STATISTICAL ANALYSIS PLAN
Protocol: IVH06

Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III (CLEAR III)

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1 INTRODUCTION

IVH occurs in about 40% of primary intracerebral hemorrhage (ICH) and 15% of aneurysmal subarachnoid hemorrhage (SAH).[1-4] The incidence of IVH in ICH is about twice that of SAH; respectively, they account for about 10% and 5% of the 500,000 new strokes occurring yearly in the U.S,[2, 5] translating to about 22,000 people per year with an IVH. Most recent research supports the assertion that IVH is a significant and independent contributor to morbidity and mortality in both.[1, 3, 6-12] Mortality estimates for this condition are from 40-80%.[9, 13] Recently, two large randomized clinical trials (RCT), with well-established monitoring and adjudication mechanisms, have demonstrated the importance of IVH as a severity factor. The Surgical Trial in ICH (STICH) trial, an international effort funded by the Medical Research Council of Great Britain (MRC), enrolled 964 ICH patients to test the value of early surgery vs. medical management. Ventricular extension occurred in 42%; hydrocephalus occurred in 55% of these. IVH with and without hydrocephalus were strongly associated with poor outcome: whereas 31% without IVH had good outcome, only 15% with IVH experienced good outcome ($p<0.00001$). When IVH and hydrocephalus were combined, good outcome fell to 11%[14] Similarly, IVH occurred in 49% of all patients enrolled in the NovoSeven ICH trial (n=399). Modified Rankin scores were consistently worse in this group of patients[15] Although IVH severely complicates a large percentage of ICH patients, little organized clinical research has been directed at improving the management of IVH, including the use of EVDs. This proposal is directed specifically to explore the possibility that amelioration of IVH benefits ICH patients.

2 STUDY OBJECTIVES

Primary objectives: To define precisely the long-term effects of lysing ventricular blood clots with rt-PA on the functional outcomes of cerebral hemorrhage patients. We propose to test if this intervention promotes a recovery of function, as defined as a modified Rankin score of ≤ 3 at 180 days post ictus, by facilitating more rapid clot resolution as compared to treatment with extraventricular drainage (EVD) with placebo.

Secondary objectives: To test if mortality at 180 days is improved for subjects receiving rt-PA, if the amount of residual blood at 72 h correlates directly with the functional outcome at 180 days post bleed, and if rt-PA use in IVH patients leads to less intense ICU management, including fewer ICU days, shorter periods of CSF drainage, decreased intensity of ICP management, lower rate of needing permanent ventriculoperitoneal shunt, and fewer general critical care complications.

3 DESIGN

3.1 Overview

This study is a multicenter, international, double-blind, randomized study comparing the use of EVD combined with rt-PA against EVD combined with placebo for the treatment of intraventricular hemorrhage.

3.2 Expected Sample Size

Approximately 500 patients with onset of intraventricular hemorrhage will be randomized between EVD management with rt-PA or placebo. All patients will receive external ventricular drainage, prior to randomization, via placement of an intraventricular catheter when indicated by neurosurgical standard of care.

