DEPARTMENT OF HEALTH & HUMAN SERVICES

National Institutes of Health
Bethesda, Maryland 20892

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Daniel F. Hanley, MD
Jeffrey and Harriet Legum Professor
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Director, Division of Brain Injury Outcomes
The Johns Hopkins Medical Institutions
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Baltimore, MD 21231

Dear Dr. Hanley:

I am writing to confirm that the NINDS-appointed Data and Safety Monitoring Board (DSMB) for the CLEAR III trial met in Washington, DC on October 19, 2011 to review the latest data from the study. The DSMB found no issues of concern regarding safety or study implementation and thus recommended the study proceed as planned.

The DSMB will meet by teleconference in June 2012 to conduct its next detailed data review.

Sincerely,

Peter R. Gilbert, Sc.M.
Clinical Research Project Manager
Office of Clinical Research
National Institute of Neurological Disorders and Stroke
National Institutes of Health

BIOS Brain Injury OutcomeS Clinical Trial Coordinating Center

JOHNS HOPKINS MEDICINE

CLEAR III Annual Report to Enrolling Centers and Regulatory Agencies

November 2011

Overview

We report on the status of the CLEAR III trial, a Phase III efficacy and outcome trial assessing the effect of EVD with rt-PA or placebo to treat intraventricular hemorrhage. Enrollment has increased steadily since the enrollment of the first subject in September 2009. As of the generation of the DSMB report on September 15, 2011, 73 sites have been trained and 61 sites are activated. Of the 61 activated sites, 52 have enrolled one or more subjects, totaling 163 randomized subjects.

The Data Safety Monitoring Board (DSMB) was selected by the NIH NINDS. The DSMB met on April 26, 2010 to review the protocol. The DSMB complemented the investigators on the quality of the trial design and organization. The protocol was approved and the trial leadership was directed to proceed as planned. The DSMB next met on October 21, 2010 and reviewed the first 41 subjects enrolled. The DSMB directed the trial leadership to continue enrollment. The DSMB recently met again on October 19, 2011 and reviewed the first 100 subjects. An excerpt of the report shared with the DSMB for this meeting follows.

Excerpt of the report from the October 19, 2011 DSMB meeting
Data freeze September 15, 2011; Subjects 1 to 100

Clinical Summary of First 100 Subjects

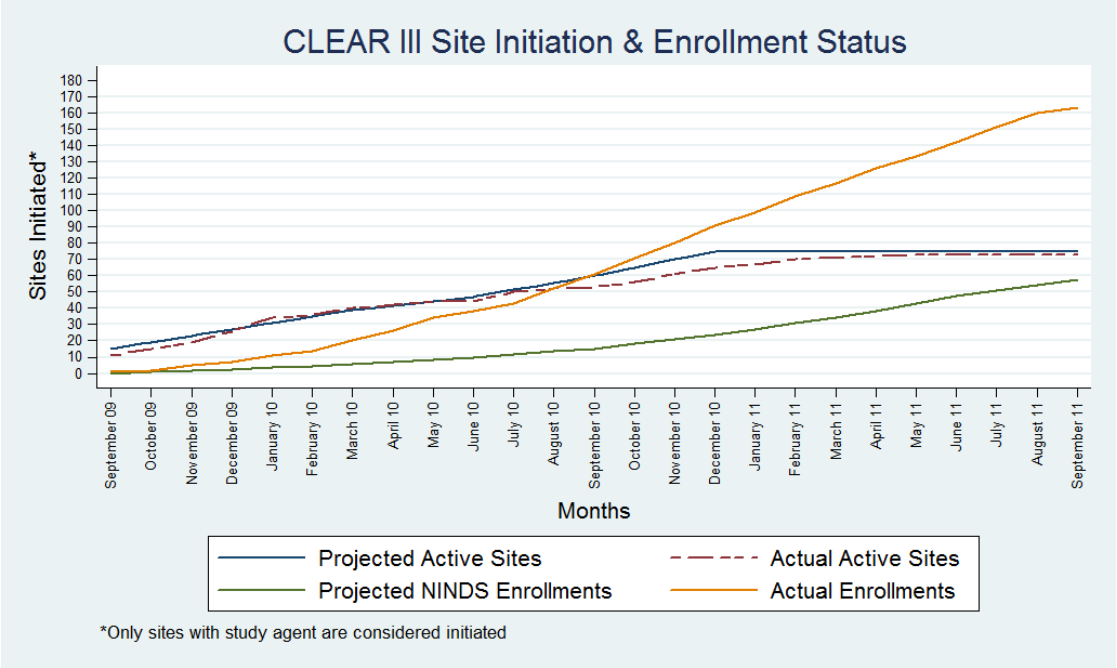
Approximately 499 days (16.39 months) elapsed from the enrollment of the first subject to the last subject in this reviewed cohort. Subjects in the current CLEAR III study cohort were enrolled by 38 sites. Protocol performance has been very good at most sites and adequate at all currently active sites, as determined by surgical committee, PI, and data monitor reviews. SAEs and AEs have occurred in the expected organ systems and clinical categories. Some variations in surgical performance categories of catheter location and overall clot removal have been observed. These are within expected range of protocol variation.

