CLINICAL PROTOCOL TITLE

rFVIIa for Acute Hemorrhagic Stroke Administered at Earliest Time (FASTEST) Trial

INVESTIGATOR-SPONSORED STUDY PROPOSAL
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LIST OF COMMONLY USED ABBREVIATIONS

AE	adverse event
AESI	adverse events of special interest
BP	blood pressure
CIRB	central institutional review board
CRF	case report form
CT	computed tomography
DCU	Data Coordination Unit
DSMB	data safety monitoring board
EFIC	exception from informed consent
FDA	Food and Drug Administration
FVII	coagulation factor seven
FVIIa	activated coagulation factor seven
FIX	coagulation factor nine
FX	coagulation factor ten
GCP	Good Clinical Practice
ICH	intracerebral hemorrhage
INR	international normalized ratio international units
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous
IVH	intraventricular hemorrhage
LAR	Legally Authorized Representative
mRS	modified Rankin Scale
MSU	mobile stroke unit
MUSC	Medical University of South Carolina
NCC	National Coordinating Center
NDMC	National Data Management Center
NIH	National Institutes of Health
NIHSS	NIH Stroke Scale
NINDS	National Institute of Neurologic Disorders and Stroke
Non-STEMI	myocardial infarction without ST segment elevation
PI	principal investigator
PT	prothrombin time
RBC	red blood cell
RCC	Regional Coordinating Center
REB	Research Ethics Board
rFVIIa	recombinant activated coagulation factor seven
SADR	serious adverse drug reaction
SAE	serious adverse event
SAH	subarachnoid hemorrhage
SAR	serious adverse reaction
STEMI	ST segment elevation myocardial infarction
SUSAR	suspected unexpected serious adverse reaction
t-PA	tissue plasminogen activator
UCMC	University of Cincinnati Medical Center

CONDENSED PROTOCOL SYNOPSIS	
Protocol Title	Recombinant Factor VIIa (rFVIIa) for Acute Hemorrhagic Stroke Administered at Earliest Time (FASTEST) Trial
Acronym	**FASTEST Trial**
Study Sites	Approximately 115 hospital sites and 15 mobile stroke units (MSUs) in the NINDS-funded StrokeNet in the U.S. and key global institutions
Study Period	5 years with estimated 3½ years of study recruitment
Study Population	Adult patients with spontaneous intracerebral hemorrhage (ICH) treated within two hours of stroke onset or last known well
Primary Study Objective	To test the hypothesis that treatment with rFVIIa within two hours of onset in appropriately selected patients with spontaneous ICH improves outcome as measured by the ordinal distribution of the modified Rankin Scale (mRS) at 180 days, as compared to placebo
Secondary Study Objective	To test the hypothesis that treatment with rFVIIa within two hours of onset in appropriately selected patients with spontaneous ICH decreases bleeding between baseline and 24-hour head imaging, as compared to placebo
Study Design	Two-arm, randomized, double-blinded clinical trial
Sample Size	860 subjects (maximum)
Informed Consent	(Exception from Informed Consent for) Emergency Research
Inclusion Criteria	1) Patients aged 18-80 years, inclusive 2) Patients with spontaneous ICH 3) Able to treat with study medication (rFVIIa/placebo) within 120 minutes of stroke onset or last known well 4) Efforts to obtain informed consent per EFIC guidelines (U.S.) or adherence to country-specific emergency research informed consent regulations (Canada, Germany, Spain, U.K., Japan)
Exclusion Criteria	1) Score of 3 to 7 on the Glasgow Coma Scale 2) Secondary ICH related to known causes (e.g., trauma, aneurysm, arteriovenous malformation (AVM), oral anticoagulant use (vitamin K antagonists or novel oral anticoagulants) within the past 7 days, coagulopathy, etc.) 3) ICH volume < 2 cc or ≥ 60 cc 4) Blood filling 2/3 or more of one lateral ventricle of the brain, OR, blood filling at least 1/3 of both lateral ventricles 5) Pre-existing disability (mRS > 2) 6) Symptomatic thrombotic or vaso-occlusive disease in past 90 days (e.g., cerebral infarction, myocardial infarction, pulmonary embolus, deep vein thrombosis, or unstable angina) 7) Clinical or EKG evidence of ST elevation consistent with acute myocardial ischemia 8) Brainstem location of hemorrhage (patients with cerebellar hemorrhage may be enrolled) 9) Refusal to participate in study by patient, legal representative, or family member 10) Known or suspected thrombocytopenia (unless current platelet count documented above 50,000/μL) 11) Unfractionated heparin use with abnormal PTT 12) Pro-coagulant drugs within 24 hours prior to patient enrollment into the FASTEST trial (example, tranexamic acid or aminocaproic acid) 13) Low-molecular weight heparin use within the previous 24 hours 14) Recent (within 90 days) carotid endarterectomy or coronary or cerebrovascular angioplasty or stenting Advanced or terminal illness or any other condition the

	investigator feels would pose a significant hazard to the patient if rFVIIa were administered 15) Recent (within 30 days) participation in any investigational drug or device trial or earlier participation in any investigational drug or device trial for which the duration of effect is expected to persist until to the time of FASTEST enrollment 16) Planned withdrawal of care or comfort care measures 17) Patient known or suspected of not being able to comply with trial protocol (e.g., due to alcoholism, drug dependency, or psychological disorder) 18) Known or suspected allergy to trial medication(s), excipients, or related products 19) Contraindications to study medication 20) Previous participation in this trial (previously randomized) 21) Females of childbearing potential who are known to be pregnant or within 12 weeks post-partum and/or lactating at time of enrollment
Study Intervention	We will randomly assign patients in a 1:1 ratio to intravenous rFVIIa or placebo at a dose of 80 μg/kg (maximum 10,000 μg or 10 mg) and administered intravenously over 2 minutes. All investigators and participants will be blinded throughout the course of the study. Due to the emergency nature of the intervention, a simple randomization scheme will be implemented.
Primary Outcome Measure	The primary outcome measure is the following distribution of the ordinal mRS at 180 days: 0-2, 3, and 4-6.
Primary Safety Measure	The primary safety measure of the study will be life-threatening thromboembolic complications during the first four days after completion of study drug. A significant life-threatening complication will be defined as development of: 1) acute myocardial infarction, 2) acute cerebral infarction, and 3) acute pulmonary embolism.
Statistical Analysis for Primary Outcome Measure	We will compare the ordinal values of the 180-day mRS by treatment group via an ordinal logistic regression adjusted for age, baseline ICH volume, baseline IVH volume, and pre-stroke mRS. Since the baseline covariates are continuous, we will rely on comparisons of nested models to assess the proportionality assumption (a full description will be added to the Statistical Analysis Plan, rather than the protocol). If the proportionality assumption is violated, then the primary analysis would be a partial proportional odds model.