3.3 Inclusion/Exclusion Criteria

3.3.1 Inclusion Criteria

1. Age 18-80.
2. Symptom onset less than 24 hrs prior to diagnostic CT scan.
3. Spontaneous ICH ≤ 30 cc and IVH obstructing 3rd and/or 4th ventricles.
4. ICH clot stability: ICH must be ≤ 30 cc on initial presentation and not exceed 35 cc on subsequent pre-randomization stability scans. A CT scan performed 6 hours or more after IVC placement must be stable (difference is ≤ 5 cc) compared to the most previous CT scan as determined by the (AxBxC)/2 method.
   Temporary Criterion: If the clot is not stable (i.e., difference is > 5 cc), a repeat CT scan must be performed at least 12 hours later and compared to the most previous CT scan. Investigator may continue to screen every 12 hours up to 72 hours for the initial bleeding to stabilize, as long as the subject is able to be randomized within 72 hours of time of diagnostic CT scan and the clot remains ≤ 35 cc. If the size stabilizes (i.e., enlargement ≤ 5 cc between 2 sequential CT scans) and remains ≤ 35 cc, the patient is eligible.
5. IVH clot stability: The width of the lateral ventricle most compromised by blood clot must not increase by > 2 mm, allowing for movement of blood under influence of gravity.
   Temporary Criterion: If the clot is not stable (i.e., difference is > 2 mm), a repeat CT scan must be performed at least 12 hours later and compared to the most previous CT scan. Investigator may continue to screen up to 72 hours for the initial bleeding to stabilize, as long as the subject is able to be randomized within 72 hours of time of diagnostic CT scan. If the size stabilizes (i.e., enlargement ≤ 2mm between 2 sequential CT scans), the patient is eligible.
6. Catheter tract bleeding must be less than or equal to 5 cc on CT scan for stability.
   Temporary criterion: If a catheter tract hemorrhage is present on the CT scan done 6 hours after IVC placement and is > 5 cc or > 5 mm, obtain a repeat CT scan 12 hours later. This includes any bleeding at the entry site or along the catheter tract that is 5 mm in diameter seen on any CT slice or is 5 mL on more than one CT slice. If the catheter tract hemorrhage further enlarges by > 5 cc or > 5 mm as compared to the most previous CT scan, the investigator may continue to screen by repeat CT scan every 12 hours for the bleeding to stabilize, as long as the subject is able to be randomized within 72 hours of time of diagnostic CT scan. If the size stabilizes (i.e., enlargement ≤ 5 cc or ≤ 5 mm between 2 sequential CT scans), the patient is eligible.
7. On stability CT scan, the 3rd and/or 4th ventricles are occluded with blood.
8. All patients randomized will have had EVD placed, ideally using no more than 2 complete passes (including “soft passes” using the original trajectory), on an emergent basis as defined by the “standard of care” neurosurgical/critical care decisions of the managing physicians. If more than 2 passes are required for placement, additional stabilization of IVC site will be determined with a CT performed at 24 hours after IVC placement.
   Temporary criterion: If no IVC is in place at the time the patient is initially screened, the decision to place an IVC may occur after the patient is initially screened but an IVC must be in-place and stable at the time of randomization.
9. Patients with primary IVH are eligible (i.e. with ICH=0).
10. SBP < 200 mmHg sustained for the 6 h before drug administration (closest to randomization).

Temporary criterion: Blood pressure inclusion criteria not met when the patient is screened: Most vital signs are stabilized within the time window for enrollment.

11. No test article may be administered until at least 12 hours after symptom onset.
12. Able to randomize within 72 h of CT scan diagnosing IVH (provided the time of symptom onset to diagnostic CT does not exceed 24 h).
    Temporary criterion: The 72 hour limit may be extended with approval from the Coordinating Center to allow for clot stability (ICH, IVH, catheter tract), INR stability, or other valid reason.
13. Historical Rankin of 0 or 1.

3.3.2 Exclusion Criteria

1. Suspected (unless ruled out by angiogram or MRA/MRI) or untreated ruptured cerebral aneurysm, ruptured intracranial AVM, or tumor. Treatment of an existing aneurysm or AVM must have occurred at least 3 months before the current onset.
   Temporary criterion: This is especially important in primary IVH, when no ICH source is found. CT angiogram, angiogram, MRA/MRI, or general diagnostic study (prior to confirming patient eligibility in the protocol) is standard of care to rule out underlying etiology. If the CT angiogram, angiogram or MRA/MRI is negative, the patient is eligible. The PI must document rationale if imaging is not done.
2. Presence of a choroid plexus vascular malformation or Moyamoya disease.
3. Clotting disorders. Subjects requiring long-term anti-coagulation are excluded.
   Temporary criterion: Reversing anticoagulation will be permitted where long-term anticoagulation is not required.
4. Use of Dabigatran, Apixaban, and/or Rivaroxaban (or a medication from the same medication class) prior to symptom onset.
5. Platelet count < 100,000, INR > 1.4.
   Temporary criterion: Low platelet counts etc. on admission can normalize within 24 hours as can an INR normalize to $\leq$ 1.4.
6. Pregnancy (positive serum or urine pregnancy test).
7. Infratentorial hemorrhage
8. Thalamic bleeds with apparent midbrain extension with third nerve palsy or dilated and non-reactive pupils. Other (supranuclear) gaze abnormalities are not an exclusion. Note: Patients with a posterior fossa ICH or cerebellar hematomas are ineligible.
9. SAH at clinical presentation (an angiogram (angiogram, CTA, MRA/MRI) must be obtained when the diagnostic CT scan shows SAH or any hematoma location or appearance not strongly associated with hypertension. If the angiogram or other imaging does not detect a bleeding source to account for the hemorrhage, the patient is eligible for the study.) Subsequent appearance of cortical SAH secondary to clot lysis is not a dosing endpoint.
   Temporary criterion: An angiogram must be obtained when the diagnostic CT scan demonstrates subarachnoid hemorrhage or any hematoma location suggestive of aneurysm or appearing not strongly associated with hypertension. If the angiogram/imaging does not demonstrate a bleeding source that accounts for the hemorrhage, the patient is eligible for the study.
10. ICH/IVH enlargement that cannot be stabilized in the treatment time window.
    Temporary criterion: ICH enlargement during the 6-hour stabilization period (6 hours after IVC placement): It is permitted to screen up to 72 hours after diagnostic scan. If the ICH clot size stabilizes (i.e., enlarges no more than 5 cc)