The data reflected in this report are based on the data freeze date of September 15, 2011. It should be noted that the data compiled herein are a preliminary snapshot of this ongoing clinical trial having individual case report forms in various stages of data entry and monitor verification. In preparation for this report, an effort was made to collect and verify as much of the data as possible, but none of the data are currently considered final and none of the case forms included in this compilation have been formally released by the investigators or locked to prevent further changes. As such, all data herein are subject to possible change as the study progresses and any such changes will be reflected in subsequent reports. For continuous variables, the minimum and maximum values are only reported.

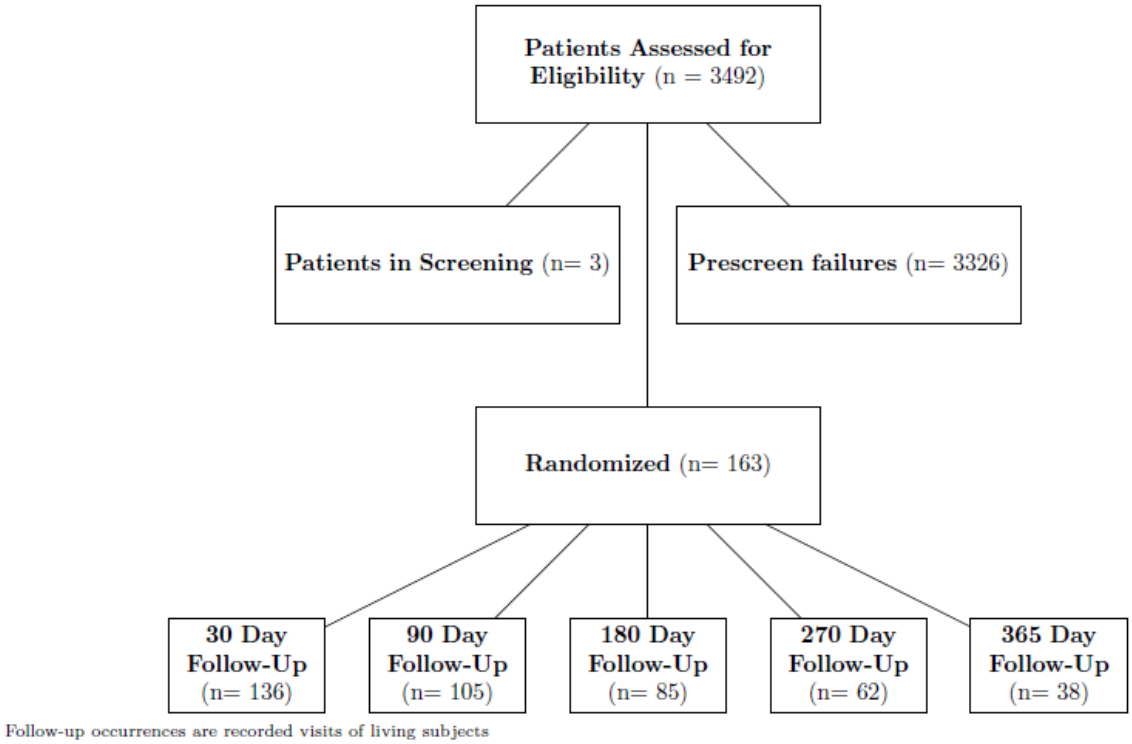
The actual versus expected enrollments graph (3.1.1), listing of screening status by site (3.1.2) and the population flowchart (4.1) represent the entire cohort of 163 randomized subjects.

The remainder of the listings, tables and figures represent the first 100 randomized subjects. Of the first 100 subjects, 61% were male and 39% were female. African American subjects comprise 40% of the sample along with 2% other ethnic groups, 53% Caucasian, and 5% not specified. Clinical severity characteristics are similar to the previous IVH protocols conducted by the Coordinating Center. There have been 24 deaths in the 0-365 day protocol timeframe. Currently, 78 alive subjects have reached 180 days. The mortality rate for this group is 24 percent. Follow-up for subjects has been adequate with no subjects withdrawing consent and no subjects refusing follow-up prior to 30 days after enrollment. Fourteen subjects have experienced re-bleeding events: 12 with asymptomatic and 2 with symptomatic. The one symptomatic bleed was categorized as clinically insignificant (with respect to study intervention); thought to be related to amyloid angiopathy, occurred 77 days after the last dose was given, but required hospitalization due to a change in mental status. Adverse events (AEs) occurred in 93 of 100 (93.0%) subjects and serious adverse events (SAEs) have occurred in 54 of 100 (54.0%). In the first 100 randomized subjects, 262 AEs (2.6 AEs per subject) and 76 SAEs (0.8 SAEs per subject) were reported.