1.0 STUDY OBJECTIVE

The *objective* of the rFVIIa for Acute Hemorrhagic Stroke Administered at Earliest Time (FASTEST) Trial is to establish the first treatment for acute spontaneous ICH within a time window and subgroup of patients that is most likely to benefit. Our *central hypothesis* is that rFVIIa, administered within 2 hours from onset with an identified subgroup of subjects most likely to benefit, will improve outcomes at 180 days as measured by the modified Rankin score (mRS) and decrease ongoing bleeding, as compared to placebo. The *rationale* for this study is that there is no scientifically proven treatment for acute ICH. We will test our central hypothesis by pursuing the following *specific aim*:

Primary Specific Aim: *To test the hypothesis that treatment with rFVIIa within two hours of onset in appropriately selected patients with spontaneous ICH improves outcome as measured by the ordinal distribution of the modified Rankin Scale (mRS) at 180 days, as compared to placebo.*

Secondary Specific Aim: *To test the hypothesis that treatment with rFVIIa within two hours of onset in appropriately selected patients with spontaneous ICH decreases bleeding between baseline and 24-hour head imaging, as compared to placebo.*

2.0 BACKGROUND AND SIGNIFICANCE

Intracerebral hemorrhage (ICH) accounts for more than 10% of the estimated 17 million strokes worldwide each year or about 1,700,000 cases per year.[1-3] ICH is the deadliest type of stroke with a mortality of more than 40% and only 20% of survivors are functionally independent at 6 months.[4-8] There is no scientifically proven effective treatment for ICH.

The baseline factors associated with ICH mortality and functional outcome are volume of ICH, volume of intraventricular hemorrhage (IVH), growth of ICH during first hours of onset, age, Glasgow Coma Scale (GCS), and infratentorial location.[6,9,10] Of these factors, only growth of ICH and the resulting volumes of ICH and IVH are biologically modifiable.

Growth of ICH has a rapid time course with the majority of bleeding completed within 3 hours of onset.[9,11] Substantial growth (> 1/3 increase of initial volume of ICH) occurred in 35-40% of ICH subjects in the rFVIIa Phase IIb trial, although nearly ¾ of patients had some growth in bleeding between the baseline and 24 hour scan.[9,12] In this trial, percentage growth (cumulative OR 0.84 [95% CI: 0.75, 0.92; p < 0.0001]), initial ICH volume (cumulative OR 0.94 [95% CI: 0.91, 0.97; p < 0.0001]), GCS (cumulative OR 1.46 [95% CI: 1.21, 1.82; p < 0.0001]), and age (cumulative OR 0.95 [95% CI: 0.92, 0.98; p = 0.0009]) predicted outcome on the modified Rankin Scale (mRS). For each mL increase in ICH from the baseline ICH volume and for each 10% increase in ICH growth, patients were 6% and 16% more likely to increase 1 full point on the modified Rankin Scale (mRS).[9]

The only medical treatment consistently demonstrated to decrease ICH growth in spontaneous ICH is recombinant Factor VIIa (rFVIIa).[12-14] FVIIa is a key protein in the coagulation cascade that complexed with tissue factor, or on the surface of activated platelets, can activate coagulation Factor X to Factor Xa, as well as coagulation Factor IX to Factor IXa. Factor Xa, in complex with other factors, then converts prothrombin to thrombin, which leads to the formation of a hemostatic plug by converting fibrinogen to fibrin and thereby inducing local hemostasis.[15,16] Thus, rFVIIa effects are concentrated at the site of vessel injury where tissue factor is released and activated platelets are present.

The effectiveness of rFVIIa in slowing ICH growth is strongly related to time from ICH onset to administration, with a 6 cc decrease in the volume of ICH as compared to placebo when administered within 2 hours of onset.[12,14,17] The initial rFVIIa Phase IIb trial demonstrated that rFVIIa decreased ICH growth and had better clinical outcomes as compared to placebo; the effect of the dose on ICH growth and side effects of clinical thrombotic events were dose related.[12] Based upon the Phase IIb data, an 80 micrograms/kilogram dose was chosen for the Phase III FAST Trial. The FAST Trial once again showed that rFVIIa slowed ICH growth but showed no difference in clinical outcomes.[14]

This discrepancy between the two trials is explained in part to a major imbalance in volume of IVH (favoring rFVIIa in Phase IIb and favoring placebo in the FAST Trial). However, the major reason for failure of rFVIIa was that a large number of patients were treated in a time window in which intracerebral bleeding had been completed, or they were already destined to a poor outcome due to the larger baseline volumes of ICH and/or IVH. A post-hoc analysis of the FAST trial demonstrated that rFVIIa given within 150 minutes to patients with an ICH < 60 cc, < 5 cc of IVH (a small volume of IVH), and age ≤ 70 had an adjusted OR for poor outcome with rFVIIa treatment of 0.28 (95% CI: 0.08, 1.06); the strong effect was replicated in the Phase IIb trial data.[17]

2.1 The Importance of Minimizing Time to Treatment

Table 1: SPOTLIGHT Trial – Volume of ICH+IVH at 3 time points

Scan	Stroke onset to CT (h)	rFVIIa ICH+IVH vol (mL) Median (IQR) n = 19	Placebo ICH+IVH vol (mL) Median (IQR) n = 25
Baseline CT	1.4 (1.2, 2.6)	**24.1 (16.0, 41.4)**	**23.1 (11.5, 53.0)**
Immediate post-dose CT	3.0 (2.5, 4.3)	**35.9 (20.8, 63.0)**	**30.4 (21.4, 63.1)**
24-hour CT	26.6 (26.1, 27.8)	**31.3 (17.4, 64.8)**	**33.3 (18.5, 59.6)**

Minimization of time from onset to treatment with rFVIIa is critical given the small time window for stopping or slowing growth of ICH. In the SPOTLIGHT Trial, subjects with a positive "spot sign" on CT angiography indicating ongoing bleeding had imaging at baseline, immediately after start of study medication, and 24 hours (written communication, Andrew Demchuk). *Almost all additional bleeding occurred between the baseline CT imaging and the CT scan immediately after treatment.* Thus, there was little opportunity for rFVIIa to biologically modify ongoing bleeding.