and does not exceed 35 cc (an ICH clot size of 35 cc allows for stabilization of a 5cc expansion for those patients at the upper limit of the ICH clot size limit), the patient is eligible.

11. Ongoing internal bleeding, involving retroperitoneal sites, or the gastrointestinal, genitourinary, or respiratory tracts. (Patient with prior bleeding that is clinically stable for 12 h or more without any coagulopathy or bleeding disorder is eligible).
12. Multi-focal, superficial bleeding, observed at multiple vascular puncture and access sites (e.g., venous cutdowns, arterial punctures) or site of recent surgical intervention.
13. Prior enrollment in the study.
14. Any other condition that the investigator believes would pose a significant hazard to the subject if the investigational therapy were initiated. Subjects who are not expected to survive to the day 180 visit due to co-morbidities and/or are DNR/DNI status prior to randomization are excluded.

    Temporary criterion: Although these situations are often irreversible, under other conditions, change can occur over 24 hours.
15. Planned or simultaneous participation (between screening and Day-30) in another interventional medical investigation or clinical trial. Patients involved in observational, natural history, and/or epidemiological studies not involving an intervention are eligible.
16. No subject or legal representative to give written informed consent.

3.4 Intervention

The intervention to be compared is EVD + rt-PA against EVD + placebo (normal saline). In the EVD + rt-PA group, a low dose (1.0 mg q 8 hours) of the thrombolytic rt-PA will be administered via an EVD to the intraventricular clot. This will be performed as intermittent, isovolumetric injections of 1.0 mg of Cathflo® followed by up to 4.0 ml of flush (normal saline) given every 8 hours for up to 12 doses. Placebo patients will receive 1.0 mL of sterile normal saline given every 8 hours for up to 12 doses.

4 STUDY SCHEMA

	Screening	Pre-Randomization (Baseline)	Randomization (Day 1)	Days 1-7	IVC Removal	Day 30 (+/- 7 days)	Day 90 (+/-7 days)	Day 180 (+/-14 days)	Day 270 (+/- 14 days)	Day 365 (+/- 14 days)
Informed Consent		X								
Diagnostic CT (SOC)	X									
Diagnostic CTA or routine angiogram (SOC; not required in Germany)	X									
IVC Placement (SOC)	X									
Stability CT (SOC)	X									
Neurosurgical Center review of IVC		X		X	X					
Blood pressure (over 6 hours)		X								
Medical/Treatment History	X									
Pregnancy Testing	X									
Toxicology Screen	X									
Dosing Q8Hr +/-2 hrs				Up to 12 doses	Open to drain for 24 hr post last dose					
CT Scan				Days 1-5 & 1 & 3 days post last dose		X				X
Vital Signs Q4Hr +/- 1hr				X	Daily for EVD management only	BP only		BP only		BP only
Lab Assessments	X	X		X						
AE/SAE capture			Starting point for recording AE/SAEs	X	Neurological AEs, all SAEs, and all Medical Events of Interest only					
NIHSS		X (capture if done SOC)	X	Day 7		X		X		X
Barthel Index	X (Historical)					X	X	X	X	X
Modified Rankin	X (Historical)					X	X	X	X	X
GOSE						X		X		X
Stroke Impact Scale						X		X		X
Mini-Mental Exam						X		X		X
EQ-5D						X	X	X	X	X
PBSI						X		X		X
Personal Health Utility Assessment Interview								X		

†Certified examiners must complete the 1, 3, 6, 9, and 12 month follow-up visits.

