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A multicenter, randomized, double-blinded, placebo-controlled phase III study of Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III)

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Abstract

Background and hypothesis—In adults, intraventricular thrombolytic therapy with tissue plasminogen activator (rt-PA) facilitates resolution of intraventricular hemorrhage (IVH), reduces intracranial pressure, decreases duration of CSF diversion and may ameliorate direct neural injury secondary to obstructive hydrocephalus. We hypothesize that patients with small parenchymal hematoma volumes (ICH vol < 30 cc), and relatively large IVH causing acute obstructive

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hydrocephalus would have improved clinical outcomes when given injections of low-dose t-PA to accelerate lysis and evacuation of IVH compared to placebo.

Study design—The CLEAR III trial is an investigator-initiated, phase III, randomized, multicenter, double-blind, placebo-controlled study comparing the use of external ventricular drainage (EVD) combined with intraventricular injection of rt-PA to EVD versus intraventricular injection of normal saline (placebo) for the treatment of IVH. Patients with known symptom onset within 24 hours of the CT scan confirmed IVH and third or fourth ventricle obstruction, with or without supratentorial intracerebral hemorrhage (ICH) volume < 30 cc, who require an EVD are screened with a CT scan at least 6 hours after EVD placement and, if necessary, at consecutive 12 hour intervals until stabilization of any intracranial bleeding has been established. Patients who meet clinical and imaging criteria (no ongoing coagulopathy and no suspicion of aneurysm, arteriovenous malformation (AVM), or any other vascular anomaly) will be randomized to either intraventricular tissue plasminogen activator or placebo.

Study outcomes—The primary outcome measure is dichotomized modified Rankin Scale (mRS) 0–3 vs. 4–6 at 180 days. Clinical secondary outcomes include additional mRS dichotomizations at 180 days (0–4 vs. 5–6), ordinal mRS (0 – 6), mortality and safety events at 30 days, mortality at 180 days, functional status measures, type and intensity of ICU management, rate and extent of ventricular blood clot removal, and quality of life measures.

Keywords

randomized clinical trial; protocols; intracerebral hemorrhage; stroke; thrombolysis

Introduction

Intraventricular hemorrhage (IVH) occurs in about 40% of primary intracerebral hemorrhage (ICH) and 15% of aneurysmal subarachnoid hemorrhage (SAH) patients.(1–3) IVH is a significant and independent contributor to morbidity and 30 day mortality is estimated at 40–80%.(4,5) Recently, two large randomized clinical trials (RCT) demonstrated the importance of IVH as a predictor of poor outcome. The Surgical Trial in ICH (STICH) enrolled 964 ICH patients, 42% of whom had intraventricular extension; of these, over half (55%) had obstructive hydrocephalus.(6) IVH with or without hydrocephalus was strongly associated with poor outcome; 31% without IVH and 15% with IVH experienced good outcome ($p<0.00001$).(7) When IVH and hydrocephalus were combined, good outcome rates fell to 11%. Similarly, IVH occurred in 49% of all patients enrolled in the NovoSeven ICH trial ($n=399$). Modified Rankin scores at 3 months were consistently worse in this group of patients.(8) A prospective study of ICH patients indicates a direct, continuous relationship between the volume of IVH and mortality.(9)

IVH contributes to morbidity by causing acute obstructive hydrocephalus, which elevates intracranial pressure (ICP) and decreases cerebral perfusion pressure and, if severe enough, results in brain herniation. The current therapy for IVH with obstructive hydrocephalus is an external ventricular drainage (EVD). EVD alone is often inadequate therapy and is complicated by catheter occlusion with blood clots.(10) EVD does not alter the rate of blood

clot resolution (11) and therefore fails to decrease the degree and incidence of communicating hydrocephalus.