These data are consistent with prior prospective imaging data of ICH from Greater Cincinnati and Northern Kentucky in the 1990s that showed the majority of bleeding occurring between the baseline CT scan done at a median of 89 minutes and the CT scan done 1 hour later.[11,18] The mean combined volume of ventricular and parenchymal hemorrhage was 35±35 mL on the baseline CT scan and 44±44 mL on the 1-hour CT scan. The post-hoc analysis of the Phase IIb and FAST ICH trials also indicate that for rFVIIa to slow bleeding and improve outcome, it must be given within 150 minutes and for most patients, even sooner. **In summary, to maximize the benefit/risk ratio of rFVIIa, it must be administered even more quickly than the time window for t-PA.**

Mobile Stroke Units

Mobile stroke units (MSUs) that include CT imaging of the brain, intravenous medications, equipment, and critical care personnel including physicians, whether in-person or by telemedicine, can dramatically decrease time from onset to IV t-PA treatment as compared to emergency department settings.[19] As an example, in the Prehospital Acute Neurological Treatment and Optimization of Medical Care in Stroke (PHANTOM-S) substudy in Berlin, thrombolysis rates in ischemic stroke were 200 of 614 patients (32.6%) when an MSU was deployed and 330 of 1497 patients (22.0%) when conventional care was administered ($p < 0.001$).[20,21] Among all patients who received thrombolysis, the proportion of golden hour thrombolysis (treatment within an hour of stroke onset) was 6-fold higher after MSU deployment (62 of 200 patients [31.0%] vs. 16 of 330 [4.9%]; $p < 0.01$). Compared with patients with a longer time from symptom onset to treatment, patients who received golden hour thrombolysis had no higher risks for 7- or 90-day mortality (adjusted OR, 0.38 [95% CI: 0.09, 1.70]; $p = 0.21$ and 0.69 [95% CI: 0.32, 1.53]; $p = 0.36$) and were more likely to be discharged home (adjusted OR, 1.93 [95% CI: 1.09, 3.41]; $p = 0.02$). The Houston MSU evaluated and treated 12 patients with t-PA during their run-in phase.[19,22] The MSU on scene to t-PA time, minimum was 25 minutes (range 18-42) and last seen normal to t-PA time was 98 minutes (range 47-265).

Four of the 12 patients were treated within 60 minutes.

The FASTEST Trial also requires CT imaging of the brain in MSUs or emergency department settings to identify eligible ICH patients. To this point, the MSUs have focused only on clinical trials that compare IV t-PA administered by mobile stroke units as compared to administered in the emergency department. The ongoing Houston experience provides the best estimate of the volume of ICH using MSUs.

From August 2014 to May 31 2017, the Houston MSU assessed 80 ICH patients. The time from onset to imaging was 0-60 min: 35%, 61-120 min: 31.25%, 121-180 min: 13.75%, > 180 min or undocumented: 20%. Of the 80 ICHs, approximately 20% would be excluded because of anticoagulation. This equates to about 15 patients per year with spontaneous ICH who are imaged within 120 minutes. This was accomplished using only an MSU from 8:00 AM to 6:00 PM and much less intensively every other week (standard EMS management week in ongoing randomized trial of t-PA treatment).

The PRESTO group, which is a group representing mobile stroke units around the world, views acute treatment of ICH as a unique opportunity for MSUs given the small time window for ongoing bleeding.[23]

Exception from Informed Consent (EFIC)

This is the first trial of ICH to use Exception from Informed Consent or EFIC. FASTEST requires CT imaging to document ICH and eligibility criteria for the trial. Thus, randomization and treatment can only be done after brain imaging. EFIC is justified in the FASTEST Trial because of the need for an ultra-short time window and because there was only a 5% increased risk in thrombotic serious adverse events (SAEs) in pilot studies of rFVIIa. Per EFIC requirements, investigators will attempt to obtain consent, but this should be done within 30 minutes of baseline CT imaging and 120 minutes from stroke onset/last known well. Given the 90-minute delay between baseline imaging and treatment in the SPOTLIGHT and STOP-IT Trials, EFIC is critical to minimize time to treatment. Detailed description of the need for EFIC, why the FASTEST Trial meets requirements for EFIC, and methodology for EFIC for the FASTEST Trial, including use of central IRB (CIRB), are outlined in section on Protection of Human Subjects.

With these three approaches, we will decrease the time from onset to treatment with rFVIIa from a mean time of 160±37 minutes as seen in the FAST trials to treatment of all participants within 120 minutes.

3.0 PRELIMINARY STUDIES OF rFVIIa AND ICH TREATMENT

rFVIIa Pharmacology and Use in Clinical Practice

rFVIIa is a protein that complexed with tissue factor can activate coagulation Factor X to Factor Xa, as well as coagulation Factor IX to Factor IXa.[15,16] Acting through these other factors, rFVIIa converts prothrombin to thrombin, which leads to the formation of a hemostatic plug by converting fibrinogen to fibrin and thereby inducing local hemostasis. When administered to supraphysiologic concentrations, rFVIIa binds to the surface of activated platelets in a TF-independent manner and promotes factor X (FX) activation and thrombin generation on the activated platelet surface. In the hemophilias, platelet-bound rFVIIa partially restores platelet surface FX activation, which is deficient because of the absence of factor VIIIa/IXa complexes. In non-hemophilic conditions, platelet-bound rFVIIa increases activation of both FIX and FX and increases thrombin generation above normal levels. Increased thrombin generation then promotes increased activation and local accumulation of platelets, including dysfunctional platelets, potentially improving hemostasis in a wide range of bleeding conditions. The half-life of rFVIIa is about 2.5 to 3 hours.