5 ENDPOINTS

5.1 Primary Endpoints

5.1.1 Modified Rankin Scale ≤ 3 at 180 days

The primary comparison is a dichotomized comparison of the 180 day mRS scale: 0-3 vs. 4-6 which is predicated on the preliminary data from earlier CLEAR IVH trials. The primary analysis will be a direct comparison using an intent-to-treat analysis of dichotomized mRS by treatment group and a logistic regression model with one covariate, treatment. Subsequently the more extensive data modeling will be used as suggested to explore all the effects of severity factors and co-morbidity on functional outcomes.

Addendum (Sep 2015): Clarifications to analysis plan accounting for covariate randomization: In accordance with the literature on covariate-adaptive randomized designs, the primary analysis will adjust for the covariates used in the randomization process. Based on the randomization scheme, there are six possible pairs of covariate combinations (IVH volume low, medium, high; ICH (intracerebral hemorrhage) location in thalamus or not). We consider these as six possible baseline categories. The estimator of the average treatment effect involves first computing, within each of the six baseline categories, the difference between the observed proportion with mRS ≤ 3 at 180 days in treatment versus control arms. Next, a weighted sum of these category-specific estimates is computed with weights set as the sample proportion in each category (pooled across the two arms). For example, if 10% of the participants are in category 1 (low IVH volume, ICH in thalamus), then the estimated treatment effect in that category is given weight 0.1. The 95% confidence interval estimated by the percentile method for the average treatment effect is computed by the nonparametric bootstrap method, such that the covariate-adaptive design is adhered to in each resampled (bootstrap sample) data set. Each resampled data set has the same size as the original data set. Specifically, for each resampled participant within a bootstrap sample (N=500), the baseline category is a random draw from the observed (empirical) distribution of the baseline categories, e.g., 10% from category 1, etc. Next, the study arm is assigned using the covariate-adaptive algorithm. For the first 100 resampled participants, randomization is 1:1 for treatment versus control irrespective of baseline variables; for subsequent resampled participants in each successive resampled data set, the covariate-adaptive algorithm (which uses the Pocock-Simon[16] procedure to improve balance on IVH volume and ICH location) is applied. The outcome is random drawn from the empirical distribution of observed mRS outcomes based on the participant's baseline clinical characteristics and study arm assignment, e.g., a participant with baseline category 1 assigned to control has outcome drawn at random according to the observed proportion (using all trial data) in that category and study arm with mRS ≤ 3 at 180 days. The average treatment effect estimator described in the above paragraph is computed for each resampled data set, and the BCa bootstrap is used to construct a 95% bootstrap confidence interval. This will form the primary hypothesis test of the null hypothesis of no difference in average treatment effect, i.e., the test will reject the null hypothesis if 0 is excluded from the 95% confidence interval. Advantages of the above procedure are that it does not make parametric model assumptions (such as those made when using logistic regression) and it results in consistent estimates (i.e., converges to the true average treatment effect). However, a more precise estimator may be obtained by further adjusting for study baseline covariates within each category that are prognostic and are imbalanced by treatment group. These potential covariates include age, ICH volume, GCS, and NIHSS at presentation. The challenge with incorporating these additional covariates is that parametric model assumptions must be made.[17-18] A version of the method

from Shao, Yu, and Zhong[17] with logistic regression and the bootstrap t-test, will be used as a pre-specified sensitivity analysis to investigate potential baseline imbalance.