EVD lowers ICP, but controlling ICP does not usually result in immediate mental status improvement.(12) Thus, direct mass effect of IVH may be a significant pathophysiologic factor independent of ICP elevation. Persistent IVH is also associated with both mortality (12, 13) and decreased level of consciousness,(14,15) which for poorly understood reasons, EVD does not consistently improve. Indeed, EVD may worsen edema and inflammation when complicated by bacterial meningitis. Other possible explanations include pro-inflammatory effects of the blood components (16) and permanent occlusion and scarring of arachnoid granulations where CSF is absorbed.(17,18) The latter results in delayed communicating hydrocephalus, which necessitates permanent CSF shunt placement and is associated with impaired cognition, gait, balance, and urinary continence.

The natural history of IVH is for radiographically observed blood to gradually disappear over a period of 2–4 weeks, although remnants of IVH may persist for many months. Intraventricular thrombolysis facilitates blood clot removal and, in experimental studies, ameliorates prolonged inflammation and protects against delayed hydrocephalus.(14,19) In a canine IVH model 20,000 IU of urokinase, administered every 12 hours through an EVD until evidence of clot resolution, resulted in more rapid clearance of intraventricular blood (3–6 days vs. 38–65 days), more rapid return of consciousness (3 days vs. 7–9 days), lower incidence of delayed communicating hydrocephalus, and improved neurological outcome without increased injury to surrounding brain tissue (14,19) compared to control animals. There were no intracranial or systemic hemorrhages and no chronic changes in the brain or meninges on histology at 3 months in the treated group. In a pig model, Mayfrank et al. showed that the mass effect of clots distending the ventricle wall is the most important mechanism responsible for hemorrhagic ventricular dilatation and that this mass effect significantly diminished at the 1.5 hour and 7 day time point when rt-PA was used for intraventricular thrombolysis.(20) In both canine and porcine models, the greater the volume of blood clot injected into the ventricles the greater the likelihood of animal death.

Observational clinical studies and one small randomized trial have demonstrated improved clot resolution, ICP, ventricular size, and mortality with both intraventricular rt-PA (off-label use) and urokinase (not currently available in US).(21–33) A Cochrane review of 10 independent studies (8 case series or retrospective studies, 1 quasi-randomized study, 1 randomized study with a biased control group) using intraventricular thrombolytic agents found anecdotal evidence supporting safety and possible therapeutic value.(34) A more recent meta-analysis of 4 randomized and 10 observational studies found that intraventricular fibrinolysis was superior to EVD alone in terms of survival and short-term functional outcome.(35) Thus far, there are no randomized trials of sufficient size and quality to evaluate the safety and efficacy of this treatment modality.

The Intraventricular Hemorrhage Thrombolysis trial was a phase II, double-blind, randomized study that evaluated rt-PA for clot lysis rate and safety. Forty-eight patients were randomized 1:1 to receive intraventricular injections of either 3.0 mg of rt-PA (n=26) or placebo (normal saline, n=22) every 12 hours until complete IVH resolution, EVD removal,

or a safety endpoint, whichever came first.(36) Frequency of death and ventriculitis was lower than expected and bleeding events remained below the pre-specified threshold: mortality (18% rt-PA; 23% placebo), ventriculitis (8% rt-PA; 9% placebo), symptomatic bleeding (23% rt-PA; 5% placebo; $P=0.1$). The median duration of dosing was 7.5 days for rt-PA and 12 days for placebo. There was a significant beneficial effect of rt-PA on the rate of clot resolution ($p<0.001$).

Dose interval finding studies (Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage [CLEAR] A and B) randomized patients 1:1 to receive intraventricular rt-PA either at doses 0.3 or 1.0 mg q12h ($n=16$) (CLEAR A) or to receive 1.0 mg q12h or q8h ($n=36$) (CLEAR B). Direct measurement of the initial clot lysis rate (first three days of treatment) demonstrated dose specific rates of 21.73%/day, 25.14%/day, 24.20%/day, and 19.98%/day for the 3.0 mg, 1.0 mg (q12hr), 0.3 mg, and 1.0 mg (q8hr) groups, respectively. The safety profile for the two lower doses was numerically superior to the 3.0 mg dose with a symptomatic hemorrhage rate of 5.8% (3/52 patients).