The first proof of principle for using pharmacological doses of rFVIIa as a hemostatic agent was obtained by producing small amounts of pure plasma-derived rFVIIa, which showed encouraging effect in 2 patients with haemophilia A and inhibitors.[15] To make pure rFVIIa available for use in a larger number of patients, recombinant FVIIa was produced that was approved for use in patients with inhibitors against coagulation factors (congenital hemophilia and acquired hemophilia) in 1996 (E.U.), 1999, 2005 (U.S.), and 2000 (Japan).[15]

The efficacy rate in severe bleedings and in major surgery including major orthopedic surgery has been found to be around 90% in controlled studies, and no serious safety concerns have been demonstrated. It has been used widely and extensively in hemophilia patients, with and without inhibiting factors, since the 1990s as well as many off-label indications for sustained and severe bleeding.[15]

When Novo Nordisk A/S was first considering the use of rFVIIa in patients with bleeding who didn't have hemophilia, physician consultants pointed out that ICH represented a great opportunity to measure the biological effectiveness of rFVIIa in ongoing intracerebral bleeding since the bleeding could be quantitated on prospective serial CT imaging as demonstrated by Brott, Broderick, and colleagues in the late 1990s.[11,18] Based upon these clinical data, and pharmacology of rFVIIa, Novo Nordisk A/S initiated a program of clinical trials for spontaneous ICH.

Phase IIa rFVIIa Non-U.S. Trial[24]

In this randomized, double-blind, placebo-controlled, dose-escalation trial, 48 subjects with spontaneous ICH diagnosed within 3 hours of onset were treated with placebo (n=12) or rFVIIa (10, 20, 40, 80, 120, or 160 µg/kg; n = 6 per group). The study was conducted between August 2001 and October 2002 at 14 trial centers in Australia, Germany, Italy, Singapore, Spain, Taiwan, and the United Kingdom. Patients with any history of thromboembolic or vaso-occlusive disease were excluded.

The primary endpoint was the frequency of adverse events (AEs). Safety assessments included serial electrocardiography (ECG), troponin and coagulation testing, lower extremity Doppler ultrasonography, and calculation of edema/ICH volume ratios. At admission, mean National Institutes of Health Stroke Scale (NIHSS) score was 14 (range 1-26), median Glasgow Coma Scale score was 14 (range 6-15), and mean ICH volume was 21 mL (range 1-151). Mean time from onset to treatment was 181 minutes (range 120-265). Twelve serious AEs occurred, including five deaths (mortality 11%). Six AEs were considered possibly treatment-related, including rash, vomiting, fever, ECG T-wave inversion, and 2 cases of deep vein thrombosis (placebo and 20-µg/kg groups). No myocardial ischemia, consumption coagulopathy, or dose-related increase in edema/ICH volume occurred. In summary, this small phase II trial evaluated a wide range of rFVIIa doses in acute ICH and raised no major safety concerns.

Table 2: Relevant Outcomes in Phase IIa Non-U.S. Trial

Outcome	Placebo	10µg/kg	20µg/kg	40µg/kg	80µg/kg	120µg/kg	160µg/kg
Mean ICH volume at baseline (ccs)	31±31	7±6	10±5	22±25	21±20	29±32	42±60
Mean % growth of ICH (ccs) from baseline to 24 hours*	9	33	0	33	0	33	66
mRS > 3 at 90 days (%)	45%	0%	33%	67%	50%	50%	67%
Mortality at 90 days (%)	33%	0%	0%	33%	0%	33%	33%
Serious ischemic events (arterial or venous) within 90 days (%)	8%	0%	0%	17%	0%	0%	0%

*ICH growth defined as a > 33% or 12.5 mL increase from baseline at 24 hours

Phase IIa rFVIIa U.S. Trial[25]

In this multi-center, randomized, double-blind, placebo-controlled, dose-escalation trial, 40 patients diagnosed with ICH by computed tomography within 3 hours of onset were treated with placebo or 5, 20, 40, or 80 μ g/kg of rFVIIa (n = 8 per group). Patients with any history of thromboembolic or vaso-occlusive disease were excluded. The primary endpoint was the frequency of AEs.

Table 3: Relevant Outcomes in Phase IIa U.S. Trial (n= 8 per group)

Outcome	Placebo	5 μg/kg	20μg/kg	40μg/kg	80μg/kg
Mean ICH volume (ccs)	15±17	17±9	18±11	25±44	11±14
Mean percentage increase in ICH growth from baseline to 24-hour CT (%)	11%	64%	79%	37%	4%
Absolute growth in ICH+IVH from baseline to 24-hour CT (ccs)	2	13	10	1	1
mRS > 3 at 90 days (%)	50%	63%	38%	63%	25%
Mortality at 90 days (%)	20%	40%	40%	38%	0%
Serious adverse ischemic events (arterial or venous) (%)	13%	0%	13%	13%	13%

Phase IIb rFVIIa Trial[12]

The trial randomly assigned 399 patients with ICH diagnosed by CT within 3 hours after onset to receive placebo (96 patients) or 40 μg of rFVIIa per kilogram of body weight (108 patients), 80 μg per kilogram (92 patients), or 160 μg per kilogram (103 patients) within 1 hour after the baseline scan. The primary outcome measure was the percent change in the volume of the ICH at 24 hours. Clinical outcomes were assessed at 90 days.

