion pressure of 50 to 70 mm Hg, depending on the status of cerebral autoregulation[125,126] (see Figure). ICH patients with a GCS score of ≤8, those with clinical evidence of transtentorial herniation, or those with significant IVH or hydrocephalus may be considered for ICP monitoring and treatment.

Numerous studies have assessed ventricular size and effects of enlargement on ICH outcome.[127–130] Among 902 patients with follow-up data randomized into the international Surgical Trial of Intracerebral Hemorrhage (STICH) trial of early hematoma evacuation, 377 had IVH and 208 of these had hydrocephalus (23% of all patients, 55% of those with IVH).[131] Hydrocephalus predicted poor outcome in this study, as well as other previous studies.[127] Thus, hydrocephalus is an important cause of ICH-related morbidity and mortality,[1] and treatment should be considered in patients with decreased level of consciousness.

Small case series have described the use of brain tissue oxygen and cerebral microdialysis monitoring in patients with ICH.[132,133] Because of the small numbers of patients and limited data, no recommendation can be made regarding the use of these technologies at this time.

Recommendations

1. **Patients with a GCS score of ≤8, those with clinical evidence of transtentorial herniation, or those with significant IVH or hydrocephalus might be considered for ICP monitoring and treatment. A cerebral perfusion pressure of 50 to 70 mm Hg may be reasonable to maintain depending on the status of cerebral autoregulation *(Class IIb; Level of Evidence: C)*.** (New recommendation)
2. **Ventricular drainage as treatment for hydrocephalus is reasonable in patients with decreased level of consciousness *(Class IIa; Level of Evidence: B)*.** (New recommendation)

Intraventricular Hemorrhage

IVH occurs in 45% of patients with spontaneous ICH.[134] IVH can be primary (confined to the ventricles) or secondary (originating as an extension of an ICH). Most IVHs are secondary and are related to hypertensive hemorrhages involving the basal ganglia and the thalamus.[134,135]

Although inserting a VC should theoretically aid in drainage of blood and cerebrospinal fluid from the ventricles, VC use alone may be ineffective because of difficulty maintaining catheter patency and the slow removal of intraventricular blood.[136] Thus there has been recent interest in the use of thrombolytic agents as adjuncts to VC use in the setting of IVH.

Animal studies and clinical series reported that intraventricular administration of fibrinolytic agents, including urokinase, streptokinase, and recombinant tissue-type plasminogen activator, in IVH may reduce morbidity and mortality by accelerating blood clearance and clot lysis.[137–142] Recently the Clot Lysis: Evaluating Accelerated Resolution of IVH (CLEAR-IVH) Trial prospectively evaluated the safety of open-label doses of intraventricular recombinant tissue-type plasminogen activator in 52 IVH patients. Symptomatic bleeding occurred in 4% and bacterial ventriculitis in 2%, and the 30-day mortality rate was 17%.[143] The efficacy of this treatment requires confirmation before its use can be recommended outside of a clinical trial.

Some reports suggest alternative procedures for IVH such as endoscopic surgical evacuation and ventriculostomy,[144–146] ventriculoperitoneal shunting,[147] or lumbar drainage for hydrocephalus.[148] Few data exist to support these strategies.

Recommendation

1. **Although intraventricular administration of recombinant tissue-type plasminogen activator in IVH appears to have a fairly low complication rate, efficacy and safety of this treatment is uncertain and is considered investigational *(Class IIb; Level of Evidence: B)*.** (New recommendation)

Clot Removal

Surgical Treatment of ICH

The decision about whether and when to surgically remove ICH remains controversial. The pathophysiology of brain injury surrounding the hematoma is due to the mechanical effects of the growing mass of blood as well as the subsequent toxic effects of blood in the surrounding brain tissue. Early surgery to limit the mechanical compression of brain and the toxic effects of blood may limit injury, but the surgical risks in a patient with ongoing bleeding may be greater. In addition, operative removal of hemorrhage by craniotomy in all but the most superficial hemorrhages involves cutting through uninjured brain. Among the limitations of ICH surgical trials is that young and middle-aged patients at risk of herniation from large ICHs were unlikely to be randomized for treatment. Recommendations for these patients are uncertain.

Craniotomy by Location of ICH

Most but not all[149] of the randomized trials of surgery for ICH excluded patients with cerebellar ICH, which comprises 10% to 15% of cases. Previous versions of these guidelines[6] cited nonrandomized studies showing that patients with cerebellar ICH larger than 3 cm in diameter or those with brainstem compression or hydrocephalus had good outcomes with surgery to remove the hematoma, whereas similar patients managed medically did poorly.[150–155] If the hemorrhage is <3 cm in diameter and there is no brainstem compression or hydrocephalus, reasonable outcomes may be achieved without surgery. Even though randomized trials of cerebellar hematoma evacuation have not been undertaken, the differences in outcome in the earlier studies are such that clinical equipoise does not exist for a trial. Furthermore, the use of a VC alone instead of immediate cerebellar hematoma evacuation is generally considered insufficient and is not recommended, especially in patients with compressed cisterns.[155]

The STICH trial found that patients with hematomas extending to within 1 cm of the cortical surface had a trend toward more favorable outcome with surgery within 96 hours, although this finding did not reach statistical significance (odds ratio, 0.69; 95% confidence interval, 0.47 to 1.01).[156] Patients with lobar hemorrhages and a GCS score of 9 to 12 also had a trend toward better outcome. Because the benefit of surgery for patients with superficial ICH was not statistically significant after adjusting for multiple testing, the authors recommended additional clinical trials to confirm this benefit.[157]

By contrast, patients in the STICH study with an ICH >1 cm from the cortical surface or with a GCS score of ≤8 tended to do worse with surgical removal as compared with medical management. Another study randomized 108 patients with supratentorial subcortical or putaminal ICH >30 mL in volume to craniotomy or medical management within 8 hours of onset.[158] Good outcome (good recovery or moderate disability on the Glasgow Outcome Scale at 1 year) was significantly better in those treated with surgery, but there was no difference in overall survival. Other randomized trials have had too few patients to determine outcomes in subgroups by location, randomized only patients with deep ICH, or did not report these results.[159–161] Enthusiasm for surgical evacuation of thalamic and pontine ICH has been limited.[154,162,163]

Minimally Invasive Surgical Removal of ICH

If the indications for surgical evacuation of intracerebral hematomas are controversial, the means by which to achieve this evacuation are even less well established. Several groups have developed minimally invasive clot removal techniques. These techniques tend to make use of stereotactic guidance combined with either thrombolytic-enhanced or endoscopic-enhanced aspiration. Both randomized trials of thrombolytic-enhanced aspiration for subcortical ICH[149,161,164] and endoscopic-enhanced aspiration[165–167] with or without stereotaxis have reported increased clot removal and decreased mortality in those subjects treated surgically within 12 to 72 hours, but improved functional outcome has not been consistently demonstrated.

Timing of Surgery

One key issue has been the lack of consensus on the time frame of what constitutes early surgery. Clinical studies have reported a wide variability in the timing of surgery, ranging from within 4 hours up to 96 hours from the onset of symptoms to time of operation.[156,158,161,168] Such time variance among the studies has made direct comparison and analysis of the impact of surgical timing difficult. A retrospective Japanese series of surgical removal of 100 putaminal ICHs within 7 hours of onset (60 within 3 hours) reported better than expected outcomes.[169] However, subsequent randomized trials that treated subjects within 12 hours of onset reported mixed results.[158,161,168] An increased risk of rebleeding was noted in the small trial of subjects randomized within 4 hours of onset.[170]

Trials that randomized patients within 24 hours,[171] 48 hours,[159,165] 72 hours,[149,160] and 96 hours[156] have also demonstrated no clear benefit for surgery as compared with initial medical management except for improved outcome in the subgroup of patients in the STICH trial with superficial ICH and decreased mortality in those patients with subcortical hemorrhages treated with minimally invasive methods within 12 to 72 hours, as noted above.

Recommendations

1. **For most patients with ICH, the usefulness of surgery is uncertain *(Class IIb; Level of Evidence: C).*** (New recommendation) **Specific exceptions to this recommendation follow**
2. **Patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible *(Class I; Level of Evidence: B).*** (Revised from the previous guideline) **Initial treatment of these patients with ventricular drainage alone rather than surgical evacuation is not recommended *(Class III; Level of Evidence: C).*** (New recommendation)
3. **For patients presenting with lobar clots >30 mL and within 1 cm of the surface, evacuation of supratentorial ICH by standard craniotomy might be considered *(Class IIb; Level of Evidence: B).*** (Revised from the previous guideline)
4. **The effectiveness of minimally invasive clot evacuation utilizing either stereotactic or endoscopic aspiration with or without thrombolytic usage is uncertain and is considered investigational *(Class IIb; Level of Evidence: B).*** (New recommendation)
5. **Although theoretically attractive, no clear evidence at present indicates that ultra-early removal of supratentorial ICH improves functional outcome or mortality rate. Very early craniotomy may be harmful due to increased risk of recurrent bleeding *(Class III; Level of Evidence: B).*** (Revised from the previous guideline)

Outcome Prediction and Withdrawal of Technological Support

Many observational and epidemiological studies have identified a wide range of factors that are predictive of outcome after acute ICH. From these studies numerous outcome prediction models have been developed for mortality and functional outcome. Features found in most of these prediction models include individual patient characteristics such as the score on the GCS or National Institutes of Health Stroke Scale, age, hematoma volume and location, and the presence and amount of IVH.[12,172–180] No outcome prediction model for ICH, however, has considered the impact of care limitations such as do not resuscitate (DNR) orders or withdrawal of technological support.

Most patients that die from ICH do so during the initial acute hospitalization, and these deaths usually occur in the setting of withdrawal of support due to presumed poor prognosis.[181,182] Several studies, however, have now identified withdrawal of medical support and other early care limitations, such as DNR orders within the first day of hospitalization, as independent outcome predictors.[2,183,184] It is likely that current outcome prediction models as well as more informal methods of early prognostication after ICH are biased by the failure to account for these care limitations. Concern has been raised that decisions by physicians to limit care early after ICH are resulting in self-fulfilling prophecies of poor outcome due to inaccurately pessimistic prognostication and failure to provide initial aggressive therapy in severely ill ICH patients who nonetheless still have the possibility of favorable outcome.

Although a DNR order by definition means that no attempt at resuscitation should be made in the event that a cardiopulmonary arrest occurs, in practical use, when administered early after ICH, it is a proxy for overall lack of aggressiveness of care.[2] This implies that the overall aggressiveness of ICH care at a hospital may be critically important in determining patients' outcome, irrespective of specific individual characteristics.[2,83,185]

Although prognostication early after ICH may be desired by physicians, patients, and families, it is currently based on uncertain ground. Given this uncertainty and the potential for self-fulfilling prophecies of poor outcome, great caution should be undertaken in attempting precise prognostication early after ICH, especially if the purpose is to consider withdrawal of support or DNR orders.[186] Thus, aggressive guideline-concordant therapy is recommended for all ICH patients who do not have advanced directives specifying that this should not be undertaken. Care limitations such as DNR orders or withdrawal of support should not be recommended by treating physicians during the first few days after ICH.

Recommendation

1. **Aggressive full care early after ICH onset and postponement of new DNR orders until at least the second full day of hospitalization is probably recommended *(Class IIa; Level of Evidence: B).* Patients with preexisting DNR orders are not included in this recommendation. Current methods of prognostication in individual patients early after ICH are likely biased by failure to account for the influence of withdrawal of support and early DNR orders. Patients who are given DNR status at any point should receive all other appropriate medical and surgical interventions unless otherwise explicitly indicated.** (Revised from the previous guideline)

Prevention of Recurrent ICH

Population-based studies of survivors of a first hemorrhagic stroke have identified rates of recurrent ICH of 2.1% to 3.7% per patient-year,[187,188] substantially higher than these individuals' rate of subsequent ischemic stroke.