Intraventricular thrombolysis is a rational therapy, with some data supporting its safety. At this point, however, there is insufficient evidence to recommend routine use in clinical practice. We have therefore designed a randomized controlled trial to test the hypothesis that intraventricular thrombolysis improves clinical outcomes in IVH patients.

Study objectives

The primary aim of this study is to test the hypothesis that IVH patients requiring EVD placement, with stabilized clots, will have better clinical outcomes when treated with intraventricular rt-PA (1 mg q8h, up to 12 doses) relative to those receiving placebo within 72 hours of onset.

Methods

Design

The CLEAR III study is a randomized, multicenter, double-blinded, placebo-controlled phase III trial (two arms with 1:1 randomization for the first 104 patients followed by adaptive randomization) in ICH/IVH patients (figure 1). The protocol is registered with clinicaltrials.gov () and approved by each site's Institutional Review Board.

Inclusion criteria

- Spontaneous ICH ≥ 30 cc and IVH obstructing 3rd and/or 4th ventricles
- Symptom onset less than 24 hours prior to diagnostic CT scan
- Age 18–80 years
- An EVD must be in-place and stable at the time of randomization, ideally using no more than 2 complete passes
- Systolic blood pressure (SBP) <200 mmHg sustained for the 6 h before drug administration (closest to randomization)

- No test article may be administered until at least 12 hours after symptom onset
- Randomization within 72 h of CT scan diagnosing IVH
- Modified Rankin Score (mRS) before ICH of 0 or 1

Imaging inclusion criteria

- ICH/IVH clot stability: ICH must be ≤ 30 cc on initial presentation and not exceed 35 cc on subsequent pre-randomization stability scans. Stability Scan: A CT scan performed 6 hours or more after EVD placement must be stable as defined by: (i) ICH size difference is ≤ 5 cc compared to the most recent previous CT scan determined by the $(A \times B \times C)/2$ method; (ii) 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; (iii) Catheter tract bleeding must be ≤ 5 cc or mm; (iv) 3rd and/or 4th ventricles are occluded with blood. The investigator may continue to screen up to 72 hours for the initial bleeding to stabilize, as long as the subject can be randomized within 72 hours from time of the diagnostic CT scan. If clot sizes stabilize between 2 sequential CT scans at least 12 hours apart, the patient is eligible.

Exclusion Criteria

- Suspected (unless ruled out by conventional or CT angiogram or MRA/MRI) or untreated ruptured cerebral aneurysm, ruptured intracranial AVM, choroid plexus malformation, Moyamoya disease or tumor (treatment of an existing aneurysm or AVM must have occurred at least 3 months before the current onset)
- Clotting disorders (reversing anticoagulation will be permitted where long-term anticoagulation is not required)
- Platelet count $< 100,000$, INR > 1.4 (low platelet counts on admission can normalize within 24 hours as can an INR normalize to < 1.4)
- Pregnancy
- Infratentorial hemorrhage
- ICH/IVH enlargement that cannot be stabilized in the treatment time window
- Ongoing internal bleeding, involving retroperitoneal sites, or the gastrointestinal, genitourinary, or respiratory tracts
- Multi-focal, superficial bleeding, observed at multiple vascular puncture and access sites (e.g., venous cutdowns, arterial punctures) or site of recent surgical intervention
- Prior enrollment in the study
- Any other condition that 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 have DNR/DNI status prior to randomization

- Planned or simultaneous participation (between screening and day 30) in another interventional medical investigation or clinical trial

Clinical and imaging assessment

Eligible patients are identified upon diagnosis of IVH, and EVD placement. The INR must remain <1.4 during dosing. Infection is monitored through daily cultures of CSF drawn from the intraventricular catheter.