The mean time from symptom onset to treatment was 167 minutes. Hematoma volume increased more in the placebo group than in the rFVIIa groups (p = 0.01 for the comparison of the 3 rFVIIa groups with the placebo group, Table 3). The combined comparison for ICH+IVH of rFVIIa vs. placebo was also significant (p = 0.006). The hemostatic effect of rFVIIa was more evident when treatment was given within 3 hours after the onset of symptoms. In this subgroup (269 patients), the mean increase in volume of ICH was 34% for the placebo group, as compared with 13% for the rFVIIa-treated patients (p = 0.004), and the absolute increase in volume of ICH was 10.7 mL for the placebo group, as compared with 4.4 mL for the rFVIIa-treated patients (p = 0.009). Among those treated more than 3 hours after onset (115 patients), the mean increase in ICH volume was 14% for the placebo group, as compared with 16% for the rFVIIa groups (p = 0.86), and the absolute increase was 3.1 mL, as compared with 3.8 mL (p = 0.76).

Sixty-nine percent of placebo-treated patients died or were severely disabled (as defined by a modified Rankin Scale score of 4-6), as compared with 55%, 49%, and 54% of the patients who were given 40, 80, and 160 μg of rFVIIa, respectively (p = 0.004 for the comparison of the 3 rFVIIa groups with the placebo group). Mortality at 90 days was 29% for patients who received placebo, as compared with 18% in the 3 rFVIIa groups combined (p = 0.02). Serious thromboembolic AEs, mainly myocardial or cerebral infarction, occurred in 7% of rFVIIa-treated patients, as compared with 2% of those given placebo (p = 0.12). Based upon these data, the 80 μg/kg dose was selected for the Phase III trial as having the best balance in slowing ICH growth, clinical outcome, and ischemic side effects.

Table 4: Baseline ICH Volumes and Relevant Outcomes in Phase IIb Trial

Outcome	Placebo	40µg/kg	80µg/kg	160µg/kg
Mean ICH volumes at baseline (ccs)	24±22	22±22	23±24	26±30
Mean percentage increase in ICH growth from baseline to 24-hour CT (%)	29%	16%	14%	11%
Mean percentage increase in ICH+IVH growth from baseline to 24-hour CT (%)	31%	16%	14%	13%
Absolute growth in ICH+IVH from baseline to 24-hour CT (ccs)	11	7	5	4
mRS > 3 at 90 days (%)	69%	55%	49%*	54%
Mortality at 90 days (%)	29%	18%	18%	19%
Serious ischemic events (arterial or venous) within 90 days (%)	2%	6%	4%	10%

*p = 0.0097, number needed to treat = 6

Phase III FAST Trial[14]

The trial randomly assigned 841 patients with intracerebral hemorrhage to receive placebo (268 patients), 20 µg/kg of rFVIIa (276 patients), or 80 µg/kg (297 patients) within 4 hours after the onset of stroke. The primary endpoint was poor outcome, defined as severe disability or death (mRS 5-6) according to the mRS at 90 days after the stroke. The mean time from onset of symptoms to treatment was 160±137 minutes. Treatment with 80 µg/kg of rFVIIa per kilogram resulted in a significant reduction in growth in volume of the hemorrhage. The mean estimated increase in volume of the intracerebral hemorrhage at 24 hours was 26% in the placebo group, as compared with 18% in the group receiving 20 µg/kg of rFVIIa per kilogram (p = 0.09) and 11% in the group receiving 80 µg/kg (p < 0.001). The growth in volume of intracerebral hemorrhage was reduced by 2.6 mL (95% CI: -0.3, 5.5; p = 0.08) in the group receiving 20 µg/kg of rFVIIa per kilogram and by 3.8 mL (95% CI: 0.9, 6.7; p = 0.009) in the group receiving 80 µg/kg, as compared with the placebo group. In a post-hoc analysis, the absolute reduction in the growth of ICH volume in patients receiving 80 µg of rFVIIa per kilogram as compared with those receiving placebo was even greater among patients treated within 3 hours after the onset of symptoms (-4.5 mL; 95% CI: -8.0, -1.0) and was greater still among those treated within 2 hours after onset (-5.6 mL; 95% CI: -13.1, -2.0).

Despite this reduction in bleeding, there was no significant difference among the 3 groups in the proportion of patients with poor clinical outcome of mRS 5-6 (24% in the placebo group, 26% in the group receiving 20 µg/kg of rFVIIa per kilogram, and 30% in the group receiving 80 µg/kg). The overall frequency of thromboembolic SAEs was similar in the 3 groups; however, arterial events were more frequent in the group receiving 80 µg/kg of rFVIIa than in the placebo group (9% vs. 4%, p = 0.04).

Table 5: Relevant Outcomes in FAST Trial

Outcome	Placebo	20µg/kg	80µg/kg
Mean ICH volumes at baseline (ccs)	22±24	24±26	23±26
Mean IVH volumes at baseline (ccs)	2.7±7.5	3.6±8.0	5.3±11.7
Mean percentage increase in ICH growth from baseline to 24-hour CT (%)	26%	18%	11%*
Absolute growth in ICH from baseline to 24-hour CT (ccs)	7.5	4.9	3.7
Absolute growth in ICH+IVH from baseline to 24-hour CT (ccs)	9.1	6.9	4.7
Absolute growth in ICH+IVH from baseline to 72-hour CT (ccs)	29	26	22
mRS > 3 at 90 days (%)	46%	47%	49%
Mortality at 90 days (%)	18%	19%	21%
Serious ischemic events (arterial or venous) within 90 days (%)	8%	9%	10%**