The most consistently identified risk factor for recurrent ICH is lobar location of the initial ICH.[187,189] This finding likely represents the association of cerebral amyloid angiopathy with lobar location and increased recurrence.[190,191] Hemorrhage in locations characteristic of hypertensive vasculopathy, such as basal ganglia, thalamus, or brainstem,[192] also recur, but less frequently. Other factors linked to ICH recurrence in some studies include older age,[188] post-ICH anticoagulation,[188] previous hemorrhage before the presenting ICH,[191] carriership of the apolipoprotein E ε2 or ε4 alleles,[191,193] and greater number of microbleeds on T2*-weighted gradient-echo MRI.[194]

Hypertension is the most important currently modifiable risk factor for prevention of ICH recurrence.[195,196] The importance of BP control was supported by data from the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) showing that subjects with cerebrovascular disease randomized to perindopril plus optional indapamide had significantly lower risk of first ICH (adjusted hazard ratio, 0.44; 95% confidence interval, 0.28 to 0.69) and a similar, though statistically insignificant, reduction in recurrent ICH (adjusted hazard ratio, 0.37; 95% confidence interval, 0.10 to 1.38).[193] Notably, this reduction appeared to apply to lobar as well as deep hemispheric ICH. Although specific data on the optimal BP for reducing ICH recurrence are not available, a reasonable target is a BP $<$140/90 (or $<$130/80 in the presence of diabetes or chronic kidney disease) as suggested by the most recent report from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[197]

Oral anticoagulation is associated with worse ICH outcome[198,199] and increased risk of recurrence,[188] raising the question of whether the benefits of anticoagulation for preventing thromboembolism outweigh its risks after initial ICH. For a hypothetical 69-year-old man with nonvalvular atrial fibrillation and prior *lobar* ICH, Markov modeling predicted that long-term anticoagulation would shorten quality-adjusted survival because of the high risk of recurrence after lobar ICH.[200] The results for anticoagulation after deep hemispheric ICH were less clear-cut and varied depending on assumptions about risk of future thromboembolism or ICH. The effects of antiplatelet agents on ICH recurrence and severity appear to be substantially smaller than for anticoagulation,[16,62,189,201] suggesting that antiplatelet treatment may be a safer alternative to anticoagulation after ICH. Recently, the ACTIVE A (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events–Aspirin) study reported on a randomized, double-blind study of the safety and efficacy of adding clopidogrel 75 mg daily to aspirin 75 to 100 mg daily in patients with high-risk atrial fibrillation and a contraindication to warfarin. Although previous ICH was listed as one of the many reasons for study entry, the authors did not report the proportion of subjects with previous ICH, and therefore the study results may not directly apply to those with previous ICH. Subjects who received clopidogrel added to aspirin had a 0.8% per year absolute risk reduction of major vascular events at the cost of 0.7% per year increase in major bleeding events.[202]

The recent Stroke Prevention with Aggressive Reductions in Cholesterol Levels (SPARCL) study found increased risk of subsequent ICH (unadjusted hazard ratio, 1.68; 95% confidence interval, 1.09 to 2.59) among subjects with prior stroke randomized to high-dose atorvastatin.[203] It remains unclear whether this effect outweighs the benefits of statin treatment in reducing ischemic cardiac and cerebral events in ICH survivors. Frequent alcohol use (defined in the Greater Cincinnati/Northern Kentucky study as $>$2 drinks per day) has been linked to increased ICH risk[204] and is therefore reasonable to avoid after ICH. Other behaviors, such as physical exertion, sexual activity, or stress, have not been linked to ICH,[205] though little systematic data have been reported.

Recommendations

1. **In situations where stratifying a patient's risk of recurrent ICH may affect other management decisions, it is reasonable to consider the following risk factors for recurrence: lobar location of the initial ICH, older age, ongoing anticoagulation, presence of the apolipoprotein E ε2 or ε4 alleles, and greater number of microbleeds on MRI *(Class IIa; Level of Evidence: B).*** (New recommendation)
2. **After the acute ICH period, absent medical contraindications, BP should be well controlled, particularly for patients with ICH location typical of hypertensive vasculopathy *(Class I; Level of Evidence: A).*** (New recommendation)
3. **After the acute ICH period, a goal target of a normal BP of $<$140/90 ($<$130/80 if diabetes or chronic kidney disease) is reasonable *(Class IIa; Level of Evidence: B).*** (New recommendation)

4. **Avoidance of long-term anticoagulation as treatment for nonvalvular atrial fibrillation is probably recommended after spontaneous lobar ICH because of the relatively high risk of recurrence *(Class IIa; Level of Evidence: B).* Anticoagulation after nonlobar ICH and antiplatelet therapy after all ICH might be considered, particularly when there are definite indications for these agents *(Class IIb; Level of Evidence: B).*** (Unchanged from the previous guideline)
5. **Avoidance of heavy alcohol use can be beneficial *(Class IIa; Level of Evidence: B).* There is insufficient data to recommend restrictions on use of statin agents or physical or sexual activity *(Class IIb; Level of Evidence: C).*** (New recommendation)

Rehabilitation and Recovery

Knowledge of differences in the natural history of recovery patterns and prognosis for residual disability and functioning between ICH and ischemic stroke is complicated by the disproportionately lower rate of ICH compared with ischemic stroke and the lumping of subarachnoid hemorrhage and ICH together in many studies. There are also problems associated with the insensitivity of many of the outcome measures used in rehabilitation to allow detection of clinically meaningful differences between groups. Even so, there is some evidence that patients with ICH make slightly greater and faster gains in recovery[206–208] compared with patients with ischemic stroke.

In general, recovery is more rapid in the first few weeks but may continue for many months after ICH,[208,209] with approximately half of all survivors remaining dependent on others for activities of daily living.[176] However, patients vary in their speed and degree of recovery, and there is no hard rule regarding when recovery is over. Cognition, mood, motivation, and social support all influence recovery, and it is difficult to separate intrinsic from adaptive recovery. A simple prognostic score utilizing age, ICH volume and location, level of consciousness at admission, and pre-ICH cognitive impairment has been shown to predict independence at 90 days.[176] Given that ICH is often located in lobar regions and complicated by intraventricular extension, some patients with specific cognitive deficits or delayed recovery that is disproportionate to the size of the lesion may require specialized therapy in rehabilitation.

The provision of stroke rehabilitation services has received considerable attention in recent years. In part this represents a need to tailor services to ensure optimal recovery for patients and in part is due to fiscal pressures on costly health services. Given strong evidence for the benefits of well-organized, multidisciplinary inpatient (stroke unit) care in terms of improved survival, recovery, and returning home compared with conventional nondedicated stroke wards,[210] efforts have been made to extend this service model of coordinated care into the community. Specifically, early supported hospital discharge and home-based rehabilitation programs have been shown to be cost-effective,[210] whereas home-based therapy in stable patients has been shown to produce comparable outcomes to conventional outpatient rehabilitation.[211] The success of these programs depends on caregiver training and support. However, the likely configuration of stroke rehabilitation services in any region will depend on available resources and funding options. A key portion of rehabilitation should include education for the patient and caregiver regarding secondary stroke prevention and means to achieve rehabilitation goals. Rehabilitation programs should consider lifestyle changes, depression, and caregiver burden as important issues to work on with the patient and caregivers.

Recommendations

1. **Given the potentially serious nature and complex pattern of evolving disability, it is reasonable that all patients with ICH have access to multidisciplinary rehabilitation *(Class IIa; Level of Evidence: B).* Where possible, rehabilitation can be beneficial when begun as early as possible and continued in the community as part of a well-coordinated (seamless) program of accelerated hospital discharge and home-based resettlement to promote ongoing recovery *(Class IIa; Level of Evidence: B).*** (New recommendation)

Future Considerations

The future of ICH treatment centers on a cluster of targets. The first is clearly prevention. Community-based projects to reduce BP through healthy lifestyles and medication adherence are likely to be quite successful in reducing ICH incidence.[212] Animal studies aimed at preventing cerebral amyloid angiopathy show early promise.[213,214]

Once an ICH has occurred, efforts to mobilize communities to facilitate prompt treatment are similar to efforts aimed at acute ischemic stroke treatment.[215] Advanced imaging currently may identify patients with ongoing bleeding and provides a target for improved patient selection for testing of hemostatic agents.[28] Hemostatic agents' efficacy must be clearly weighed against potential arterial and venous thrombotic risk.

BP control theoretically may reduce hematoma growth and/or reduce cerebral edema. Early studies suggest that a randomized controlled BP-lowering study is feasible.[79,81] Safety and efficacy remain to be shown in larger studies.

There is active research on interfering with oxidative injury after ICH. Iron-chelating agents such as deferoxamine are being studied in early-phase trials.[107,115] Pathways that center around hypoxia-inducible factors and prolyl hydroxylases offer other potential targets for intervention centered around oxidative stress.[216] The role of microglia and macrophages in hematoma resolution is getting more attention.[217] Autophagy may be a cellular process that could be altered to prevent ICH-related cell death.[218]

There are probably many factors that contribute to injury after ICH, including mass effect, toxicity related to blood, and displacement of underlying tissue. Seemingly, a simple solution is hematoma removal. To date, however, surgery has not proved to be the panacea for this condition. New efforts utilizing minimally invasive surgical techniques that may remove blood's toxic and pressure effects while avoiding the damage caused by more invasive procedures, as well as new treatments to dissolve and drain intraventricular blood, are currently being studied.[143,164]

Priorities for ICH research have been published and reviewed extensively.[13] An aggressive, collaborative approach to both basic and clinical research in this field is likely to promote the highest yield. In the mean time, it is clear that our ability to prognosticate about ICH is limited,[184] and that aggressive care now, and hope for the future, are both clearly indicated.

Disclosures

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Lewis B. Morgenstern	University of Michigan	NIH (R01 NS057127) Consultant—Safety and Tolerability of Deferoxamine in Acute Cerebral Hemorrhage (generic study drug)*; NINDS (U01 NS052510) Co-I (Deferoxamine therapy for intracerebral hemorrhage—animal translational grant examining generic deferoxamine in ICH)†; NIH (R01 NS38916) PI—Brain Attack Surveillance in Corpus Christi (observational study of stroke in a biethnic community)†	None	None	None	None	None	Medical adjudication board member Wyeth*
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*Modest.

†Significant.

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Karen C. Johnston	University of Virginia	NIH-NINDS R01 NS050192 - GRASP trial†	None	Multiple grand rounds, national talks on stroke*	None	None	Diffussion Pharmaceuticals, Inc.*; Remedy Pharmaceuticals, Inc.*	AAN as associate editor of neurology through July 2009†
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*Modest.

†Significant.

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DETERMINATION OF THE ICH SCORE[⌂]

COMPONENT	ICH SCORE POINTS
GCS SCORE	
3-4	2
5-12	1
13-15	0
ICH VOLUME (CM^3)[§]	
≥30	1
<30	0
INTRAVENTRICULAR HEMORRHAGE	
PRESENT	1
ABSENT	0
INFRATENTORIAL ICH	
YES	1
NO	0
AGE	
≥80 YEARS	1
<80	0
	____

TOTAL SCORE: 0-6

⌂ Hemphill C, Bonovich D, Besmertis L, Manley G, Johnston C. The ICH Score: A simple, reliable grading scale for Intracerebral Hemorrhage. Stroke. 2001;32:891-897.

§ using the AB C/2 method.

THE ABC METHOD OF MEASURING ICH VOLUME[⌂]

A = the greatest hematoma diameter on CT scan.

B = the diameter 90^{o} (perpendicular to) A.

C = the number of CT slices with hemorrhage, multiplied by the slice thickness (0.5 cm thickness in most cases).

⌂ Kothari R, Brott T, Broderick J, Barsan W, Auerbeck L, Zuccarello M, Khoury J. The ABCs of Measuring Intracerebral Hemorrhage Volumes. Stroke. 1996;27:1304-1305.

MODIFIED RANKIN SCALE (mRS)

0 [ ] No symptoms at all

1 [ ] No significant disability despite symptoms; able to carry out all usual duties and activities

2 [ ] Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance

3 [ ] Moderate disability requiring some help, but able to walk without assistance

4 [ ] Moderate severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

5 [ ] Severe disability; bedridden, incontinent and requiring constant nursing care and attention

6 [ ] Dead

Structured Interview for the Modified Rankin Scale

Questionnaire and Guidelines

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May 2002

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Structured Interview for the Modified Rankin Scale

Introduction

The Modified Rankin Scale (MRS) (van Swieten et al., 1988) is widely used as a functional outcome measure in stroke. The purpose of the Structured Interview is to assign patients to MRS grades in a systematic way. The interview consists of five sections corresponding to the levels of disability on the MRS (see Table).

Modified Rankin Scale		**Section of the Structured Interview**
5	**Severe disability**: bedridden, incontinent and requiring constant nursing care and attention.	1. Constant care
4	**Moderately severe disability**: unable to walk without assistance, and unable to attend to own bodily needs without assistance.	2. Assistance for bodily needs / walking
3	**Moderate disability**: requiring some help, but able to walk without assistance.	3. Assistance to look after own affairs
2	**Slight disability**: unable to carry out all previous activities but able to look after own affairs without assistance.	4. Usual duties and activities
1	**No significant disability:** despite symptoms: able to carry out all usual duties and activities.	5. Symptom checklist
0	**No symptoms at all**	

General Instructions

Timing

The interview is intended for use after discharge from hospital.