5.1.2 mRS as Ordinal Score

EVD+ rt-PA for IVH clot removal produces improved outcome(s) assessed by the ordinal mRS score when compared to EVD + placebo. Analyses: To retain information in the full ordinal mRS, a proportional odds model will be estimated of the form:

$$\log\left(\frac{\gamma_k}{1-\gamma_k}\right) = \alpha_k + \beta X + \theta \cdot TRT$$

where: α_k = Prob(mRS $\leq$ k), k=0,1,...,5

The proportional odds model is very similar to the logistic regression model described above, with the difference being that the interpretation of the estimated treatment effect considers the likelihood of a patient being in any subsequently lower mRS category. The set of intercepts, α_k k=0, 1,..., 5, are now initial cumulative probabilities which incorporate all outcomes below any given level, covariates are again included through β and X, and the treatment difference θ now describes the log-odds of moving from any cumulatively higher (worse) category, into any cumulatively lower (better) category. For instance, here θ describes both how the intervention moves patients from the mRS category of 'Dead' (6), to 'living' (0-5), as well as how the intervention moves patients from 'Severe Disability or Dead' (5,6) to 'No Symptoms through Moderate Disability' (0-4) and so forth. This model is more efficient than the simple dichotomous approach since it uses the available information across the entire scale of the measure. To examine the proportional odds assumption, generalized logistic models that replace β and θ with β_k and θ_k will be used, allowing non-parallel effects between successive cumulative categories. In the event that the proportional odds assumption is rejected, results from the generalized logistic models will be presented.

5.1.3 180 day mRS (0-4)

Clot removal with EVD + rt-PA can increase the percent of patients with a good functional outcome, compared to management with EVD + placebo. For a disease with very high mortality, the 0-3 and 0-4 thresholds are the critical thresholds for evaluating a biologic benefit of intervention. Thus, these will be examined first. There is some degree of controversy in the literature regarding the choice of mRS cutoff thresholds. Thus, the treatment effects for alternate definitions of "good outcome" also will be estimated. Analyses will be similar to the primary outcome analyses above.

5.1.4 Random Effects assessment of site effect (mRS 0-3)

Accounting for Clinical Center Effects: Center effects will be examined as both fixed effects in the GLM framework above and random effects, incorporated through a GLMM framework. Given the expected 30-75 centers, variation between centers should be well estimable. Probit-link GLMMs may be utilized to facilitate marginalization of the desired population-averaged treatment effects.

5.1.5 Longitudinal (mRS 0-3)

The next evaluation of Hypothesis 1.1 will be to examine differences between dichotomized mRS scores (such as mRS $\leq$ 3) between the EVD + rt-PA and EVD + placebo groups using a logistic regression model of the form:

$$\log\left(\frac{p}{1-p}\right) = \alpha_0 + \beta X + \theta \cdot TRT$$

where: p = Prob (function recovery), α_0 is an intercept parameter (i.e. log-odds of function recovery under EVD + placebo), β is a vector of regression coefficients pertaining to relative effects of interest such as initial clot size, ICH clot location, etc., as incorporated in the covariate matrix X, and θ is the treatment effect parameter for EVD + rt-PA. These formulations allow similar alternative models to be entertained as well, such as stronger treatment effects in some clot locations as compared to others, and sensitivity towards functional assessments and including/excluding death in the scale. Note that the mean model pertaining to 180-day outcomes has been specified, as specification of the longitudinal models is similar with the addition of working 'association' aspects and potential time-dependent effects.

Addendum (Sep 2015): Longitudinal efficacy analyses using random effects models that consider clinical sites as random effects will be performed for dichotomized functional outcomes at: 1, 3, 6, 9 and 12-month follow-up as related to treatment (ITT), taking into account within-subject correlations between successive time points. These analyses will be adjusted for potential covariates and mediators. Note that mRS values for 3 and 9 months were only assessed at the clinical sites and were not independently adjudicated.

5.2 Secondary Endpoints

5.2.1 All-Cause Mortality – 180 days

Mortality at 180 days post treatment for EVD + rt-PA treated patients will be improved as compared to that of patients managed with EVD + placebo. Analyses: For initial evaluations of secondary Hypothesis 2.3, differences between the EVD + rt-PA and EVD + placebo groups will be examined using a logistic regression model similar to that shown above for Hypothesis 1.1.

Addendum (Sep 2015): Mortality by group will be graphically displayed with Kaplan-Meier curves and the statistical association between treatment assignment and mortality assessed with the log-rank test. Multivariable Cox regression models will then be created to assess for treatment differences in the hazards of survival after adjusting for potential group imbalances in the covariates listed above. Finally, we will account for the effect of the decision to withdraw patient care on treatment differences in mortality.