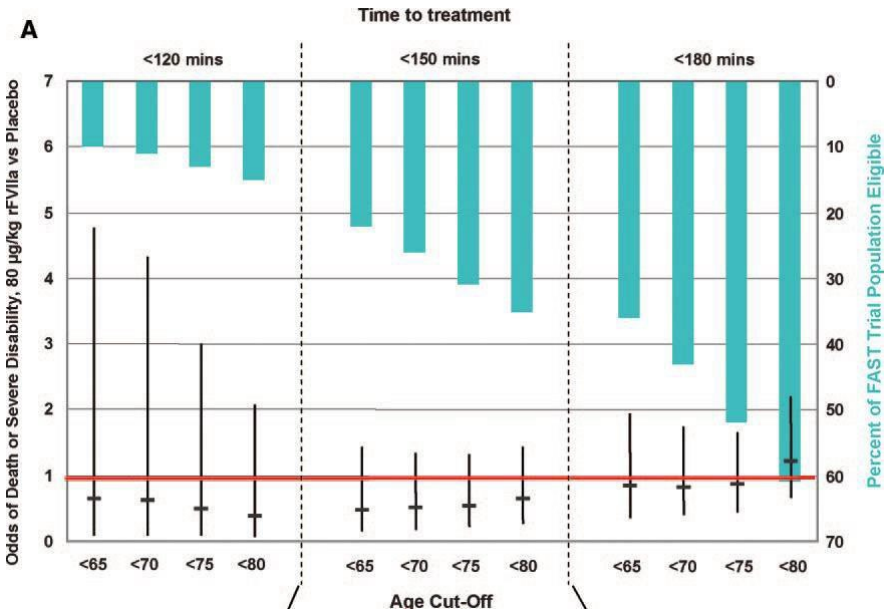
*p < 0.001, **while the overall rate of serious ischemic events was not different, there was a significant

increase in the arterial events for 80 µg/kg group.

The difference in clinical outcomes between the Phase IIb and FAST trials is explained in part by major imbalances in IVH, a factor known to be strongly associated with poor outcome (41% in the rFVIIa group vs. 29% in placebo group). The difference is unlikely to be explained by SAEs related to arterial thrombosis. In the Phase IIb Trial, 5% of the patients treated with rFVIIa had an arterial thromboembolic SAE, as compared with none of those who received placebo, and there was no increase in venous thromboembolic events. In the FAST Trial, there was an identical absolute increase of 5% in arterial thromboembolic SAEs in the group receiving 80 µg of rFVIIa per kilogram as compared with the placebo group (9% vs. 4%), with a higher frequency of events most likely due to centralized screening of cardiac troponin levels.

In a pooled analysis of the 3 randomized trials,[26] there was no overall increase in risk of total thromboembolic events in rFVIIa-treated patients; however, there were more arterial, but not venous, thromboembolic events in the high dose group (120-160 µg/kg) compared with placebo (5.4% vs. 1.7%; p = 0.13). Arterial events occurring within 7 days of drug administration classified as possibly or probably associated with study drug included myocardial ischemia (n = 9, 8 were non-ST-segment elevation and non-Q-wave events; 2 of the 9 had sequelae) and ischemic stroke (n = 9, 4 of which had likely causes other than rFVIIa).

In a detailed and retrospective review of centralized troponin and EKG measurements in the FAST Trial,[27] there were a greater number of centrally identified myocardial events in all 3 groups as compared to investigator-identified events, largely due to elevations of troponin levels. When combining all DMC and investigator-identified myocardial events, the frequency of STEMIs was 4 (1.5%), 1 (0.4%), and 6 (2.0%) in the placebo, 20 µg/kg, and 80 µg/kg groups, respectively. The frequency of NSTEMI and STEMI events combined was 18 (6.4%) for placebo, 21 (7.6%) for 20 µg/kg, and 36 (12.1%) for 80 µg/kg (p = 0.015). Ischemic strokes possibly or probably related to study drug occurred in 7 (2.6%), 5 (1.1%), and 8 (3.0%) patients in the placebo, 20 µg/kg, and 80 µg/kg groups, respectively.



Post-Hoc Analysis of Subgroup from FAST and Phase IIb Trials[17]

The FAST investigators performed a post-hoc analysis of patients who were most likely to benefit from rFVIIa based on time from treatment, no evidence of large ICH or IVH (patients destined to have poor outcome even if additional bleeding was less) and younger age (older subjects have generally poorer outcomes for a given volume of ICH/IVH). This analysis, as illustrated by Figure A, shows the strong effect of time to treatment and potential benefit of rFVIIa.

A post-hoc analysis of the FAST Trial demonstrated that rFVIIa given within 150 minutes to patients with an ICH < 60 cc, < 5 cc of IVH (a small volume of IVH), and ≤ age 70 had an adjusted OR for poor outcome with rFVIIa treatment of 0.28 (95% CI: 0.08, 1.06). The strong treatment effect was replicated in the Phase IIb Trial data (OR for poor outcome with rFVIIa treatment relative to placebo in this patient subgroup from the Phase IIb Trial was 0.02 (95% CI: 0.00, 0.64; p = 0.016).

With granted access to the VISTA database for the rFVIIa trials, FAST Trial results were reanalyzed specifically looking at the 80 µg/kg dose group and placebo using the FASTEST subgroup. These new data emphasize the need to treat within 2 hours to maximize clinical benefit (see Tables 6 and 7). While this is most marked in those subjects ≤ age 70, a higher age criteria of 80 was chosen for the FASTEST Trial to improve generalizability. Using 2 hours, there are larger clinical effect sizes (14% for those ≤ 80 years and treated within 2 hours and

even higher effect sizes for those ≤ 70 years).

Table 6: FAST Trial Results by Time to Treatment (FASTEST Subgroup)

Minutes from onset to treatment in patients age ≤ 80	mRS 0-2 rFVIIa	mRS 0-2 Placebo	Absolute % in mRS 0-2 in favor of rFVIIa at 90 days
≤ 150	42%	42%	0%
≤ 140	46%	41%	5%
≤ 130	49%	41%	9%
≤ 120*	52%	38%	14%

*n = 25 in rFVIIa and n = 32 in placebo groups

Minutes from onset to treatment in patients age ≤ 70	mRS 0-2 rFVIIa	mRS 0-2 Placebo	Absolute % in mRS 0-2 in favor of rFVIIa at 90 days
≤ 150	53%	39%	14%
≤ 140	59%	38%	21%
≤ 130	62%	38%	24%
≤ 120	69%	33%	36%

These data are confirmed by the rFVIIa IIb Trial looking at the same subgroup of participants except for IVH volumes but with very small number of patients. Some of the larger difference is in favor of rFVIIa is likely due to lower IVH volumes as compared to placebo in the IIb trial (volumes of IVH were not available in database).