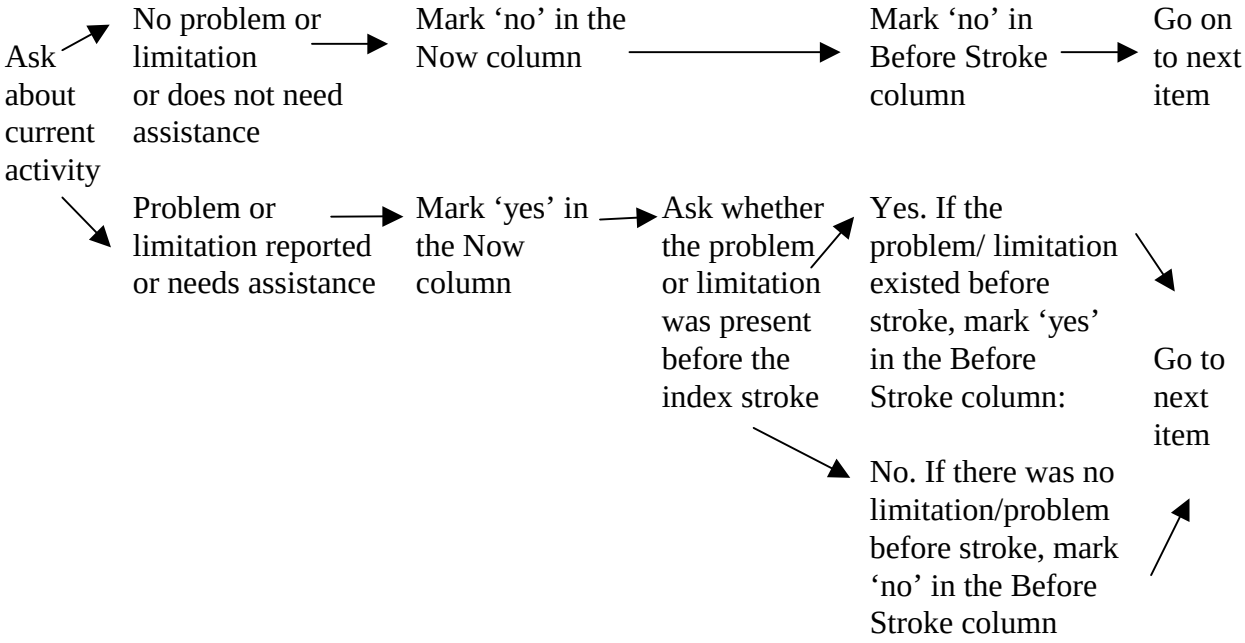
Respondents

Use the best source of information available. Information can be obtained from the patient and/or a person who is familiar with the daily routine of the patient. Interview the patient and a close friend or caregiver whenever possible. If the patient lacks insight into some difficulties, or responses are inconsistent it is often helpful to interview a caregiver or relative independently.

Procedure

For sections 1, 2, 3, & 5 first ask about current activities. If there is currently no problem or limitation in a particular activity, it is not necessary to ask about status ‘before stroke’, but please tick the relevant boxes. If the person indicates a problem or limitation on a particular activity, then establish whether this was present before the stroke and record the response appropriately in the ‘before stroke’ column. (This sequence is illustrated in the diagram on the next page)

Diagram: Interview procedure for sections 1, 2, 3 & 5



For Section 4 ask about ability to perform the activity before stroke and then ask about a change in ability after the stroke. If the person did not participate in an activity (e.g. work) before stroke then move to the next question as indicated on the questionnaire. Sometimes it can be difficult to establish whether or not someone could do an activity before stroke (particularly if the person had one or more previous strokes) - in this case use your judgement and focus on the index stroke for which the patient was enrolled in the study.

The responses to the separate sections should generally be hierarchical (for example if a person indicates that they require assistance to attend to bodily needs, then it is inconsistent if they then say that they go out alone for social and leisure activities). Thus, responses to later questions may suggest revisions to earlier responses. Check for consistency as you proceed. Ask all questions and go back to clarify, if necessary.

Notes for specific sections of the interview are given on the following pages. The document is formatted so that the notes appear opposite the interview questions when double-sided printing is used.

Sources:-
Section 2 of the interview is adapted from the Barthel Index (Collin et al. 1988), and Section 4 is adapted from the Extended Glasgow Outcome Scale (Wilson et al., 1998).

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Wilson, J. T. L., Pettigrew, L. E. L., & Teasdale, G. M. (1998). Structured interviews for the Glasgow Outcome Scale and Extended Glasgow Outcome Scale: Guidelines for their use. Journal of Neurotrauma, 15, 573-585.

Notes

1. CONSTANT CARE

Patients are usually bedridden: patients may not actually remain in bed all the time, but moving them from the bed to sitting will require major assistance. Patients will also need assistance with other activities.

SECTIONS 2 AND 3: ASSISTANCE FOR ACTIVITIES OF DAILY LIVING

Assistance may be considered essential when there is the need for physical help (by another person) with an activity or there is a need for supervision, or the person needs prompting or reminding to do a task.

Mark responses based on the ability of the patient to perform the activity and not whether the patient actually performs the activity currently. Please probe using the specific questions given in the sections below. Please use your judgement to decide whether the person can actually do something before recording a response. The need for supervision for safety reasons should be due to objective danger that is posed, rather than 'just in case'. People may feel that a person who has had stroke should not be left on their own, but that does not make the person with stroke dependent. A general need for companionship, care, or protection should not be considered assistance.

2.ASSISTANCE TO ATTEND TO BODILY NEEDS/ FOR WALKING

2.1. Assistance for eating

Patient may eat a modified diet on their own. This should not be considered assistance.

2.2. Assistance for using the toilet

Using toilet without assistance include, reaching the toilet/commode; undress sufficiently; clean self; dress and leave.

2.3. Assistance for routine daily hygiene

Daily Hygiene includes just the three activities indicated (washing face, doing hair, cleaning teeth/ fitting false teeth). It does not include bathing and showering, or shaving, which are more complex activities for which the person may require assistance. The ability to bath, shower or shave is not relevant for this section.

2.4. Assistance for walking

Specific question to ask: "If absolutely necessary could you walk across the room, even if your caregiver was not present?"

3. ASSISTANCE TO LOOK AFTER OWN AFFAIRS

3.1 Preparing a simple meal. Specific questions to ask: "If the person were on their own: Would they go hungry? Might they be at risk of burning the house down if they tried to cook?"

3.2 Performing basic household chores. Specific questions to ask: "Are they *able to do* chores, if necessary, even if they do not normally do them." Men may, report that they need assistance more often than women. Please clarify by probing about the person's *ability* to perform the chores.

3.3 Looking after household expenses. Specific questions to ask: "Do you look after your own pension/income? Do you arrange to pay bills?" Look for a change from previous level of responsibility. Note: the person may be reluctant to admit a problem. The question is NOT about financial needs (e.g. assistance from benefit agencies). It refers to whether or not patients are able to take responsibility for the money that they have.

3.4 Local travel. Specific questions to ask: "If you need to get somewhere can you manage to call a taxi?" The patient should be able to at least order and take a taxi alone. This question is NOT about being able to afford a taxi, but about the tasks involved. The question refers to whether or not the patients can get around locally by themselves.

On the 'shopping' and 'local travel' questions (independence outside the home) there is quite often some restriction before stroke. Please ask about this and record the response in the 'Before Stroke' column

3.5 Local shopping. Specific Questions to ask: "If your life depended on it – could you get out and buy even single items?" "Can the person go to a local shop to buy milk or a loaf of bread?" Could also include going to the pub/bar, ordering and paying for a drink by themselves

Interview

Please mark (X) in the appropriate box. Please record responses to all questions (unless otherwise indicated in the text), including those concerning status before stroke. See guidelines on the facing page for further information.

1	**CONSTANT CARE**		
	Constant care means that someone needs to be available at all times. Care may be provided by either a trained or an untrained caregiver. The patient will usually be bedridden and may be incontinent.	**Now**	**Before stroke**
1.1	**Does the person require constant care?**	☐ Yes ☐No (5)	☐Yes ☐No

2	**ASSISTANCE TO ATTEND TO BODILY NEEDS/ FOR WALKING**		
	Assistance includes physical assistance, verbal instruction, or supervision by another person.	**Now**	**Before stroke**
2.1	**Is assistance essential for eating?** (Eating without assistance: food and implements may be provided by others).	☐ Yes ☐ No (4)	☐ Yes ☐ No
2.2	**Is assistance essential for using the toilet?** (Using toilet without assistance: reach toilet/commode; undress sufficiently; clean self; dress and leave).	☐ Yes ☐ No (4)	☐ Yes ☐ No
2.3	**Is assistance essential for routine daily hygiene?** (Routine hygiene: washing face, doing hair, cleaning teeth/fitting false teeth. Implements may be provided by others and this should not be considered assistance).	☐ Yes ☐ No (4)	☐ Yes ☐ No
2.4	**Is assistance essential for walking?** (Walking without assistance: Able to walk indoors around house or ward, may use any aid (e.g. stick/cane, walking frame/walker), however not requiring physical help or verbal instruction or supervision from another person).	☐ Yes ☐ No (4)	☐ Yes ☐ No

3	**ASSISTANCE TO LOOK AFTER OWN AFFAIRS**		
	Assistance includes physical assistance, or verbal instruction, or supervision by another person.	**Now**	**Before stroke**
3.1	**Is assistance essential for preparing a simple meal?** (For example, able to prepare breakfast or a snack)	☐ Yes ☐ No (3)	☐ Yes ☐ No
3.2	**Is assistance essential for basic household chores?** (For example, finding and putting away clothes, clearing up after a meal. Exclude chores that do not need to be done every day, such as using a vacuum cleaner.)	☐ Yes ☐ No (3)	☐ Yes ☐ No
3.3	**Is assistance essential for looking after household expenses?**	☐ Yes ☐ No (3)	☐ Yes ☐ No
3.4	**Is assistance essential for local travel?** (Patients may drive or use public transport to get around. Ability to use a taxi is sufficient, provided the person can phone for it themselves and instruct the driver.)	☐ Yes ☐ No (3)	☐ Yes ☐ No
3.5	**Is assistance essential for local shopping?** (Local shopping: at least able to buy a single item)	☐ Yes ☐ No (3)	☐ Yes ☐ No

Notes

4. USUAL DUTIES AND ACTIVITIES

The set of questions in Section 4 are about how the patient usually spends his/her day. In this section, questions concerning status before stroke are asked first, to establish which areas are relevant. If an activity is not relevant (e.g. the person was not working before stroke), then it is assumed that there is no change, and the interviewer proceeds to ask about the next area.
Concentrate on key areas relevant to the particular person. Not all will apply, but almost everyone will have some regular pre-stroke social & leisure activities.

It is change that is important. The section concerns fulfilment of major social roles, relative to the previous roles that the person had.

Change should come from impairment (not social circumstances). For example, change in financial circumstances may produce a change in social activities but this is not relevant.

Possible improvement in the future is not relevant (e.g. "I plan to go back to work next month"). The relevant time period is within the previous week or so.

4.1 Work

4.1.1 Work refers to paid employment, and does not include voluntary work (which can be included under 'social and leisure activities'). Many elderly patients will have retired and this section will not be relevant.

4.1.2 Change in ability to work or study includes loss of employment or reduction in level of responsibility; change in education, or problems with study. Special arrangements which allow someone to return to work even though they would not normally be able to work should be considered as 'reduced level of work'.

4.2 Family responsibilities

Refers to the patient's ability to look after others. Probe using specific examples such as "babysitting, looking after your partner, your parents, your grandchildren or dependent others".

4.3 Social & leisure activities

This refers to any specific free-time activities which the person did for pleasure. It is useful to first establish the person's main activities before stroke, and then ask about change in participation since the stroke. Probe with specific questions: "How did you spend your day before the stroke? How often did you get out? What activities did you do in your free time at home? Do you think your level of activity has changed?"

Interview

4. USUAL DUTIES AND ACTIVITIES. The next sets of questions are about how the patient usually spends his/her day.

4.1 Work

4.1.1	**Before stroke, was the person working or seeking work (or studying as a student)?** (If the person was not employed or seeking work before stroke, or the person was retired then indicate 'No' and go to 4.2)	☐ Yes ☐ No
4.1.2	**Since stroke has there been a change in the person's ability to work or study?** (Change in ability to work or study includes loss of employment or reduction in level of responsibility; change in education or problems with study). **If 'Yes', how restricted are they?** Reduced level of work e.g. change from full-time to part-time or change in level of responsibility**.** ☐(2) Currently unable to work. ☐(2)	☐ Yes ☐ No

4.2 Family responsibilities

4.2.1	**Before stroke was the person looking after family at home?** (If this was not a major role before stroke, indicate 'No' and go to 4.3)	☐ Yes ☐ No
4.2.2	**Since stroke has there been a change in their ability to look after family at home?** *If 'Yes', how restricted are they?* (a) Reduced responsibility for looking after family. ☐(2) (b) Currently unable to look after family. ☐(2)	☐ Yes ☐ No

4.3 Social & leisure activities

(Social and leisure activities include hobbies and interests. Includes activities outside the home or at home. Activities outside the home: going to the pub/bar, restaurant, club, church, cinema, visiting friends, going for walks. Activities at home: involving "active" participation including knitting, sewing, painting, games, reading books, home improvements).