CT angiogram or digital subtraction angiogram with evaluation for “spot sign” (37) is encouraged and considered standard of care to complete the evaluation for aneurysm, AVM, or other malformations. A copy of the diagnostic and stability CT electronic images is uploaded to the VISION®-EDC (electronic data capture) online database prior to randomization (software provided by Prelude Dynamics Inc., Austin, Texas; study-specific implementation design developed by Emissary International LLC, Austin, Texas). The Surgical and Reading Centers centrally review these scans to confirm eligibility and to measure ICH, IVH, and catheter tract clot volume/stability. All imaging data is electronically transferred and read at the Reading Center on a weekly basis, to assure quality of CT-based decision making at the recruiting centers. After the last enrolled subject completes the one-year follow-up visit, data monitoring tasks will be completed to finalize and lock all clinical and radiological data. The coordinating center will remain blinded to follow-up clinical information and treatment designation until after data lock occurs.

Before dosing, the site investigator is required to view the most recent CT scan, confirming that the catheter tip is within the ventricular system. A CT scan is required daily on days 1 through 5, and then repeated approximately 24 and 72 hrs post last dose of test article. During dosing, all patients must receive a minimum of one scan per day, or at least after every three doses. The CT scan will be evaluated by the site investigator for clot lysis and asymptomatic bleeding (including new onset or expansion of catheter tract hemorrhage) prior to the next administration of test article. An unscheduled CT scan will be done if the subject improves or worsens by more than two points on the GCS motor scale for greater than 8 hours.

Randomization

Patients are randomized to receive the investigational product according to a centralized procedure coordinated via the online VISION-EDC system. The randomization system for investigational product is based on computer-generated randomization code lists, with stratification for thalamic and non-thalamic ICH location, and for IVH volume. The first 104 patients are randomized 1:1 to each treatment arm. Subsequently the adaptive randomization scheme gives patients a weighted chance of being randomized to each treatment arm based upon the distribution of IVH size and ICH location of previously enrolled subjects at the time of the enrollment. Patients will be stratified for randomization by each of the following

- ICH location (thalamic or non-thalamic), and
- IVH volume (20, >20 – 50, or >50 ml) measured using planimetric techniques.

Treatment or intervention

A neurosurgeon and neurocritical care physicians or their trained designees performs EVD injections under standard sterile technique. Either 1.0 mg/1 mL of rt-PA or 1 mL of normal saline is administered via the EVD. This is performed via iso-volumetric injection to ensure clearance of the study drug from the catheter and delivery to the clot. At least 5 ml of CSF is removed prior to injection of 1 ml of test article followed by a 4 ml flush of sterile saline into the ventricle. Injection is followed by closure of the catheter for 1 hour and then opening of the EVD for drainage of clot and CSF until the next injection every 8 hours. The first EVD injection occurs after randomization, no sooner than 12 hours after symptom onset. Treatment continues for up to 12 doses of test article unless, the EVD is discontinued, an endpoint of clot lysis is reached, or an adverse treatment endpoint occurs (e.g. symptomatic hemorrhage). Treatment success endpoints are (i) both 3rd and 4th ventricles are open; (ii) IVH related mass effect [dilated or shifted ventricle] is resolved; or (iii) an estimated 80% resolution of the IVH clot has occurred from the time clot stability was established. After the last dose, the EVD is closed for one hour and then reopened to drain for 24 hours to allow for complete removal of test article and free plasmin. The EVD is removed when the patient tolerates 24 h of EVD closure with no sustained elevation of ICP above 15 mmHg.

If the catheter does not remain patent, saline irrigation may be performed. Replacement of catheters is guided by neurosurgical clinical judgment. The Surgical Center located at the University of Chicago reviews all catheter placements and monitors clot removal assessments, catheter discontinuation protocols, and evaluates the safety and efficacy of the surgical procedure. None of these therapies are mandated in the protocol, but all are recorded in the case report form.

Supportive care includes ICP management with CSF drainage as well as osmotic therapy, hyperventilation, analgesic-sedation, induced coma, surgical management, and where indicated to control ICP.