Table 7: rFVIIa Phase IIb Trial Results by Time to Treatment

Minutes from onset to treatment in patients age ≤ 80	mRS 0-2 rFVIIa	mRS 0-2 Placebo	Absolute % in mRS 0-2 in favor of rFVIIa at 90 days
≤ 150	42%	32%	10%
≤ 140	47%	30%	17%
≤ 130	50%	25%	25%
≤ 120*	50%	20%	30%

*n = 4 in rFVIIa and n = 5 in placebo groups

We also examined the proportion of serious thrombotic AEs in the FASTEST Trial subgroup in the FAST Trial data that include myocardial infarction, ischemic stroke, and pulmonary emboli. *For FAST Trial subjects treated with 80 µg/kg of rFVIIa who were age ≤ 80 and had an onset to treatment ≤ 120 minutes, there was 1 event (4% of subjects) between 0-14 days and 0 between 14-113 days. For placebo treated subjects, there was 1 event (3.1% subjects) between 0-14 days and 3** events between 14-113 days (**two events were in the same subject, so 6.3% of subjects).*

SPOTLIGHT and STOP-IT Trials – Pooled Analysis (written communication – David Gladstone, Matt Flaherty, Joseph Broderick (members of the Executive Committee))

The SPOTLIGHT and NINDS-funded STOP-IT Trials were based upon the observation that a "spot sign" visualized on a contrast CT angiogram is a marker for ongoing bleeding.[28] The time from onset to treatment in the STOP-IT Trial was 6½ hours, and in the SPOTLIGHT Trial was 6 hours. Thus, from onset to time to treatment *was much longer* than the FAST and rFVIIa IIb Trials. The 2 pilot trials randomized 69 subjects with a spot sign to 80 µg/kg of rFVIIa or placebo within 6½ hours of stroke onset. The *median* time from onset to treatment was 195 minutes (range 157-266), the longest of any of the rFVIIa trials and only 37% of subjects were treated within 3 hours.

While these pooled trials reconfirmed the relationship of spot sign to some ongoing bleeding, there was no overall decrease in bleeding nor improvement in outcome at 90 days. A subgroup analysis of subjects treated within 3 hours of onset, placebo patients had a median 4.4 mL (range 0.4-14.7) in growth of volume of ICH

vs. 0.9 cc in rFVIIa, p = 0.8. This 3.5 cc decrease in volume of ICH is quite similar to FAST and rFVIIa IIb Trial within 3 hours (about 4-6 ccs). However, the very small number of subjects makes this a statistically non-significant difference (only 12 subjects with positive spot sign treated with rFVIIa within 3 hours). In these 2 pilot trials of rFVIIa, there was 1 ischemic stroke in the placebo group (diffusion positive infarct that was asymptomatic) and no myocardial infarctions or pulmonary emboli in either group within 4 days.

In summary, the rFVIIa trials demonstrate the biologic time-dependent effectiveness of 80 µg/kg of rFVIIa in slowing growth of ICH with a small absolute percentage of arterial SAEs. To maximize the benefits of rFVIIa in ICH patients, it must be administered within several hours of onset to a population of patients in whom its biologic activity can be expected to change outcome.

BP Trials for Acute ICH

Another potential method to slow ongoing bleeding is control of BP in the earliest minutes and hours of ICH. Three randomized trials of BP control have addressed this question: INTERACT,[29] INTERACT II,[30] and ATACH-2.[31] INTERACT randomized 404 subjects within 6 hours of onset to early intensive lowering of BP (target systolic BP 140 mm Hg; n = 203) or standard guideline-based management of BP (target systolic BP 180 mm Hg; n = 201). The primary endpoint was proportional growth of ICH at from baseline to 24 hours. Mean proportional hematoma growth was 36.3% in the guideline group and 13.7% in the intensive group (difference 22.6%, 95% CI: 0.6%, 44.5%; p = 0.04) at 24 hours. After adjustment for initial hematoma volume and time from onset to CT, the absolute difference in volume between groups was 1.7 mL (95% CI: -0.5, 3.9, p = 0.13). There was no difference in the proportion of patients with death or dependency (49% guideline-based vs. 48% intensive based).

INTERACT II randomized 2839 patients who had had a spontaneous ICH within 6 hours of onset to the same BP treatment groups. At 1 hour, the mean systolic blood pressure was 150 mm Hg in the intensive-treatment group (with 462 patients [33.4%] achieving the target blood pressure of 140 mm Hg. There was no difference in the primary outcome (mRS 3-6) between the guideline (55.6%) and intensive treatment groups (52%) but a secondary analysis using an ordinal approach showed significantly lower modified Rankin scores with intensive treatment (OR for greater disability: 0.87 [95% CI: 0.77, 1.00; p = 0.04]). There was no significant difference in hematoma growth between the groups (absolute difference: 1.4 mL [95% CI: -0.6, 3.4; p = 0.18], after adjustment for prognostic variables).

ATACH-2 randomly assigned eligible participants with intracerebral hemorrhage (volume < 60 ccs) and a Glasgow Coma Scale (GCS) score of 5 to a systolic blood pressure target of 110-139 mm Hg (intensive treatment) or a target of 140-179 mm Hg (standard treatment) in order to test the superiority of intensive reduction of systolic blood pressure to standard reduction; intravenous nicardipine to lower blood pressure was administered within 4.5 hours after symptom onset. The mean minimum systolic blood pressure during the first 2 hours was 128.9±16 mm Hg in the intensive-treatment group and 141.1±14.8 mm Hg in the standard-treatment. The primary outcome of death or disability was observed in 38.7% of the participants (186 of 481) in the intensive-treatment group and in 37.7% (181 of 480) in the standard-treatment group (RR: 1.04 [95% CI: 0.85, 1.2]). SAEs occurring within 72 hours after randomization that were considered by the site investigator to be related to treatment were reported in 1.6% of the patients in the intensive-treatment group and in 1.2% of those in the standard-treatment group. The rate of renal AEs within 7 days after randomization was significantly higher in the intensive-treatment group than in the standard-treatment group (9.0% vs. 4.0%, p = 0.002). There was no difference in growth of ICH between the 2 treatment groups. The standard treatment group was very similar to the intensive treatment group in INTERACT II.