4.3.1	**Before stroke did the person have regular free-time activities?** (If the person had very restricted social & leisure activities before stroke then indicate 'No' and go to 4.4).	☐ Yes ☐ No
4.3.2	**Since stroke has there been a change in their ability to participate in these activities?** *If 'Yes', how restricted are they?* (a) Participate a bit less: at least half as often as before the stroke. ☐ (b) Participate much less: less than half as often. ☐ (2) (c) Unable to participate: rarely, if ever, take part. ☐ (2)	☐ Yes ☐ No

Notes

4. <u>USUAL DUTIES AND ACTIVITIES</u>. …..Contd.

4.4 Family & friendships

It is useful to go through the problems listed, particularly change in mood. This includes the patient who has become isolated and / or withdrawn since suffering their stroke. In this case it is more relevant to consider how tolerable this for others rather than the frequency of the problem.

Patients can experience personality changes and may be more insensitive to their partners than before, and this may result in relationship problems. Patients may report that they are now more 'mellow' than before and can longer be bothered joining in conversations about trivia. This behaviour may also result in reduced social interaction and could lead to increased isolation.

It is useful to obtain the views of a caregiver on relationship problems.

5. SYMPTOMS AS A RESULT OF THE STOKE

5.1 This question is used to establish a spontaneous report of symptoms due to stroke, before going through the checklist

5.2 SYMPTOM CHECKLIST

These can be any symptoms or problems reported by the patient or found on neurological examination. It is important to exclude common problems and complaints not due to stroke.
If you are not sure that a symptom resulted from stroke indicate that it was present 'before stroke' by marking the 'yes' box in the before stroke column. The responses that are considered for scoring are those that are present now, but not present before the stroke, implying that the symptoms are due to stroke.

Assigning a grade on the Modified Rankin Scale

1. Examine the responses and discount items on which there were limitations before stroke.
2. If there is a 'yes' answer in the 'before stroke' column, indicating a problem before stroke, then discount (do not consider) that item. In section 4 if there is a 'no' answer to question 4.1.1, 4.2.1, 4.3.1 or a 'yes' answer to 4.4.2 then discount the specific subsection.
3. Rankin categories are given in brackets beside specific responses.
4. The overall rating is simply the lowest disability category indicated by the person's answers (after discounting limitations or problems before stroke). Rankin 5 is the lowest category, and Rankin 0 is the highest.

If the person has no limitations or symptoms then the Rankin grade is 0.

Interview

4. <u>USUAL DUTIES AND ACTIVITIES</u>. …..Contd.

4.4 Family & Friendships

(Problems with relationships include difficulties in relationships with people at home, loss of friendships or increase in isolation. Changes in the person may include: communication problems, quick temper, irritability, anxiety, insensitivity to others, mood swings, depression, and unreasonable behaviour).

4.4.1	**Since the stroke has the person had problems with relationships or become isolated?** ☐ Yes ☐ No *If 'Yes', what is the extent of disruption/strain?* Occasional- less than weekly ☐ Frequent- once a week or more, but tolerable ☐ (2) Constant- daily & intolerable ☐ (2)	
4.4.2	**Before stroke were any similar problems present?**	☐ Yes ☐ No

5. <u>SYMPTOMS AS A RESULT OF THE STOKE</u>

(Can be any symptoms or problems reported by the patient or found on neurological examination).

5.1	**"Does the patient have any symptoms resulting from stroke?"** (Record spontaneous answer to the question from respondent)	☐ Yes (1) ☐ No	
5.2.	**SYMPTOM CHECKLIST**	**Now**	**Before stroke**
5.2.1	**Does the person have difficulty reading or writing?**	☐ Yes (1) ☐ No	☐ Yes ☐ No
5.2.2	**Does the person have difficulty speaking or finding the right word?**	☐ Yes (1) ☐ No	☐ Yes ☐ No
5.2.3	**Does the person have problems with balance or co-ordination?**	☐ Yes (1) ☐ No	☐ Yes ☐ No
5.2.4	**Does the person have visual problems?**	☐ Yes (1) ☐ No	☐ Yes ☐ No
5.2.5	**Does the person have numbness (face, arms, legs, hands, feet)?**	☐ Yes (1) ☐ No	☐ Yes ☐ No
5.2.6	**Has the person experienced loss of movement (face, arms, legs, hands, feet)?**	☐ Yes (1) ☐ No	☐ Yes ☐ No
5.2.7	**Does the person have difficulty with swallowing?**	☐ Yes (1) ☐ No	☐ Yes ☐ No
5.2.8	**Any other symptoms?** (Please record: …… ……)	☐ Yes (1) ☐ No	☐ Yes ☐ No

Rankin Grade = ☐

NATIONAL INSTITUTE OF HEALTH STROKE SCALE (NIHSS)

Study ID No: _____
Pt. Date of Birth: _____
Hospital: _____
Date of Exam: _____
Time: ___ ___ : ___ ___ [ ] am [ ] pm

Person Administering Scale: _____

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.
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, and flaccid.

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

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

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.
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 manoeuvre.

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

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)

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 "9" and the examiner must clearly write the explanation for scoring as a "9".

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: _____

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: _____

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, insure 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 paralysed. Only in the case of amputation or joint fusion may the item be scored "9" and the examiner must clearly write the explanation for not scoring. In case of blindness, test by touching nose from extended arm position.

0 = Absent
1 = Present in one limb
2 = Present in two limbs

If present, is ataxia in:

Right arm 1 = Yes 2 = No 9 = amputation or joint fusion, explain: _____
Left arm 1 = Yes 2 = No 9 = amputation or joint fusion, explain: _____
Right leg 1 = Yes 2 = No 9 = amputation or joint fusion, explain: _____
Left leg 1 = Yes 2 = No 9 = amputation or joint fusion, explain: _____

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 accurately check 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 arbitrarily 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.

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. 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 arbitrarily score 3 on this item. The examiner must choose a score in the patient with stupor or limited co-operation 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.

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 "9" and the examiner must clearly write an explanation for not scoring. Do not tell the patient why he/she is being tested.

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: _____

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.

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.

ADDITIONAL ITEM, NOT A PART OF THE NIH STROKE SCALE SCORE

A. DISTAL MOTOR FUNCTION:
The patient's hand is held up at the forearm by the examiner and patient is asked to extend his/her fingers as much as possible. If the patient can't or doesn't extend the fingers the examiner places the fingers in full extension and observes for any flexion movement for 5 seconds. The patient's first attempts only are graded. Repetition of the instructions or of the testing is prohibited.

0 = Normal (No flexion after 5 seconds)
1 = At least some extension after 5 seconds, but not fully extended. Any movement of the fingers which is not command is not scored.
2 = No voluntary extension after 5 seconds. Movements of the fingers at another time are not scored.

A. LEFT ARM _____
B. RIGHT ARM _____

GLASGOW COMA SCALE (GCS)

EYE OPENING (E)
4 = Spontaneous
3 = To voice
2 = To pain
1 = None

VERBAL RESPONSE (V)
5 = Normal conversation
4 = Disoriented conversation
3 = Words, but not coherent
2 = No words...only sounds
1 = None

MOTOR RESPONSE (M)
6 = Normal
5 = Localizes to pain
4 = Withdraws to pain
3 = Abnormal flexion
2 = Abnormal extension
1 = None

Patients who are intubated will have their verbal score extrapolated from their eye opening and best motor score according to the following table:

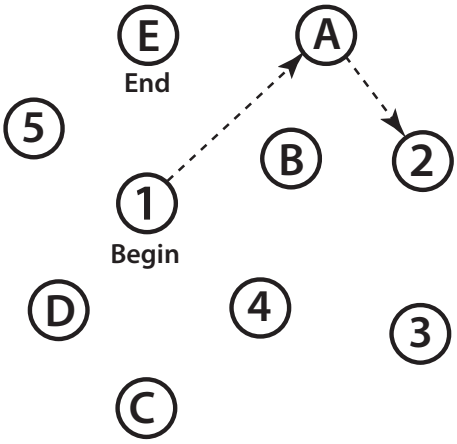
	Eye Opening Score			
Best Motor Score	1	2	3	4
1	**1**	**1**	**1**	**2**
2	**1**	**2**	**2**	**2**
3	**2**	**2**	**3**	**3**
4	**2**	**3**	**3**	**4**
5	**3**	**3**	**4**	**4**
6	**3**	**4**	**4**	**5**

TOTAL SCORE= E+V+M

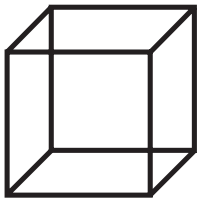
MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE



Copy cube



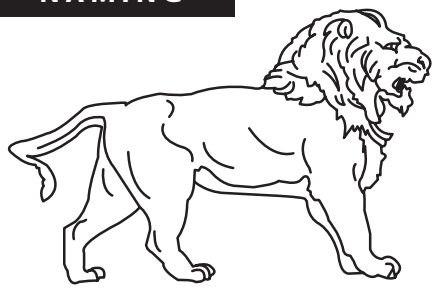
[ ] [ ]

Draw CLOCK (Ten past eleven)
(3 points)

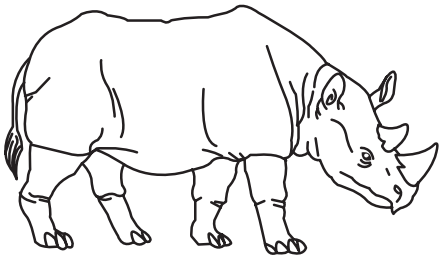
[ ] Contour [ ] Numbers [ ] Hands

POINTS ___/5

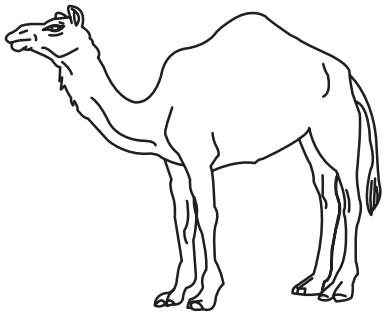
NAMING



[ ]



[ ]



[ ]

___/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

___/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

___/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

___/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]
Optional	Category cue					
	Multiple choice cue					

Points for UNCUED recall only

___/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

___/6

 Version 7.1 **www.mocatest.org** Normal ≥ 26 / 30

TOTAL ___/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

Montreal Cognitive Assessment
(MoCA)

Administration and Scoring Instructions

The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

1. Alternating Trail Making:

Administration: The examiner instructs the subject: *"Please draw a line, going from a number to a letter in ascending order. Begin here* [point to (1)] *and draw a line from 1 then to A then to 2 and so on. End here* [point to (E)]."

Scoring: Allocate one point if the subject successfully draws the following pattern: 1 –A- 2- B- 3- C- 4- D- 5- E, without drawing any lines that cross. Any error that is not immediately self-corrected earns a score of 0.

2. Visuoconstructional Skills (Cube):

Administration: The examiner gives the following instructions, pointing to the **cube**: *"Copy this drawing as accurately as you can, in the space below".*

Scoring: One point is allocated for a correctly executed drawing.

- Drawing must be three-dimensional
- All lines are drawn
- No line is added
- Lines are relatively parallel and their length is similar (rectangular prisms are accepted)

A point is not assigned if any of the above-criteria are not met.

3. Visuoconstructional Skills (Clock):

Administration: Indicate the right third of the space and give the following instructions: *"Draw a **clock**. Put in all the numbers and set the time to 10 after 11".*

Scoring: One point is allocated for each of the following three criteria:

- Contour (1 pt.): the clock face must be a circle with only minor distortion acceptable (e.g., slight imperfection on closing the circle);
- Numbers (1 pt.): all clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour;
- Hands (1 pt.): there must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centred within the clock face with their junction close to the clock centre.

A point is not assigned for a given element if any of the above-criteria are not met.

4. Naming:

Administration: Beginning on the left, point to each figure and say: *"Tell me the name of this animal".*

Scoring: One point each is given for the following responses: (1) camel or dromedary, (2) lion, (3) rhinoceros or rhino.

5. Memory:

Administration: The examiner reads a list of 5 words at a rate of one per second, giving the following instructions: *"This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn't matter in what order you say them".* Mark a check in the allocated space for each word the subject produces on this first trial. When the subject indicates that (s)he has finished (has recalled all words), or can recall no more words, read the list a second time with the following instructions: "*I am going to read the same list for a second time. Try to remember and tell me as many words as you can, including words you said the first time."* Put a check in the allocated space for each word the subject recalls after the second trial.

At the end of the second trial, inform the subject that (s)he will be asked to recall these words again by saying, "*I will ask you to recall those words again at the end of the test."*

Scoring: No points are given for Trials One and Two.

6. Attention:

Forward Digit Span: Administration: Give the following instruction: "*I am going to say some numbers and when I am through, repeat them to me exactly as I said them".* Read the five number sequence at a rate of one digit per second.

Backward Digit Span: Administration: Give the following instruction: "*Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order."* Read the three number sequence at a rate of one digit per second.

Scoring: Allocate one point for each sequence correctly repeated, (*N.B.:* the correct response for the backwards trial is 2-4-7).