Investigational medicinal product

The investigational product Alteplase (rt-PA, Genentech, Inc., San Francisco, California) is supplied as 2 mg lyophilized powder in glass vials. The dose of rt-PA to be administered is 1.0 mg in 1ml. Alteplase is reconstituted only with USP grade sterile water without preservatives for injection. The rt-PA or normal saline (placebo) is prepared by the study pharmacist at each site and delivered to the ICU along with a 4 ml flush (non-bacteriostatic saline) in a separate packet.

Blinding

The investigational product and placebo appear identical and cannot be distinguished from each other. At the time of subject randomization the EDC system transmits the treatment assignment via email or fax to the unblinded site pharmacist and the central pharmacist. This is the only documentation of treatment assignment and is not viewable in the system by other study personnel. The unblinded pharmacist prepares the investigational product, which is clear and colorless, in the same manner as the placebo. All others involved in the conduct

of the study are blinded to treatment allocation. The Data Safety Monitoring Board (DSMB) has access to pooled data and grouped by treatment assignment (A:B).

Primary outcomes

The primary outcome is the proportion of patients with modified Rankin Scale (mRS) scores of 0–3 at day 180.

Secondary outcomes

- categorical shift in mRS ordinal (0–6) scale (Cochran-Mantel-Haenszel analysis)
- proportion of patients with mRS 0–4 vs 5,6 in the two treatment groups at day 180
- mortality at day 180
- absolute intraventricular hemorrhage volume and change in volume of blood at 72 hours
- intensity of critical care management as measured by length of ICU stay, duration of EVD, intensity of ICP management, and frequency of critical care complications.
- measures of functional outcome and quality of life:
- modified Rankin Scale, Barthel Index, EQ-5D (EuroQOL), and total time at home after ICH at months 1, 3, 6, 9, and 12. The modified Rankin Scale will be videotaped, at 1, 6, and 12 month clinic follow-up visits for blinded adjudication by the Outcomes Center located at the University of Glasgow.
- Extended Glasgow Outcome Scale, the Stroke Impact Scale, the NIHSS, the Mini-Mental State Exam, and the Preference-Based Stroke Index at month 1, 6, and 12.
- The study Principal Investigator and coordinator are trained on all evaluations and may perform the evaluations. The study requires annual/bi-annual certification for NIHSS and mRS respectively.

Data monitoring body

Safety interim analysis is undertaken when 100, 150, 250, and 400 patients have completed six-month assessments. These assessments will be conducted by an independent data safety monitoring board (DSMB) appointed by NINDS. Recruitment to the trial will be suspended if a threshold level is exceeded for the events of death prior to day 30 following symptom onset (40%), symptomatic re-bleeding within 72 hours of last dose (25%) and bacterial infection within 72 hours of last dose (20%) for either treatment group. The DSMB may stop or recommend modification of the protocol at any point. No formal interim analyses for efficacy or futility are planned.

Prior to site activation and as needed, study personnel at each enrolling center are trained on the protocol, ICH Good Clinical Practices, investigator responsibilities, Food and Drug

Administration (FDA) requirements, surgical protocols, and EDC data entry screens to acquaint the center personnel with the design and methods of the trial, the study organization, treatment monitoring, and integrity of data collection. Remote monitoring of source documentation for every randomized subject serves to verify the accuracy and completeness of data in the VISION-EDC system, the existence of applicable regulatory files, and that the investigator's obligations are being fulfilled. Similar remote quality assurance methods are undertaken by the Surgical Center, the Outcomes Center, the Radiology Reading Center, the medical monitors, and the Safety Endpoint Committee to assure protocol compliance and data integrity.