5.2.2 Clot Removal

Effects of rate and extent of ventricular blood clot removal. The amount of residual blood at 72 hours and removal rates are associated with functional outcome at 180 days post bleed. Analyses: For initial evaluation of secondary Hypothesis 2.6, associations with removal amounts and rates across and within the EVD + rt-PA and EVD + placebo groups for the primary outcome will be examined using a logistic regression model similar to that shown above for Hypothesis 1.1.

Addendum (Sep 2015): Under the mediation analysis, the pre-specified mediator is volume of clot removed during active treatment (i.e. treatment time + 24 hours). If there is an impact of clot volume as measured by either absolute reduction, percent reduction, or rate of clot resolution on 180-day and 365-day mRS score, further analyses will be performed to assess whether it is a mediator of the association between intensity of EVD (external ventricular drain) intervention (or other covariates) and mRS outcomes.

5.2.3 Critical Care Management

Type and Intensity of ICU Management. EVD + rt-PA treatment of IVH leads to decreased intensity of hospital care compared to EVD + placebo. This includes fewer hospital days, ICU days, decreased intensity of ICP management, shorter periods of CSF drainage, lower utilization of ventriculoperitoneal shunts, and fewer general critical care complications. Analyses: Linear, log-linear, and logistic data models to examine secondary Hypothesis 2.5 will be similar to those presented above.

5.2.4 30-Day Mortality/Safety

Mortality attributed to EVD + rt-PA treatment plus disease–associated adverse events are similar to the morbidity and mortality attributed to EVD + placebo in the first 30 days. Analyses: For initial evaluations of secondary Hypothesis 2.2, differences between the EVD + rt-PA intervention and EVD + placebo groups will be examined using a logistic regression model similar to that shown above for Hypothesis 1.1.

5.2.5 Adverse and Serious Adverse Events

All AEs and SAEs are summarized by type and by treatment group in terms of frequency of the event, number of subjects having the event, timing relative to randomization, severity (mild, moderate, severe), and relatedness to the study treatment (definitely, probably, possibly, definitely not). At the end of the study, the cumulative incidences of these events will be compared between the two treatment groups using Fisher's exact test. Additionally, generalized linear mixed models for binary data will be used to examine AE and SAE probabilities between treatment groups while accounting for potential confounders and center clustering effects.

5.2.6 Cox Proportional Hazards Model

Additionally, survival models will be constructed to examine the mortality, morbidity and ICU distributions for the EVD + rt-PA and EVD + placebo groups. Standard Cox proportional hazard models will initially be examined. These models are commonly written as:

$$h_i(t) = \lambda_0(t)\exp(\gamma X + \phi \cdot TRT)$$

where $\lambda_0(t)$ is a non-parametric baseline hazard function, γ is again a vector of regression coefficients related to the X covariates and ϕ is the parameter for the treatment effect of EVD + rt-PA on the hazard of death (mortality). This model may be extended by including time-dependent covariates and non-proportional hazards as deemed necessary through diagnostic checks. Observed mortality will also be compared with predicted mortality based on clinical presentation, overall and by treatment group. Predicted mortality will be estimated using the most recent Tuhrim model which takes IVH volume and presence of hydrocephalus into account.

5.2.7 Sub-Group Analyses

Patients with more severe characteristics at presentation may be at risk of worse outcomes regardless of randomization group. A severity indicator or index will be constructed based upon presentation characteristics such as IVH size, ICH size, clot location, age, and gender, and potential differences in treatment effects across severity levels will be examined.

Addendum (Sep 2015): We will also perform subgroup analyses of the treatment effect stratified by IVH size, ICH size, clot location, age, gender & GCS/NIHSS.

5.2.8 Functional Status

Clot removal with EVD + rt-PA treatment produces improvements in functional outcome assessed by alternative outcome measures such as NIHSS, Barthel Index, Glasgow Outcomes Scale, extended Glasgow Outcomes Scale and mRS. Analyses: Linear, logistic and polytomous data models to examine secondary Hypothesis 2.4 will be similar to those presented above.

5.2.9 Quality of Life (QoL)

Quality of Life (QOL). Clot removal with EVD + rt-PA leads to improved health related QOL as assessed by subject and surrogate QOL domains through the Stroke Impact Scale, EQ-5D, PBSI, and time at home endpoints. Analyses: Linear, logistic and polytomous data models to examine secondary Hypothesis 2.7 will be similar to those presented above.