Vigilance: Administration: The examiner reads the list of letters at a rate of one per second, after giving the following instruction: "*I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand".*

Scoring: Give one point if there is zero to one errors (an error is a tap on a wrong letter or a failure to tap on letter A).

Serial 7s: Administration: The examiner gives the following instruction: "*Now, I will ask you to count by subtracting seven from 100, and then, keep subtracting seven from your answer until I tell you to stop."* Give this instruction twice if necessary.

Scoring: This item is scored out of 3 points. Give no (0) points for no correct subtractions, 1 point for one correction subtraction, 2 points for two-to-three correct subtractions, and 3 points if the participant successfully makes four or five correct subtractions. Count each correct subtraction of 7 beginning at 100. Each subtraction is evaluated independently; that is, if the participant responds with an incorrect number but continues to correctly subtract 7 from it, give a point for each correct subtraction. For example, a participant may respond "92 – 85 – 78 – 71 – 64" where the "92" is incorrect, but all subsequent numbers are subtracted correctly. This is one error and the item would be given a score of 3.

7. Sentence repetition:

Administration: The examiner gives the following instructions: "*I am going to read you a sentence. Repeat it after me, exactly as I say it* [pause]*:* ***I only know that John is the one to help today.*****"** Following the response, say: "*Now I am going to read you another sentence. Repeat it after me, exactly as I say it* [pause]*:* ***The cat always hid under the couch when dogs were in the room.****"*

Scoring: Allocate 1 point for each sentence correctly repeated. Repetition must be exact. Be alert for errors that are omissions (e.g., omitting "only", "always") and substitutions/additions (e.g., "John is the one who helped today;" substituting "hides" for "hid", altering plurals, etc.).

8. Verbal fluency:

Administration: The examiner gives the following instruction: "*Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will tell you to stop after one minute. Are you ready?* [Pause] *Now, tell me as many words as you can think of that begin with the letter F.* [time for 60 sec]. *Stop."*

Scoring: Allocate one point if the subject generates 11 words or more in 60 sec. Record the subject's response in the bottom or side margins.

9. Abstraction:

Administration: The examiner asks the subject to explain what each pair of words has in common, starting with the example: "*Tell me how an orange and a banana are alike"*. If the subject answers in a concrete manner, then say only one additional time: "*Tell me another way in which those items are alike"*. If the subject does not give the appropriate response (*fruit*), say, "*Yes, and they are also both fruit.*" Do not give any additional instructions or clarification.

After the practice trial, say: "*Now, tell me how a train and a bicycle are alike"*. Following the response, administer the second trial, saying: "*Now tell me how a ruler and a watch are alike"*. Do not give any additional instructions or prompts.

Scoring: Only the last two item pairs are scored. Give 1 point to each item pair correctly answered. The following responses are acceptable:

Train-bicycle = means of transportation, means of travelling, you take trips in both;

Ruler-watch = measuring instruments, used to measure.

The following responses are **not** acceptable: Train-bicycle = they have wheels; Ruler-watch = they have numbers.

10. Delayed recall:

Administration: The examiner gives the following instruction: "*I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember.* Make a check mark (✓) for each of the words correctly recalled spontaneously without any cues, in the allocated space.

Scoring: **Allocate 1 point for each word recalled freely without any cues**.

Optional:

Following the delayed free recall trial, prompt the subject with the semantic category cue provided below for any word not recalled. Make a check mark (✓) in the allocated space if the subject remembered the word with the help of a category or multiple-choice cue. Prompt all non-recalled words in this manner. If the subject does not recall the word after the category cue, give him/her a multiple choice trial, using the following example instruction, "*Which of the following words do you think it was, NOSE, FACE, or HAND?"*

Use the following category and/or multiple-choice cues for each word, when appropriate:

FACE:	category cue: part of the body	multiple choice: nose, face, hand
VELVET:	category cue: type of fabric	multiple choice: denim, cotton, velvet
CHURCH:	category cue: type of building	multiple choice: church, school, hospital
DAISY:	category cue: type of flower	multiple choice: rose, daisy, tulip
RED:	category cue: a colour	multiple choice: red, blue, green

Scoring: **No points are allocated for words recalled with a cue.** A cue is used for clinical information purposes only and can give the test interpreter additional information about the type of memory disorder. For memory deficits due to retrieval failures, performance can be improved with a cue. For memory deficits due to encoding failures, performance does not improve with a cue.

11. Orientation:

Administration: The examiner gives the following instructions: "*Tell me the date today"*. If the subject does not give a complete answer, then prompt accordingly by saying: *"Tell me the [year, month, exact date, and day of the week]."* Then say: *"Now, tell me the name of this place, and which city it is in."*

Scoring: Give one point for each item correctly answered. The subject must tell the exact date and the exact place (name of hospital, clinic, office). No points are allocated if subject makes an error of one day for the day and date.

TOTAL SCORE: Sum all subscores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 30 points. A final total score of 26 and above is considered normal.

STROKE IMPACT SCALE – 16 (SIS-16)

In the past two weeks, how difficult was it to…		Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Could not do at all
a.	Dress the top part of your body	5	4	3	2	1
b.	Bathe yourself?	5	4	3	2	1
c.	Get to the toilet on time?	5	4	3	2	1
d.	Control your bladder (not have an accident)?	5	4	3	2	1
e.	Control your bowels (not have an accident)?	5	4	3	2	1
f.	Stand without losing balance?	5	4	3	2	1
g.	Go shopping?	5	4	3	2	1
h.	Do heave household chores (e.g. vacuum, laundry or yard work)?	5	4	3	2	1
i.	Stay sitting without losing your balance?	5	4	3	2	1
j.	Walk without losing your balance?	5	4	3	2	1
k.	Move from a bed to a chair?	5	4	3	2	1
l.	Walk fast?	5	4	3	2	1
m.	Climb one flight of stairs?	5	4	3	2	1
n.	Walk one block?	5	4	3	2	1
o.	Get in and out of a car?	5	4	3	2	1
p.	Carry heavy objects (e.g. bag of groceries) with your affected hand?	5	4	3	2	1

P.W. Duncan, S.M. Lai, R.K. bode, S. Perera and J. DeRosa. "Stroke Impact Scale-16: A brief assessment of physical function." Neurology 2003;60;291-296.

APPENDIX IV

ARDSNet Ventilator Management Recommendations

Calculation of Predicted Body Weight (PBW) based on sex and height

HEIGHT	PBW	4 ml	5 ml	6 ml	7 ml	8 ml
4' 0" (48)	17.9	72	90	107	125	143
4' 1" (49)	20.2	81	101	121	141	162
4' 2" (50)	22.5	90	113	135	158	180
4' 3" (51)	24.8	99	124	149	174	198
4' 4" (52)	27.1	108	136	163	190	217
4' 5" (53)	29.4	118	147	176	206	235
4' 6" (54)	31.7	127	159	190	222	254
4' 7" (55)	34	136	170	204	238	272
4' 8" (56)	36.3	145	182	218	254	290
4' 9" (57)	38.6	154	193	232	270	309
4' 10" (58)	40.9	164	205	245	286	327
4' 11" (59)	43.2	173	216	259	302	346
5' 0" (60)	45.5	182	228	273	319	364
5' 1" (61)	47.8	191	239	287	335	382
5' 2" (62)	50.1	200	251	301	351	401
5' 3" (63)	52.4	210	262	314	367	419
5' 4" (64)	54.7	219	274	328	383	438
5' 5" (65)	57	228	285	342	399	456
5' 6" (66)	59.3	237	297	356	415	474
5' 7" (67)	61.6	246	308	370	431	493
5' 8" (68)	63.9	256	320	383	447	511
5' 9" (69)	66.2	265	331	397	463	530
5' 10" (70)	68.5	274	343	411	480	548
5' 11" (71)	70.8	283	354	425	496	566
6' 0" (72)	73.1	292	366	439	512	585
6' 1" (73)	75.4	302	377	452	528	603
6' 2" (74)	77.7	311	389	466	544	622
6' 3" (75)	80	320	400	480	560	640
6' 4" (76)	82.3	329	412	494	576	658
6' 5" (77)	84.6	338	423	508	592	677
6' 6" (78)	86.9	348	435	521	608	695
6' 7" (79)	89.2	357	446	535	624	714
6' 8" (80)	91.5	366	458	549	641	732
6' 9" (81)	93.8	375	469	563	657	750
6' 10" (82)	96.1	384	481	577	673	769
6' 11" (83)	98.4	394	492	590	689	787
7' 0" (84)	100.7	403	504	604	705	806

PBW and Tidal Volume for Females

ARDSNet Studies

HEIGHT	PBW	4 ml	5 ml	6 ml	7 ml	8 ml
4' 0" (48)	22.4	90	112	134	157	179
4' 1" (49)	24.7	99	124	148	173	198
4' 2" (50)	27	108	135	162	189	216
4' 3" (51)	29.3	117	147	176	205	234
4' 4" (52)	31.6	126	158	190	221	253
4' 5" (53)	33.9	136	170	203	237	271
4' 6" (54)	36.2	145	181	217	253	290
4' 7" (55)	38.5	154	193	231	270	308
4' 8" (56)	40.8	163	204	245	286	326
4' 9" (57)	43.1	172	216	259	302	345
4' 10" (58)	45.4	182	227	272	318	363
4' 11" (59)	47.7	191	239	286	334	382
5' 0" (60)	50	200	250	300	350	400
5' 1" (61)	52.3	209	262	314	366	418
5' 2" (62)	54.6	218	273	328	382	437
5' 3" (63)	56.9	228	285	341	398	455
5' 4" (64)	59.2	237	296	355	414	474
5' 5" (65)	61.5	246	308	369	431	492
5' 6" (66)	63.8	255	319	383	447	510
5' 7" (67)	66.1	264	331	397	463	529
5' 8" (68)	68.4	274	342	410	479	547
5' 9" (69)	70.7	283	354	424	495	566
5' 10" (70)	73	292	365	438	511	584
5' 11" (71)	75.3	301	377	452	527	602
6' 0" (72)	77.6	310	388	466	543	621
6' 1" (73)	79.9	320	400	479	559	639
6' 2" (74)	82.2	329	411	493	575	658
6' 3" (75)	84.5	338	423	507	592	676
6' 4" (76)	86.8	347	434	521	608	694
6' 5" (77)	89.1	356	446	535	624	713
6' 6" (78)	91.4	366	457	548	640	731
6' 7" (79)	93.7	375	469	562	656	750
6' 8" (80)	96	384	480	576	672	768
6' 9" (81)	98.3	393	492	590	688	786
6' 10" (82)	100.6	402	503	604	704	805
6' 11" (83)	102.9	412	515	617	720	823
7' 0" (84)	105.2	421	526	631	736	842

PBW and Tidal Volume for Males

ARDSNet Studies

Plateau Pressure

PLATEAU PRESSURE GOAL: ≤ 30 cm H_2O

Check Pplat (0.5 second inspiratory pause), at least q 4h and after each change in PEEP or V_T.

If Pplat > 30 cm H_2O: decrease V_T by 1ml/kg steps (minimum = 4 ml/kg).

If Pplat < 25 cm H_2O and V_T< 6 ml/kg, increase V_T by 1 ml/kg until Pplat > 25 cm H_2O or V_T = 6 ml/kg.

If Pplat < 30 and breath stacking or dys-synchrony occurs: may increase V_T in 1ml/kg increments to 7 or 8 ml/kg if Pplat remains $\leq$ 30 cm H_2O.

Suggested incremental Fi O_2/PEEP combinations to achieve an oxygenation goal of PaO_2 55-8- mmHg or SpO_2 88-95%

Lower PEEP/higher FiO2

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12

FiO_2	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	14	14	14	16	18	18-24

Higher PEEP/lower FiO2

FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5
PEEP	5	8	10	12	14	14	16	16

FiO_2	0.5	0.5-0.8	0.8	0.9	1.0	1.0
PEEP	18	20	22	22	22	24

APPENDIX VII

Berlin Criteria for ARDS

Berlin criteria to define ARDS and its severity

(JAMA. 2012;307 (23):2526-2533).

The Berlin Definition of ARDS requires that all of the following criteria be present to diagnose ARDS:

- Respiratory symptoms must have begun within one week of a known clinical insult, or the patient must have new or worsening symptoms during the past week.

- Bilateral opacities consistent with pulmonary edema must be present on a chest radiograph or CT scan. These opacities must not be fully explained by pleural effusions, lobar collapse, lung collapse, or pulmonary nodules.

- The patient's respiratory failure must not be fully explained by cardiac failure or fluid overload. An objective assessment (an echocardiography) to exclude hydrostatic pulmonary edema is required if no risk factors for ARDS are present.

- A moderate to severe impairment of oxygenation must be present, as defined by the ratio of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2). The severity of the hypoxemia defines the severity of the ARDS as follows:
    - Mild ARDS – The PaO_2/FiO_2 is >200 mmHg, but ≤300 mmHg, on ventilator settings that include positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥5 cm H_2O.
    - Moderate ARDS – The PaO_2/FiO_2 is >100 mmHg, but ≤200 mmHg, on ventilator settings that include PEEP ≥5 cm H_2O.
    - Severe ARDS – The PaO_2/FiO_2 is ≤100 mmHg on ventilators setting that include PEEP ≥5 cm H_2O.