Sample size

From the Safety, CLEAR IVH A and CLEAR IVH B studies we observed an absolute difference of 15 to 17% in the probability of better outcomes comparing EVD + rt-PA vs EVD + placebo with control rates around 25%. To determine a sample size which adequately powers the study, we performed Monte Carlo simulations. A variety of simulation scenarios were examined to judge the sensitivity of power towards sample size (N=500, 600, and 700), effect size (odds-ratio=1.8 to 2.2), control group outcome rates (placebo rates of good outcome mRS 3 = 20%, 30%), model choice (correctly specified vs non-correctly specified model), and site clustering (between site heterogeneity parameterized as a latent effect with standard deviation 0.1 and 0.25 [i.e. 14%, 36% of log-odds-ratio treatment effect = 0.7, (OR=2.0), respectively]). The total projected sample size of 500 participants randomized to receive either intraventricular rt-PA or placebo (250 in each group) provides 80% or greater power to detect an absolute difference of 13% in the proportion of patients with mRS 0–3 outcome at 6 months (OR = 1.92, α = 0.05, two-tailed comparison).

Statistical analyses

All randomized subjects will be included in randomized controlled trial (RCT) analyses on an intention-to-treat basis. Missing outcome data will be handled through multiple imputation procedures subject to the validity of missing-at-randomness assumptions. For the primary outcome analysis, the proportions of mRS 0–3 outcomes will be compared between treatment and placebo arms, adjusted for ICH location (thalamic and non-thalamic) and IVH volume, using a binary logistic regression model. Although both adjusted and unadjusted results will be reported, adjusted analysis is prespecified as the primary outcome analysis for this RCT.

A secondary analysis of the categorical shift in mRS will be undertaken on the full range (0–6) of the mRS using Cochran–Mantel–Haenszel shift test and proportional odds logistic regression subject to the validity of shift analysis model assumptions. Other secondary outcome analyses will be carried out according to standard statistical principles for comparison of parametric or nonparametric distributions as appropriate.

Study organization and funding

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Conclusion

CLEAR III is the first, randomized, multicenter, double-blinded, placebo-controlled phase III trial assessing the efficacy of intraventricular thrombolytic therapy in IVH patients with an EVD. The allowance for dosing and EVD placement and removal decisions by non-study team physicians reflects the practical nature and generalizability of this study. If the study outcome is positive, it will significantly improve the therapeutic options for acute hemorrhagic stroke treatment. Based on available screening data, we estimate that 10–15% of all ICH, somewhere between 10,000 and 15,000 ICH subjects in the United States yearly, and 150 to 200,000 ICH subjects worldwide would be eligible for this therapy. It is an important step towards reducing the burden of ICH worldwide.