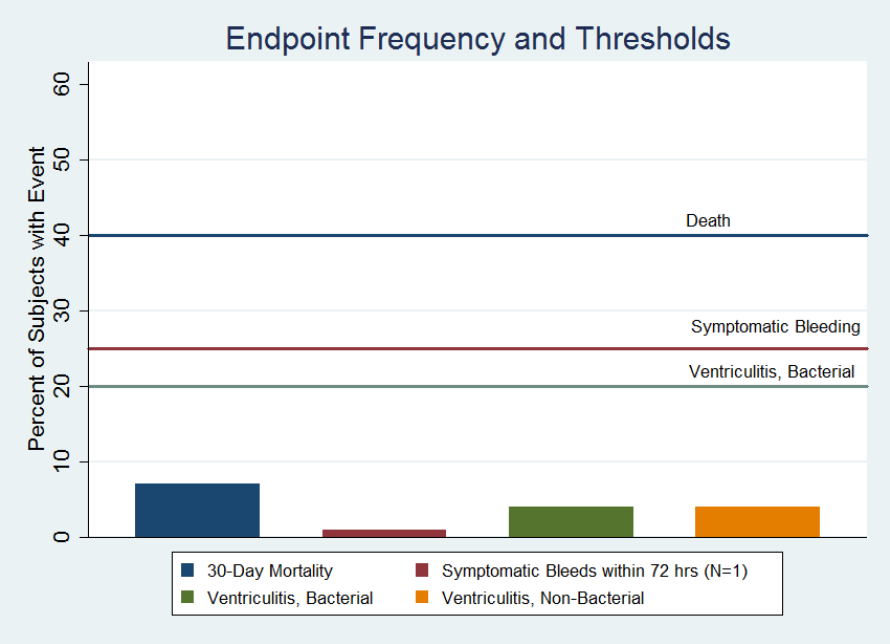
3.1.1 Comparison of Target to Actual Enrollment and Site Initiations by Month



4.1 Current Status of All Patients Assessed for Eligibility



4.3.1.3 Safety Thresholds



4.4 AE/SAEs by Body System on the First 100 Subjects

4.4.1.1 AEs

AEs	All Patients (N=100)			
Body System	Number of AEs	Percent of All AEs*	AEs per Subject**	Number of Subjects with AEs
Blood and lymphatic system disorders	8	3.1	0.08	8
Cardiac disorders	11	4.2	0.11	9
Endocrine disorders	1	0.4	0.01	1
Eye disorders	1	0.4	0.01	1
Gastrointestinal disorders	11	4.2	0.11	10
General disorders and admin site conditions	32	12.2	0.32	26
Hepatobiliary disorders	1	0.4	0.01	1
Immune system disorders	1	0.4	0.01	1
Infections, non-neurologic	41	15.6	0.41	34
Injury, poisoning & procedural complications	3	1.1	0.03	3
Investigations (Laboratory)	4	1.5	0.04	4
Metabolism & nutrition disorders	18	6.9	0.18	14
Musculoskeletal & connective tissue disorders	2	0.8	0.02	2
Nervous system disorders	65	24.8	0.65	45
Psychiatric disorders	2	0.8	0.02	2
Renal and urinary disorders	3	1.1	0.03	3
Respiratory, thoracic & mediastinal disorders	36	13.7	0.36	30
Skin and subcutaneous tissue disorders	2	0.8	0.02	2
Vascular disorders	20	7.6	0.20	18
Total	262	100.0	2.62	93

*Percent of All AEs = # AEs / Total # AEs
**AEs Per Subject = # AEs / Total N, (N=100)

4.4.1.2 SAEs

SAEs	All Patients (N=100)			
Body System	Number of SAEs	Percent of All SAEs*	SAEs per Subject**	Number of Subjects with SAEs
Cardiac disorders	2	2.6	0.02	2
Gastrointestinal disorders	1	1.3	0.01	1
General disorders and admin site conditions	11	14.5	0.11	11
Infections, non-neurologic	9	11.8	0.09	8
Metabolism & nutrition disorders	1	1.3	0.01	1
Musculoskeletal & connective tissue disorders	1	1.3	0.01	1
Nervous system disorders	27	35.5	0.27	21
Respiratory, thoracic & mediastinal disorders	18	23.7	0.18	14
Surgical and medical procedures	2	2.6	0.02	2
Vascular disorders	4	5.3	0.04	4
Total	76	100.0	0.76	54

*Percent of All SAEs = # SAEs / Total # SAEs

**SAEs Per Subject = # SAEs / Total N, (N=100)