ONLINE FIRST

Acute Respiratory Distress Syndrome
The Berlin Definition

The ARDS Definition Task Force*

The acute respiratory distress syndrome (ARDS) was defined in 1994 by the American-European Consensus Conference (AECC); since then, issues regarding the reliability and validity of this definition have emerged. Using a consensus process, a panel of experts convened in 2011 (an initiative of the European Society of Intensive Care Medicine endorsed by the American Thoracic Society and the Society of Critical Care Medicine) developed the Berlin Definition, focusing on feasibility, reliability, validity, and objective evaluation of its performance. A draft definition proposed 3 mutually exclusive categories of ARDS based on degree of hypoxemia: mild (200 mm Hg $<$ $Pao_2/Fio_2 \leq$ 300 mm Hg), moderate (100 mm Hg $<$ $Pao_2/Fio_2 \leq$ 200 mm Hg), and severe ($Pao_2/Fio_2 \leq$ 100 mm Hg) and 4 ancillary variables for severe ARDS: radiographic severity, respiratory system compliance ($\leq$40 mL/cm H_2O), positive end-expiratory pressure ($\geq$10 cm H_2O), and corrected expired volume per minute ($\geq$10 L/min). The draft Berlin Definition was empirically evaluated using patient-level meta-analysis of 4188 patients with ARDS from 4 multicenter clinical data sets and 269 patients with ARDS from 3 single-center data sets containing physiologic information. The 4 ancillary variables did not contribute to the predictive validity of severe ARDS for mortality and were removed from the definition. Using the Berlin Definition, stages of mild, moderate, and severe ARDS were associated with increased mortality (27%; 95% CI, 24%-30%; 32%; 95% CI, 29%-34%; and 45%; 95% CI, 42%-48%, respectively; $P < .001$) and increased median duration of mechanical ventilation in survivors (5 days; interquartile [IQR], 2-11; 7 days; IQR, 4-14; and 9 days; IQR, 5-17, respectively; $P < .001$). Compared with the AECC definition, the final Berlin Definition had better predictive validity for mortality, with an area under the receiver operating curve of 0.577 (95% CI, 0.561-0.593) vs 0.536 (95% CI, 0.520-0.553; $P < .001$). This updated and revised Berlin Definition for ARDS addresses a number of the limitations of the AECC definition. The approach of combining consensus discussions with empirical evaluation may serve as a model to create more accurate, evidence-based, critical illness syndrome definitions and to better inform clinical care, research, and health services planning.

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VALID AND RELIABLE DEFINITIONS are essential to conduct epidemiological studies successfully and to facilitate enrollment of a consistent patient phenotype into clinical trials.[1] Clinicians also need such definitions to implement the results of clinical trials, discuss prognosis with families, and plan resource allocation.

Following the initial description of acute respiratory distress syndrome (ARDS) by Ashbaugh et al[2] in 1967, multiple definitions were proposed and used until the 1994 publication of the American-European Consensus Conference (AECC) definition.[3] The AECC defined ARDS as the acute onset of hypoxemia (arterial partial pressure of oxygen to fraction of inspired oxygen [Pao_2/Fio_2] $\leq$ 200 mm Hg) with bilateral infiltrates on frontal chest radiograph, with no evidence of left atrial hypertension. A new overarching entity—acute lung injury (ALI)—was also described, using similar criteria but with less severe hypoxemia ($Pao_2/Fio_2 \leq$ 300 mm Hg).[3]

The AECC definition was widely adopted by clinical researchers and clinicians and has advanced the knowledge of ARDS by allowing the acquisition of clinical and epidemiological data, which in turn have led to improvements in the ability to care for patients with ARDS. However, after 18 years of applied research, a number of issues regarding various criteria of the AECC definition have emerged, including a lack of explicit criteria for defining acute, sensitivity of Pao_2/Fio_2 to different ventilator settings, poor reliability of the chest radiograph criterion, and difficulties distinguishing hydrostatic edema (TABLE 1).[4]

For editorial comment see p 2542.

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For these reasons, and because all disease definitions should be reviewed periodically, the European Society of Intensive Care Medicine convened an international expert panel to revise the ARDS definition, with endorsement from the American Thoracic Society and the Society of Critical Care Medicine. The objectives were to update the definition using new data (epidemiological, physiological, and clinical trials) to address the current limitations of the AECC definition and explore other defining variables.

Table 1. The AECC Definition[3]—Limitations and Methods to Address These in the Berlin Definition

	AECC Definition	AECC Limitations	Addressed in Berlin Definition
Timing	Acute onset	No definition of acute[4]	Acute time frame specified
ALI category	All patients with PaO_2/FIO_2 <300 mm Hg	Misinterpreted as PaO_2/FIO_2 = 201-300, leading to confusing ALI/ARDS term	3 Mutually exclusive subgroups of ARDS by severity ALI term removed
Oxygenation	PaO_2/FIO_2 ≤300 mm Hg (regardless of PEEP)	Inconsistency of PaO_2/FIO_2 ratio due to the effect of PEEP and/or FIO_2[5-7]	Minimal PEEP level added across subgroups FIO_2 effect less relevant in severe ARDS group
Chest radiograph	Bilateral infiltrates observed on frontal chest radiograph	Poor interobserver reliability of chest radiograph interpretation[8,9]	Chest radiograph criteria clarified Example radiographs created[a]
PAWP	PAWP ≤18 mm Hg when measured or no clinical evidence of left atrial hypertension	High PAWP and ARDS may coexist[10,11] Poor interobserver reliability of PAWP and clinical assesments of left atrial hypertension[12]	PAWP requirement removed Hydrostatic edema not the primary cause of respiratory failure Clinical vignettes created[a] to help exclude hydrostatic edema
Risk factor	None	Not formally included in definition[4]	Included When none identified, need to objectively rule out hydrostatic edema

Abbreviations: AECC, American-European Consensus Conference; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; FIO_2, fraction of inspired oxygen; PaO_2, arterial partial pressure of oxygen; PAWP, pulmonary artery wedge pressure; PEEP, positive end-expiratory pressure.
[a]Available on request.

Methods

Consensus Process. Three co-chairs were appointed by the European Society of Intensive Care Medicine, who in turn selected panelists based on their work in the area of ARDS and to ensure geographic representation from both Europe and North America. An overview of the consensus process used by the panel is outlined in the FIGURE. In revising the definition of ARDS, the panel emphasized feasibility, reliability, face validity (ie, how clinicians recognize ARDS), and predictive validity (ie, ability to predict response to therapy, outcomes, or both). In addition, the panel determined that any revision of the definition should be compatible with the AECC definition to facilitate interpretation of previous studies. After initial preparations and an in-person consensus discussion, a draft definition was proposed,[13] which underwent empirical evaluation. The definition was further refined through consensus discussion informed by these empirical data.

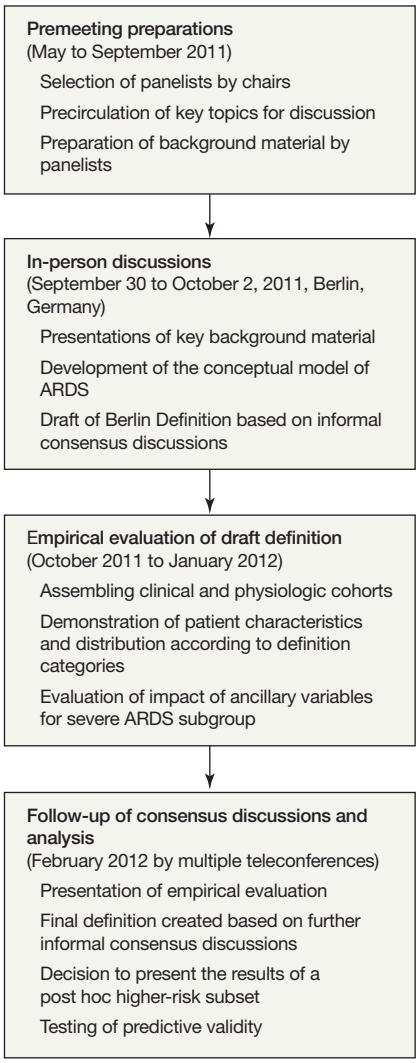
Empirical Evaluation of Draft Definition.

Cohort Assembly. Through the review of the literature presented at the consensus meeting, discussions with other experts, and review of personal files, the panel identified studies that met the following eligibility criteria: (1) large, multicenter prospective cohorts, including consecutive patients or randomized trials, or smaller, single-center prospective studies with unique radiological or physiological data that enrolled adult patients with ALI as defined by AECC; (2) studies collected granular data necessary to apply the individual criteria of both the draft Berlin Definition and the AECC definition; and (3) authors of these original studies were willing to share data and collaborate. The panel identified 7 distinct data sets (4 multicenter clinical studies for the clinical database[14-17] and 3 single-center physiological studies for the physiological database[18-20]) that met these criteria. Further details of these studies are included in the eMethods (http://www.jama.com).

Variables. Studies provided data on hospital or 90-day mortality. Ventilator-free days at 28 days after the diagnosis of ALI were calculated as a composite measure of mortality and duration of mechanical ventilation. Duration of mechanical ventilation in survivors was selected as an indirect marker of severity of lung injury because this outcome is not biased by mortality or decisions related to the withdrawal of life-sustaining treatments.[21] Progression of severity of ARDS within 7 days was assessed using the longitudinal data collected within each cohort. We distinguished patients with more extensive involvement on the frontal chest radiograph (3 or 4 quadrants) from those with the minimal criterion of "bilateral opacities" (2 quadrants).

Static compliance of the respiratory system (C_{RS}) was calculated as tidal volume (mL) divided by plateau pressure (cm H_2O) minus positive end-expiratory pressure (PEEP) (cm H_2O). The corrected expired volume per minute ($\dot{V}E_{CORR}$) was calculated as the measured minute ventilation multiplied by the arterial partial pressure of carbon dioxide ($PaCO_2$) divided by 40 mm Hg.[22] Total lung weight was estimated from quantitative computed tomography (CT) images.[23] Shunt was calculated at one site as previously reported.[24]

Figure. Outline of Consensus Process



ARDS indicates acute respiratory distress syndrome.

Analytic Framework and Statistical Methods. The analytic framework for evaluating the draft Berlin ARDS Definition was to (1) determine the distribution of patient characteristics across the defined severity categories; (2) evaluate the value of proposed ancillary variables (more severe radiographic criterion, higher PEEP levels, static respiratory compliance, and $\dot{V}E_{CORR}$) in defining the severe ARDS subgroup in the draft definition; (3) determine the predictive validity for mortality of the final Berlin Definition; and (4) compare the final Berlin Definition to the AECC definition. In addition, in a post hoc analysis, we sought thresholds for C_{RS} and $\dot{V}E_{CORR}$ that would identify a severe group of patients with ARDS who had more than 50% mortality and include more than 10% of the study population.

We did not evaluate other PaO_2/FIO_2 cutoffs or the requirement of a minimum PEEP level (5 cm H_2O) as they were selected by the panel using face validity criteria and to ensure compatibility with prior definitions. Similarly, we did not explore other variables that might improve predictive validity, such as age and severity of nonpulmonary organ failure, because they were not specific to the definition of ARDS.[25]

To compare the predictive validity of the AECC definition and the Berlin Definition, we used the area under the receiver operating curve (AUROC or C statistic) in logistic regression models of mortality with a dummy variable for the ARDS definition categories.[26] Because this technique requires independent categories to create the dummy variable and the AECC definition for ARDS is a subset of ALI, we could not compare the AECC definition as specified. Therefore, we modified the AECC definition and divided ALI into the independent categories of ALI non-ARDS (200 mm Hg $<$ $PaO_2/FIO_2 \leq$ 300 mm Hg) and ARDS alone ($PaO_2/FIO_2 \leq$ 200 mm Hg). Although the category of ALI non-ARDS is not explicitly described by the AECC, it has been used by many investigators.[27,28]

P values for categorical variables were calculated with the χ^2 test; *P* values for continuous variables were estimated with the *t* test, Mann-Whitney, analysis of variance, or Kruskal-Wallis, depending on the distribution and number of variables. The receiver operating curve statistical analyses were performed by using MedCalc for Windows version 12.1.4.0 (MedCalc Software) and other statistical tests were performed with SAS/STAT for Windows version 9.2 (SAS Institute Inc). Statistical significance was assessed at the 2-sided $P < .05$ level.

Results

Draft Consensus Definition.