5.3 Tertiary (Other Exploratory) Endpoints

5.3.1 Additional Analyses of Intermediate Surrogate Outcome

Methods similar to those mentioned above will be used to additionally describe and compare the two patient groups for characteristics such as length of stay, BP and ICP during treatment, level of consciousness (GCS), and clot resolution rate. Analyses that have examined the relationship of individual patient's rate of clot resolution with change in GCS have shown that increased rates of clot resolution are associated with greater improvements in GCS during the first few days of treatment. Similarly, analyses on the 64 patients from the safety study and CLEAR IVH A studies has shown that rate of clot resolution is associated with better outcomes on the mRS. This relationship also appears for the CLEAR IVH B study. Mediation effects of clot resolution rates on the relationship between intervention and outcomes will be characterized by contrasting our primary outcome models with and without inclusion of clot resolution rate terms. As mentioned above, other explanatory variable-confounding, moderating and mediation effects will be investigated, and ICH volume and primary bleeding location, clot resolution rate mediation effects, and differential gender and age effects will specifically be examined. Until now, controlled clinical studies have not routinely quantified the rate of resolution of the IVH clot during the first few days of treatment. In this study the amount of clot remaining at both 72 h and at 96 h will be examined, and methods developed for our studies of IVH patients to examine the rate of clot resolution early in the treatment will be used. The volumes from the stability CT and all CTs up to and including those taken 96 h immediately following the stability CT will be considered. Since the aim of active treatment is to achieve rapid removal of the clot, some analyses will be limited to the first 72 h. In any such analyses initial IVH volume will be taken into account since there will be a wide variation in initial clot volumes and our current evidence shows that volume of IVH clot resolved per day is strongly related to the initial volume.

Repeated observations per patient will again be taken into account using GEE techniques, undertaken with the centrally measured IVH clot volumes and the simpler site-derived Graeb scores.

5.3.2 Time to Death and Time to Re-Bleed

As a secondary assessment, time to death or re-bleed within the one-year follow up period are compared between the EVD + rt-PA and EVD + placebo groups adjusting for appropriate baseline covariates. Provided the model assumptions are met, a proportional hazards regression model may be used for the analysis as described above.

6 STATISTICAL METHODS

6.1 Target Population and Study Samples

6.1.1 Target Population. The target population to which the EVD + rt-PA therapy or EVD + placebo may be applied are patients with IVH secondary to supratentorial ICH, and without suspected underlying structural etiology (tumor, vascular malformation or aneurysm). Patients have IVH obstruction in the 3rd or 4th ventricle and an ICH ≤ 35 cc (≤ 30 cc at the time of diagnosis), that is stable.

6.1.2 Intent-to-Treat Sample. As the primary analysis, all efficacy and safety outcome measures are analyzed under the ITT. Under this principle, the evaluable sample includes all subjects who are randomized and who receive at least one dose of test article. Each subject is analyzed according to the treatment group to which they were assigned at the time of randomization.

6.1.3 Safety Analysis Sample. All randomized subjects are included in the safety analysis sample.

6.1.4 Per-Protocol Sample. The potential for cross-overs in this study is minimal; none have occurred to date. However, in the case of cross-overs, a per-protocol sample will be constructed and examined in which treatment-as-received is analyzed. Given that clot resolution is a potentially treatment-related post-randomization variable, clot resolution will be examined as an important potential mediator of final outcomes as part of a per-protocol analysis.

6.2 Overall Methodology Description

The initial stage of analysis is data cleaning, variable development, and exploratory data analyses (EDA). All variables will be evaluated to detect gaps, patterns, and inconsistencies in the data. The frequency distributions of categorical data will be described. Continuous variables will be described in terms of their centrality, spread, shape, and possible outliers. These analyses will emphasize examination of the nature and extent of variability for all variables. Visual techniques to explore continuous variables will include stem-and-leaf plots, box plots, and quantile-quantile plots. Outliers will additionally be examined for possible data entry errors. Summary statistics for continuous variables will include the number of patients, mean, standard deviation, minimum, median, and maximum. Summary statistics for categorical variables will include the frequency and percentage of patients in each category. Data will be summarized by treatment group (blinded for any interim analyses) and total patient population. All assessments before the first dose of study drug will be considered as Baseline.