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The CLEAR III Investigative Team: Agnieszka, Ardel MD, PhD, University of Chicago; Alan Hoffer MD, Case-Western Reserve University Hospital; Alberto Torres Díaz, Bellvitge Hospital, Barcelona; Alexandre Luiz Longo, Hospital Sao Jose, Joinville; Andreas Luft MD, University of Zurich; Ann Helms, Medical College of Wisconsin; Ashis H. Tayal MD, Allegheny General Hospital; Asma Moheet, Cedars-Sinai Medical Center; Carsten Hobohm MD, University of Leipzig; Christiana Hall MD, University of Texas, Southwestern, Dallas; Christine Wijman, Stanford University; Christos Lazaridis MD, Medical University of South Carolina; Darren Lovick, St. Luke's Brain and Stroke Institute, Kansas City; David Antezana, Providence Stroke Center; David B. Seder, Maine Medical Center; David Decker, University of South Florida; David Greer MD, Yale University; David LeDoux, NorthShore Long Island; David Newell, Swedish Medical Center; David Sinclair, Montreal Neurological Institute at McGill University; Diederik Bulters, University of Southampton Hospital; Douglas Laske, Temple University Hospital; Dr Nevo Margalit, Sourasky Medical Center Tel Aviv; Dr. Christopher Ogilvy, Massachusetts General Hospital; Dr. Guy Rosenthal, Hadassah Hebrew University Hospital; Dr. Igor Ugorec, Atlantic Neuroscience Institute; Dr. Mel Boulton, London University Health Sciences Centre; Dr. Sagi Harnof, Chaim Sheba Medical Center; Dr's. Lawrence Wechsler and Paul Gardner, University of Pittsburgh Medical Center; Fernando Santiago, Puerto Rico Medical Center; Francois Aldrich, University of Maryland; Fuat Arian, Vall d'Hebron University Hospital, Barcelona; George A. Lopez MD, PhD, University of Texas, Houston; George Newman MD-PhD, Albert Einstein Medical Center; Gisele Sampaio Silva, Hospital Sao Paulo Universidade Federal de Sao Paulo/UNIFESP; H. Mark Crabtree MD, Springfield Neurological and Spine Institute; Hagen Huttner; University of Erlangen; Harold Adams MD, University of Iowa; Inam Kureshi, MD, Hartford Hospital; Issam Awad MD, NorthShore Chicago; J Mocco, Vanderbilt; Jack Jallo MD, PhD, Thomas Jefferson University Hospital; James Holsapple, Boston University Medical Center; Jean-Louis Caron MD, University of Texas, San Antonio; Joan Marti-Fabregas, Hospital de la Santa Creu i Sant Pau, Barcelona; Jody Leonardo MD; University of Buffalo; Jorge Marcondes de Souza, Hospital Universitario Clementino Fraga Filho; Katja Wartenberg, University of Halle; Kavian Shahi, Mercy General Sacramento; Ken Butcher MD, University of Alberta; Kevin Cockcroft, Penn State Hershey Medical Center; Kristi Tucker, Wake Forest University; Laszlo Csiba, University of Debrecen; Laszlo Szapary, University of Pecs; Marcelo Kern, Hospital de Pronto Socorro de Porto Alegre; Maria Aguilar MD, Mayo Clinic Arizona; Mark Harrigan, University of Alabama at Birmingham; Martin Gizzi, New Jersey Neuroscience Institute at JFK; Mason Markowski MD, PhD, Georgetown University; Mauricio Concha, InterCoastal Medical Center; Menashe Zaaroor, Rambam Medical Center; Michael Jacoby, Ruan Neurology Clinic and Research Center; Michael Luke James MD, Duke University Medical Center; Michael Reinert MD, U Hosp, Inselspital, Bern; Michael Schneck MD, Loyola University Medical Center; Michel Torbey, Ohio State University Medical Center; Mr Hiren Patel, Salford Royal NHS Foundation Trust; Opeolu Adeoye, University of Cincinnati; Qaisar A. Shah MD, Abington Memorial Hospital; Pal Barzo, University of Szeged; Panos Varelas, Henry Ford Health System; Paul Camarata MD, Kansas University Medical Center; Paul Vespa MD, UCLA; Pedro Telles Cougo Pinto, Hospital de Clinicas de Ribeirao Preto; Peter Bazso, Budapest - Honved Korhaz; Professor A D Mendelow, Newcastle General Hospital; R. Scott Graham, Virginia Commonwealth University; Robert E. Hoesch MD, University of Utah; Salvador Cruz-Flores, M.D., Saint Louis University; Sayona John, Rush University; Sheila Cristina Ouriques Martins, Hospital de Clinicas de Porto Alegre; Stanley Tuhim, Mount Sinai; Stephan A. Mayer MD, Columbia University; Sven Poli, University of Heidelberg; Thomas Kerz, University of Mainz; Thomas Mirsen MD, Cooper University Hospital; Venkatesh Aiyagari, University of Illinois at Chicago; Wendy Ziai, Johns Hopkins Hospital; William Freeman MD, Mayo Clinic, Jacksonville; Ziad Eil-Zammar MD, SUNY Upstate Medical Center

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International Journal of Stroke

Fig 1.

Clot lysis evaluation of accelerated resolution of intraventricular hemorrhage study assessment flow chart. CT, computed tomography; IVH, intraventricular hemorrhage; EVD, external ventricular drain; ICH, intracerebral hemorrhage; ASA, American Stroke Association; AE, adverse event; SAE, severe adverse event; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; GOS, Glasgow outcome scale; EQ-5D, Euro-QuOL 5-Dimension; PBSI, Preference-Based Stroke Index