The ARDS Conceptual Model. The panel agreed that ARDS is a type of acute diffuse, inflammatory lung injury, leading to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue. The clinical hallmarks are hypoxemia and bilateral radiographic opacities, associated with increased venous admixture, increased physiological dead space, and decreased lung compliance. The morphological hallmark of the acute phase is diffuse alveolar damage (ie, edema, inflammation, hyaline membrane, or hemorrhage).[29]

Draft Definition Criteria. Following 2 days of consensus discussions, the panel proposed a draft definition with 3 mutually exclusive severity categories (mild, moderate, and severe) of ARDS. A set of ancillary variables was proposed to further characterize severe ARDS and these were explicitly specified for further empirical evaluation.[13]

Timing. Most patients with ARDS are identified within 72 hours of recognition of the underlying risk factor, with nearly all patients with ARDS identified within 7 days.[30] Accordingly, for a patient to be defined as having ARDS, the onset must be within 1 week of a known clinical insult or new or worsening respiratory symptoms.

Chest Imaging. The panel retained bilateral opacities consistent with pulmonary edema on the chest radiograph as defining criteria for ARDS, but also explicitly recognized that these findings could be demonstrated on CT scan instead of chest radiograph. More extensive opacities (ie, 3 or 4 quadrants on chest radiograph) were proposed as part of the severe ARDS category and identified for further evaluation.

Origin of Edema. Given the declining use of pulmonary artery catheters and because hydrostatic edema in the form of cardiac failure or fluid overload may coexist with ARDS,[10,11] the pulmonary artery wedge pressure criterion was removed from the defini-

Table 2. Exploration of Proposed Variables to Define Severe ARDS[a]

Severe ARDS Definition	Mild		Moderate		Severe	
	No. (%) of Patients	% Mortality (95% CI)	No. (%) of Patients	% Mortality (95% CI)	No. (%) of Patients	% Mortality (95% CI)
Consensus panel draft						
Pa_{O_2}/F_{IO_2} ≤100 mm Hg + chest radiograph of 3 or 4 quadrants + PEEP ≥10 cm H_2O + (C_{RS} ≤40 mL/cm H_2O or $\dot{V}E_{CORR}$ ≥10 L/min)	220 (22)	27 (24-30)	2344 (64)	35 (33-36)	507 (14)	45 (40-49)[b]
Consensus panel final						
Pa_{O_2}/F_{IO_2} ≤100 mm Hg	220 (22)	27 (24-30)	1820 (50)	32 (29-34)	1031 (28)	45 (42-48)[b,c]

Abbreviations: ARDS, acute respiratory distress syndrome; C_{RS}, compliance of the respiratory system; F_{IO_2}, fraction of inspired oxygen; Pa_{O_2}, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure; $\dot{V}E_{CORR}$, corrected expired volume per minute.

[a] The moderate group includes patients with Pa_{O_2}/F_{IO_2} ≤200 mm Hg and patients with Pa_{O_2}/F_{IO_2} ≤100 mm Hg who do not meet the additional criteria for severe ARDS in the draft definition. All patients are receiving at least 5 cm H_2O PEEP and have bilateral infiltrates on chest radiograph.

[b] $P < .001$ comparing mortality across stages of ARDS (mild, moderate, severe) for draft and final definitions.

[c] $P = .97$ comparing mortality in consensus draft severe ARDS to consensus final severe ARDS definitions.

tion. Patients may qualify as having ARDS as long as they have respiratory failure not fully explained by cardiac failure or fluid overload as judged by the treating physician using all available data. If no ARDS risk factor (eTable 1) is apparent, some objective evaluation (eg, with echocardiography) is required to help eliminate the possibility of hydrostatic edema.

Oxygenation. The term *acute lung injury* as defined by the AECC was removed, due to the perception that clinicians were misusing this term to refer to a subset of patients with less severe hypoxemia rather than its intended use as an inclusive term for all patients with the syndrome. Positive end-expiratory pressure can markedly affect Pa_{O_2}/F_{IO_2}[5,6]; therefore, a minimum level of PEEP (5 cm H_2O), which can be delivered noninvasively in mild ARDS, was included in the draft definition of ARDS. A minimum PEEP level of 10 cm H_2O was proposed and empirically evaluated for the severe ARDS category.

Additional Physiologic Measurements. Compliance of the respiratory system largely reflects the degree of lung volume loss.[2] Increased dead space is common in patients with ARDS and is associated with increased mortality.[24] However, because the measurement of dead space is challenging, the panel chose minute ventilation standardized at a Pa_{CO_2} of 40 mm Hg ($\dot{V}E_{CORR}$ = minute ventilation × Pa_{CO_2}/40) as a surrogate.[22] The draft definition of severe ARDS included the requirement of either a low respiratory system compliance (<40 mL/cm H_2O), a high $\dot{V}E_{CORR}$ (>10 L/min), or both. These variables were identified for further study during the evaluation phase.

The panel considered a number of additional measures to improve specificity and face validity for the increased pulmonary vascular permeability and loss of aerated lung tissue that are the hallmarks of ARDS, including CT scanning, and inflammatory or genetic markers (eTable 2). The most common reasons for exclusion of these measures were lack of routine availability, lack of safety of the measure in critically ill patients, or a lack of demonstrated sensitivity, specificity, or both for use as a defining characteristic for ARDS.

Empirical Evaluation of the Draft Definition.

Patients. A total of 4188 patients in the clinical database had sufficient data to classify as having ARDS by the AECC definition. Of these patients, 518 (12%) could not be classified by the draft Berlin Definition because PEEP was missing or was less than 5 cm H_2O. Patients who could not be classified by the draft Berlin Definition had a mortality rate of 35% (95% CI, 31%-39%), a median (interquartile range [IQR]) of 19 (1-25) ventilator-free days, and a median (IQR) duration of mechanical ventilation in survivors of 4 (2-8) days. These patients were excluded from analyses of the draft Berlin Definition and comparisons between the AECC definition and the draft Berlin Definition.

Compared with patients from the population-based cohorts, patients from clinical trials and the academic centers cohorts were younger, had more severe hypoxemia, and had more opacities on chest radiographs. The cohort of patients from the clinical trials had the lowest mortality, likely reflecting the inclusion and exclusion criteria of the trials.[31] The cohort of patients from academic centers had the highest mortality and the lowest percentage of trauma patients, reflecting the referral population (eTable 3).

There were 269 patients in the physiological database with sufficient data to classify ARDS by the AECC definition, although the numbers of patients in each cohort were small. Patients in the Turin cohort had worse Pa_{O_2}/F_{IO_2} ratios and had higher mortality than the other studies (eTable 4).

Evaluation of Ancillary Variables. The draft Berlin Definition for severe ARDS that included a Pa_{O_2}/F_{IO_2} of 100 mm Hg or less, chest radiograph with 3 or 4 quadrants with opacities, PEEP of at least 10 cm H_2O, and either a C_{RS} of 40 mL/cm H_2O or less or a $\dot{V}E_{CORR}$ of at least 10 L/min identified a smaller set of patients with identical mortality to the simpler severe ARDS category of Pa_{O_2}/F_{IO_2} of 100 mm Hg or less (**TABLE 2**). To address the possibility that the C_{RS} and $\dot{V}E_{CORR}$ thresholds might be different in patients with higher body weight, we evaluated weight-adjusted cutoffs for

these variables in one of the cohorts. There was no significant difference in the predictive validity of the weight-adjusted criteria. The consensus panel reviewed these results and considered the lack of evidence for predictive validity of these ancillary variables and their potential contribution to face validity and construct validity and decided to use the simpler definition for severe ARDS that relied on oxygenation alone.

The Berlin Definition. The final Berlin Definition of ARDS is shown in TABLE 3. Twenty-two percent (95% CI, 21%-24%) of patients met criteria for mild ARDS (which is comparable with the ALI non-ARDS category of the AECC definition; TABLE 4), 50% (95% CI, 48%-51%) of patients met criteria for moderate ARDS, and 28% (95% CI, 27%-30%) of patients met criteria for severe ARDS. Mortality increased with stages of ARDS from mild (27%; 95% CI, 24%-30%) to moderate (32%; 95% CI, 29%-34%) to severe (45%; 95% CI, 42%-48%). Median (IQR) ventilator-free days declined with stages of ARDS from mild (20 [1-25] days) to moderate (16 [0-23] days) to severe (1 [0-20] day). Median (IQR) duration of mechanical ventilation in survivors increased with stages of ARDS from mild (5 [2-11] days) to moderate (7 [4-14] days) to severe (9 [5-17] days).

Using the Berlin Definition, 29% (95% CI, 26%-32%) of patients with mild ARDS at baseline progressed to moderate ARDS and 4% (95% CI, 3%-6%) progressed to severe ARDS within 7 days; and 13% (95% CI, 11%-14%) of patients with moderate ARDS at baseline progressed to severe ARDS within 7 days. All differences between outcome variables across categories of modified AECC (ALI non-ARDS and ARDS alone) and across categories of Berlin Definition (mild, moderate, and severe) were statistically significant ($P<.001$).

Compared with the AECC definition, the final Berlin Definition had better predictive validity for mortality with an AUROC of 0.577 (95% CI, 0.561-0.593) vs 0.536 (95% CI, 0.520-0.553; $P<.001$), with the difference in AUROC of 0.041 (95% CI, 0.030-0.050). To ensure that missing PEEP data in one of the cohorts did not bias the results, the regression analysis was repeated without this cohort and yielded similar results.

The Berlin Definition performed similarly in the physiological database as in the clinical database (TABLE 5, eFigure 1, and eFigure 2). Twenty-five percent (95% CI, 20%-30%) of patients met criteria for mild ARDS, 59% (95% CI, 54%-66%) of patients met criteria for moderate ARDS, and 16% (95% CI, 11%-21%) of patients met criteria for severe ARDS. Mortality increased with stages of ARDS from mild (20%; 95% CI, 11%-31%) to moderate (41%; 95% CI, 33%-49%) to severe (52%; 95% CI, 36%-68%), with $P=.001$ for differences in mortality across stages of ARDS. Median (IQR) ventilator-free days declined with stages of ARDS from mild

Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg $<$ Pao_2/Fio_2 $\leq$ 300 mm Hg with PEEP or CPAP $\geq$5 cm H_2O[c]
Moderate	100 mm Hg $<$ Pao_2/Fio_2 $\leq$ 200 mm Hg with PEEP $\geq$5 cm H_2O
Severe	Pao_2/Fio_2 $\leq$ 100 mm Hg with PEEP $\geq$5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; Fio_2, fraction of inspired oxygen; Pao_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.
[a] Chest radiograph or computed tomography scan.
[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [Pao_2/Fio_2 × (barometric pressure/760)].
[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Table 4. Predictive Validity of ARDS Definitions in the Clinical Database

	Modified AECC Definition[a]		Berlin Definition ARDS[a]		
	ALI Non-ARDS	ARDS	Mild	Moderate	Severe
No. (%) [95% CI] of patients	1001 (24) [23-25]	3187 (76) [75-77]	819 (22) [21-24]	1820 (50) [48-51]	1031 (28) [27-30]
Progression in 7 d from mild, No. (%) [95% CI]		336 (34) [31-37]		234 (29) [26-32]	33 (4) [3-6]
Progression in 7 d from moderate, No. (%) [95% CI]					230 (13) [11-14]
Mortality, No. (%) [95% CI][b]	263 (26) [23-29]	1173 (37) [35-38]	220 (27) [24-30]	575 (32) [29-34]	461 (45) [42-48]
Ventilator-free days, median (IQR)[b]	20 (2-25)	12 (0-22)	20 (1-25)	16 (0-23)	1 (0-20)
Duration of mechanical ventilation in survivors, median (IQR), d[b]	5 (2-10)	7 (4-14)	5 (2-11)	7 (4-14)	9 (5-17)

Abbreviations: AECC, American-European Consensus Conference; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; Fio_2, fraction of inspired oxygen; IQR, interquartile range; Pao_2, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure.
[a] The definitions are the following for ALI non-ARDS (200 mm Hg $<$ Pao_2/Fio_2 $\leq$ 300 mm Hg, regardless of PEEP), ARDS (Pao_2/Fio_2 $\leq$ 200 mm Hg, regardless of PEEP), mild Berlin Definition (200 mm Hg $<$ Pao_2/Fio_2 $\leq$ 300 mm Hg with PEEP $\geq$5 cm H_2O), moderate Berlin Definition (100 mm Hg $<$ Pao_2/Fio_2 $\leq$ 200 mm Hg with PEEP $\geq$5 cm H_2O), and severe Berlin Definition (Pao_2/Fio_2 $\leq$ 100 mm Hg with PEEP $\geq$5 cm H_2O).
[b] Comparisons of mortality, ventilator-free days, and duration of mechanical ventilation in survivors across categories of modified AECC (ALI non-ARDS and ARDS) and across categories of Berlin Definition (mild, moderate, and severe) are all statistically significant ($P<.001$).