Analyses will proceed in two phases; i.) cross-sectional evaluations (30 day mortality and safety events, 180 day outcomes, etc.), and ii.) full longitudinal evaluations. The first phase will compare 180-day outcomes for subjects receiving EVD + rt-PA (intervention) treatment against subjects receiving EVD + placebo. Analyses for these comparisons will be guided by exploratory analyses. Logistic regression will be used to assess treatment differences in the primary dichotomized outcome (mRS ≤3 vs. >3) and will account for design aspects such as potential within-site clustering. Since dichotomization of categorical measures results in a loss of efficiency and power, appropriate categorical data analysis techniques (such as generalized logit, proportional odds and two-stage models) will be performed to retain use of the full ordinal outcome scales and maximize power to capture intervention effects. Generalized linear model formulations also allow investigation into other explanatory variable confounding as well as moderating and mediation effects. ICH volume and location, clot resolution rate mediation effects, and differential gender and age effects will specifically be examined.

The second phase of analysis will examine outcomes in terms of longitudinal components, using data collected at initial entry into the study, ICU discharge, and follow-up at 1, 3, 6, 9, and 12 months. These data will contain within-subject correlations from one time point to the next. Since the overall goal of the trial is to compare subjects receiving the intervention of EVD + rt-PA with subjects receiving EVD + placebo, a marginal model estimated using a generalized estimating equations (GEE) technique is appropriate. The GEE technique requires specification of the standard 'mean' model, as well as specification of a working 'association' model. One strength of the technique is that the parameters of main interest in the mean model (i.e. the intervention effect) are consistent regardless of whether the association model is specified correctly. All analyses will initially be examined with a working independence assumption. When the entire model is specified correctly, optimally efficient estimates are obtained. Hence, analyses will be augmented with Toeplitz-type and autoregressive-type working correlation matrices. Generalized Linear Mixed Models (GLMMs) may also be examined to provide subject and site-specific effects. Analyses for specific hypotheses follow below.

6.3 Patient Disposition

Summary statistics will be presented for the analysis sets and subgroups, the patients who completed the study, the patients who discontinued early from the study, and the reasons for early discontinuation including bleeding, loss to follow up, patient withdrawal or refusal, other complicating disease, error, or other reasons.

6.4 Missing Data

Minimal loss to follow up for the 6-month assessment of the primary outcome is expected, based on our previous studies with this group of stroke patients (observed experience of 2% missing). Substantial efforts will be made to ensure complete follow up, such as collection of contact information for patients and patient surrogates for collection of outcome measures. All efficacy outcome measures will be analyzed under the intent-to-treat principle, and the sample analyzed will include all randomized subjects who receive at least one dose of test article. Rates of missing data and losses to follow-up will be reported and effects of incompleteness/noncompliance will be quantified through sensitivity analyses, the gold standard in the field.

6.5 Outliers, Noncompliance, Multiplicity & Interim Analyses

Outliers for primary outcomes should not cause concern for this study as the outcomes are categorical in nature. For other continuous outcomes examined in this study, outliers will be examined for validity, incorporated in and removed from primary models to assess sensitivity, and potentially transformed to another scale or modeled with skewed distributions depending on appropriateness.

Noncompliance should not cause concern for this study as the randomization by center should minimize treatment cross-over. Any effects of noncompliance that do arise will be examined by contrasting the per-protocol and intent-to-treat analyses.

The study design for the primary comparison is a two-arm randomized trial with a single treatment contrast, hence, multiplicity from several tests is not an issue.

The Johns Hopkins Biostatistics Center will generate blinded periodic interim reports on efficacy for the DSMB after a pre-established number of patients have been recruited. To eliminate statistical paradoxes that may arise with multiple look group-sequential testing rules, we will propose to the DSMB to use evidence based likelihood intervals rather than confidence intervals to depict the blinded group differences. This evidential technique allows us to represent the information accumulated in the data at each reporting period while avoiding difficulties inherent in multiple look decision rule classifications based on frequentist theory. The monitoring approach will be discussed and formalized at the first DSMB meeting. If an alternative approach is preferred, group-sequential stopping boundaries will be used.

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