Table 5. Predictive Validity of ARDS Definitions in the Physiologic Database

	Modified AECC Definition[a]		Berlin Definition ARDS[a]		
	ALI Non-ARDS	ARDS	Mild	Moderate	Severe
No. (%) [95% CI] of patients	66 (25) [19-30]	203 (75) [70-80]	66 (25) [20-30]	161 (59) [54-66]	42 (16) [11-21]
Mortality, No. (%) [95% CI][b]	13 (20) [11-31]	84 (43) [36-50]	13 (20) [11-31]	62 (41) [33-49]	22 (52) [36-68]
Ventilator-free days					
Median (IQR)	8.5 (0-23.5)	0 (0-16.0)	8.5 (0-23.5)	0 (0-16.5)	0 (0-6.5)
Missing, No.	10	26	10	25	1
Duration of mechanical ventilation in survivors, median (IQR), d	6.0 (3.3-20.8)	13.0 (5.0-25.5)	6.0 (3.3-20.8)	12.0 (5.0-19.3)	19.0 (9.0-48.0)
Lung weight, mg[c]					
Mean (SD)	1371 (360.4)	1602 (508.1)	1371 (360.4)	1556 (469.7)	1828 (630.2)
Missing, No.	16	48	16	32	16
Shunt, mean (SD), %[c,d]	21 (21)	32 (13)	21 (12)	29 (11)	40 (16)

Abbreviations: AECC, American-European Consensus Conference; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; F_{IO_2}, fraction of inspired oxygen; IQR, interquartile range; Pa_{O_2}, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure.

[a] The definitions are the following for ALI non-ARDS (200 mm Hg $<$ $Pa_{O_2}/F_{IO_2} \leq$ 300 mm Hg, regardless of PEEP), ARDS ($Pa_{O_2}/F_{IO_2} \leq$ 200 mm Hg, regardless of PEEP), mild Berlin Definition (200 mm Hg $<$ $Pa_{O_2}/F_{IO_2} \leq$ 300 mm Hg with PEEP $\geq$5 cm H_2O), moderate Berlin Definition (100 mm Hg $<$ $Pa_{O_2}/F_{IO_2} \leq$ 200 mm Hg with PEEP $\geq$5 cm H_2O), and severe Berlin Definition ($Pa_{O_2}/F_{IO_2} \leq$ 100 mm Hg with PEEP $\geq$5 cm H_2O).

[b] Eight patients are missing in the moderate Berlin Definition ARDS group. $P = .001$ for difference in mortality across Berlin stages of ARDS.

[c] Comparisons of lung weight and shunt across categories of modified AECC (ALI non-ARDS and ARDS) and across categories of Berlin Definition (mild, moderate, and severe) are statistically significant ($P < .001$).

[d] Only available at 1 site.

(8.5 [0-23.5] days) to moderate (0 [0-16.5] days) to severe (0 [0-6.5] days), with $P = .003$ for differences in ventilator-free days across stages of ARDS. Median (IQR) duration of mechanical ventilation in survivors increased with stages of ARDS from mild (6.0 [3.3-20.8] days) to moderate (12.0 [5.0-19.3] days) to severe (19.0 [9.0-48.0] days), with $P = .045$ for differences in duration of mechanical ventilation in survivors across stages of ARDS.

Using the Berlin Definition, stages of mild, moderate, and severe ARDS had increased mean lung weight by CT scan (1371 mg; 95% CI, 1268-1473; 1556 mg; 95% CI, 1474-1638; and 1828 mg; 95% CI, 1573-2082; respectively) and increased mean shunt (21%; 95% CI, 16%-26%; 29%; 95% CI, 26%-32%; and 40%; 95% CI, 31%-48%; respectively). Comparisons of lung weight and shunt (from the single site providing these data) across categories of modified AECC (ALI non-ARDS and ARDS alone) and across categories of Berlin Definition (mild, moderate, and severe) were statistically significant ($P < .001$) (Table 5, eFigure 3, and eFigure 4).

In a post hoc analysis, combining a Pa_{O_2}/F_{IO_2} of 100 mm Hg or less with either a C_{rs} of 20 mL/cm H_2O or less or a $\dot{V}E_{CORR}$ of at least 13 L/min identified a higher-risk subgroup among patients with severe ARDS that included 15% of the entire ARDS population and had a mortality of 52% (95% CI, 48%-56%). Patients with severe ARDS who did not meet the higher-risk subset criteria included 13% of the entire ARDS population and had a mortality rate of 37% (95% CI, 33%-41%). The difference between the mortality of patients with higher-risk severe ARDS and patients with severe ARDS who did not meet these criteria was statistically significant ($P < .001$).

Comment

Developing and disseminating formal definitions for clinical syndromes in critically ill patients are essential for research and clinical practice. Although previous proposals have relied solely on the consensus process, this is to our knowledge the first attempt in critical care to link an international consensus panel endorsed by professional societies with an empirical evaluation.

The draft Berlin Definition classified patients with ARDS into 3 independent categories but relied on ancillary variables (severity of chest radiograph, PEEP $\geq$10 cm H_2O, C_{RS} $\leq$40 mL/cm H_2O, and $\dot{V}E_{CORR}$ $\geq$10 L/min) in addition to oxygenation to define the severe ARDS group. When the ancillary variables selected by the panel were subjected to evaluation, these parameters did not identify a group of patients with higher mortality and were excluded from the final Berlin Definition after further consensus discussion. Without this evaluation, a needlessly complex ARDS definition would have been proposed. However, static respiratory system compliance and an understanding of minute ventilation are important variables for clinicians to consider in managing patients with ARDS, even though those variables were not included as part of the definition.[32]

The Berlin Definition addresses some of the limitations of the AECC definition, including clarification of the exclusion of hydrostatic edema and adding minimum ventilator settings, and provides slight improvement in predictive validity. Our study presents data on the outcomes of patients with ARDS defined according to the Berlin Definition in a large heterogeneous cohort of patients including patients managed with modern approaches to lung protective ventilation. Estimates of the prevalence and clinical outcomes of mild, moderate, and severe ARDS can be assessed from this database for research and health services planning.

Acute respiratory distress syndrome is a heterogeneous syndrome with com-

plex pathology and mechanisms. The proposed definition does not resolve this problem. Investigators may choose to design future trials using 1 or more of the ARDS subgroups as a base study population, which may be further refined using criteria specific to the putative mechanism of action of the intervention (eg, IL-6 levels for an anti–IL-6 trial or more stringent hypoxemia criteria for a study on extracorporeal membrane oxygenation). Furthermore, some variables that were excluded from the Berlin Definition because of current feasibility and lack of data on operational characteristics may become more useful in the future. We anticipate that clinical research using our model of definition development will be used to revise the definition in the future.

There are limitations to our approach. First, although the Berlin Definition had statistically significantly superior predictive validity for mortality compared with the modified AECC definition, the magnitude of this difference and the absolute values of the AUROC are small and would be clinically unimportant if the Berlin Definition was designed as a clinical prediction tool. However, predictive validity for outcome is only one criterion for evaluating a syndrome definition and the purpose of the Berlin Definition is not a prognostication tool.[33] Although the Berlin Definition was developed with a framework including these criteria, we did not empirically evaluate face validity, content validity, reliability, feasibility, or success at identifying patients for clinical trial enrollment.

Second, it is possible that our results are not generalizable because of the data sets we studied. This seems unlikely because patients from a broad range of populations, including clinical trials, academic centers, and community patients, were included in the analyses.

Third, some variables (eg, C_{RS} and PEEP) were missing in some patients in the data sets we used, either due to the mode of mechanical ventilation that precluded their measurement or the practicalities of population-based research. However, bias due to cohort selection or missing data seem unlikely because our results were robust to sensitivity analyses that excluded individual cohorts.

Fourth, it is possible that the ancillary variables did not identify a higher-risk subset because the number of quadrants on the chest radiograph cannot be assessed reliably, PEEP was not used in a predictable fashion, or C_{RS} and $\dot{V}E_{CORR}$ were not accurately measured. However, if this is true, it is likely also to be true in future studies and in clinical practice because the study database was constructed from clinical trial, academic, and community sites reflecting practice in the real world of clinical research. In addition, we evaluated PEEP and C_{RS} as used by clinicians in practice and not as a test of prespecified ventilator settings that may be better than the variables evaluated herein, but may not be practical, particularly in observational cohort studies.[5,6]

Fifth, because our study was not an exercise in developing a prognostic model for ARDS, we only considered the variables and cutoffs proposed by the consensus panel. We could not compare this definition directly to the AECC definition because the categories of that definition overlap. It is possible that the outcomes as well as the relative proportion of patients within each category of ARDS will change if the underlying epidemiology of the syndrome evolves due to changes in clinical practice or risk factors.[34] This is particularly true for the post hoc higher-risk subset reported, for which the cut points were derived from the data sets.

Conclusion

In conclusion, we developed a consensus draft definition for ARDS with an international panel using a framework that focused on feasibility, reliability, and validity. We tested that definition using empirical data on clinical outcome, radiographic findings, and physiological measures from 2 large databases constructed from 7 contributing sources to assess the predictive value of ancillary variables, refine the draft definition, and compare the predictive validity of the definition to the existing AECC definition. This approach for developing the Berlin Definition for ARDS may serve as an example for linking consensus definition activities with empirical research to better inform clinical care, research, and health services planning.

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Additional Contributions: Salvatore Maggiore, MD, PhD (Department of Anesthesiology and Intensive Care, Agostino Gemelli University Hospital, Università Cattolica del Sacro Cuore, Rome, Italy), and Anders Larsson, MD, PhD (Department of Surgical Sciences, Anesthesiology and Critical Care Medicine, Uppsala University, Uppsala, Sweden), attended the roundtable as representatives of the European Society of Intensive Care Medicine. Drs Maggiore and Larsson received no compensation for their roles. Karen Pickett, MB BCh (Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium), provided technical assistance. Dr Pickett received compensation for her role in the conference.

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DECLARATION OF HELSINKI

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of subjects, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the subject's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on subjects or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent,
preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious subjects, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been
approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research

on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the subjects who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the subjects who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, subjects entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the subject which aspects of the care are related to the research. The refusal of a subject to participate in a study or the subject's decision to withdraw from the study must never interfere with the subject-physician relationship.

35. In the treatment of a subject, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the subject or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

INVESTIGATOR RESPONSIBILITIES

The Investigator must comply with all requirements regarding the obligations of the clinical Investigators and all other pertinent requirements listed in 21 CFR Part 312 (see below).

General responsibilities of investigators
An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. An investigator shall, in accordance with the provisions of 21 CFR Part 50, obtain the informed consent of each human subject to whom the drug is administered.

Control of the investigational product
An investigator shall administer the investigational product only to subjects under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator. The investigator shall not supply the investigational product to any person not authorized under this part to receive it.

Investigator recordkeeping and record retention
(a) *Disposition of drug.* An investigator is required to maintain adequate records of the disposition of the investigational product, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the investigational product to the sponsor, or otherwise provide for disposition of the unused supplies of the investigational product.
(b) *Case histories.* An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational product or employed as a control in the investigation. Case histories include the case report forms and supporting data including signed and dated consent forms and medical records, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
(c) *Record retention.* An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the investigational product for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

Investigator reports
(a) *Progress reports*. The investigator shall furnish all reports to the sponsor of the investigational product who is responsible for collecting and evaluating the results obtained. The sponsor is required to submit annual reports to FDA on the progress of the clinical investigations.
(b) *Safety reports.* An investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the investigational product. If the adverse effect is alarming, the investigator shall report the adverse effect immediately.

Assurance of IRB review
An investigator shall assure that an IRB that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the proposed

clinical study. The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Inspection of investigator's records and reports
An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

Disqualification of a clinical investigator
If FDA has information indicating that an investigator (including a sponsor-investigator) has repeatedly or deliberately failed to comply with the requirements of 21 CFR Parts 312, 50, 54 or 56, the FDA has the right to investigate the matter and make a determination of the events. The FDA has, when warranted, disqualified investigators from further clinical research.

Additional Investigator Responsibilities:
By signing the Form FDA 1572, the Investigator agrees to:
1. Conduct the study in accordance with the relevant current protocol and will only make changes after notifying the Sponsor, except to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Inform any subjects enrolled in the study that the drug is being used for investigational purposes.
4. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet Federal guidelines, as stated in 21 CFR, Parts 50 and 56.
5. Report to the Sponsor any AEs that occur during the course of the study, in accordance with 21 CFR 312.64.
6. Have read and understood the Investigator Brochure, including potential risks and side effects of the investigational product.
7. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
8. Maintain adequate and accurate records, in accordance with 21 CFR 312.62 (or the requirements of other regulatory agencies) and to make those records available for inspection with the Sponsor, their designated representative, the FDA or any agency authorized by law.
9. Ensure that an IRB that complies with the requirements of 21 CFR Part 56 (or the requirements of another regulatory agency) will be responsible for initial and continuing review and approval of the clinical study.
10. Report promptly to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
11. Not make any changes in the research study without approval, except when necessary to eliminate hazards to the subjects.
12. Provide a list of the names of the sub-Investigators (e.g., research fellows, residents) who will be assisting the Investigator in the conduct of the investigation.