In summary, the target systolic BP of 140 mm Hg offers the best outcomes for patients with acute ICH and is the target BP in the FASTEST Trial.

4.0 GENERAL INVESTIGATIONAL PLAN

We will perform a global, Phase III, randomized, double-blind controlled trial of rFVIIa plus best standard therapy vs. placebo and best standard therapy alone. We will include subjects with a volume of ICH ≥ 2 and <

60 cc, with no IVH or a smaller volume of IVH, age 18-80 (inclusive), Glasgow Coma Scale of ≥ 8, and treated within 120 minutes from stroke onset or last known well. To minimize time-to-treatment, the study will use exception from informed consent (EFIC) in the U.S., emergency research informed consent procedures globally, and mobile stroke units (MSUs), with a goal of ½ of patients treated within 90 minutes, as accomplished in the NINDS t-PA trials. At approximately 115 hospital sites and 15 MSUs in the NINDS-funded StrokeNet and key global institutions with large volumes of ICH patients and ability to treat within 2 hours of onset/last known well, we plan to recruit 860 participants over 3½ years. Countries participating in the trial include the United States, Canada, Japan, Germany, United Kingdom, and Spain.

We will randomize participants in a double-blinded fashion to rFVIIa 80 µg/kg dose (maximum 10 mg dose) or placebo. Subjects in both arms will receive best medical therapy as per published AHA Guidelines for ICH,[32] including a target blood pressure of 140 mm Hg. Primary outcome will be determined at 180 days, but we will follow participants by remote assessment at 30 and 90 days. To measure growth of ICH, all subjects will have a baseline non-contrast CT of the head and a repeat non-contrast CT of the head at 24 hours from stroke onset/last known well. We will perform centralized volumetric measurements of ICH, IVH, and edema for both time points.

Novo Nordisk A/S will manufacture and supply recombinant FVIIa as a research medication for use in the FASTEST Trial. Novo Nordisk A/S will also manufacture and supply matching placebo that is identical in appearance and administration for the FASTEST Trial.

4.1 Primary Specific Aim

To test the hypothesis that treatment with rFVIIa within two hours of onset in appropriately selected patients with spontaneous ICH improves outcome as measured by the ordinal distribution of the modified Rankin Scale (mRS) at 180 days, as compared to placebo.

4.2 Secondary Specific Aim

To test the hypothesis that treatment with rFVIIa within two hours of onset in appropriately selected patients with spontaneous ICH decreases bleeding between baseline and 24-hour head imaging, as compared to placebo.

4.3 Primary Endpoint

As per Food and Drug Administration (FDA) recommendation, the primary outcome measure is the following distribution of the ordinal mRS at 180 days: 0-2, 3, and 4-6.

4.4 Secondary Endpoints

Secondary endpoints include the ordinal mRS (all seven steps), utility-weighted Rankin Score,[33] mRS of 0-2, and EQ-5D[34,35] at 90 days and 180 days; and change in the volume of ICH and ICH+IVH between the baseline CT and 24-hour CT.

4.5 Primary Safety Measure

The primary safety measure of the study will be life-threatening thromboembolic complications during the first four days after completion of study drug.

4.6 Study Population

4.61 Rationale for Study Population

Earlier trials of rFVIIa did not focus on the time window most likely to alter bleeding *and included subjects in whom volumes of ICH and IVH at the time of treatment were so large that the likelihood of death was greater*

than 90%, even if further reduction in bleeding could be achieved. A post-hoc analysis of the neutral FAST rFVIIa trial, which focused on subjects treated very early in the FAST trial and with baseline volumes of ICH and IVH not associated with high likelihood of death, demonstrated a strong effect size in the distribution of mRS scores at 90 days in favor of rFVIIa. We will also exclude subjects with recent ischemic stroke, myocardial infarction, pulmonary embolus, etc., or clinical or EKG evidence of acute myocardial ischemia because of the thrombotic risks associated with rFVIIa, even though ICH is a life-threatening illness.

Subjects to be enrolled – **860**
Subjects expected to be screened – approximately **5,058** (17% of subjects in rFVIIa trials imaged within 100 minutes of onset who meet FASTEST criteria)
Anticipated number of trial sites – **115 hospitals and 15 mobile stroke units**
Anticipated number of subjects to be randomized/started on trial medication at each trial site during the study – **Approximately 21 subjects per mobile stroke unit and 6 subjects per hospital site**
Countries to participate – **United States, Canada, Germany, Japan, Spain, and the United Kingdom**

4.62 Inclusion Criteria

1) Patients aged 18-80 years, inclusive
2) Patients with spontaneous ICH
3) Able to treat with study medication (rFVIIa/placebo) within 120 minutes of stroke onset or last known well
4) Efforts to obtain informed consent per EFIC guidelines (U.S.) or adherence to country-specific emergency research informed consent regulations (Canada, Germany, Spain, U.K., Japan)

4.63 Exclusion Criteria

1) Score of 3 to 7 on the Glasgow Coma Scale
2) Secondary ICH related to known causes (e.g., trauma, aneurysm, arteriovenous malformation (AVM), oral anticoagulant use (vitamin K antagonists or novel oral anticoagulants) within the past 7 days, coagulopathy, etc.)
3) ICH volume < 2 cc and ≥ 60 cc
4) Blood filling 2/3 or more of one lateral ventricle of the brain, OR, blood filling at least 1/3 of both lateral ventricles
5) Pre-existing disability (mRS > 2)
6) Symptomatic thrombo-embolic or vaso-occlusive disease in past 90 days (e.g., cerebral infarction, myocardial infarction, pulmonary embolus, deep vein thrombosis, or unstable angina)
7) Clinical or EKG evidence of ST elevation consistent with acute myocardial ischemia
8) Brainstem location of hemorrhage (patients with cerebellar hemorrhage may be enrolled)
9) Refusal to participate in study by patient, legal representative, or family member
10) Known or suspected thrombocytopenia (unless current platelet count documented above 50,000/μL)
11) Unfractionated heparin use with abnormal PTT
12) Pro-coagulant drugs within 24 hours prior to patient enrollment into the FASTEST trial (example, tranexamic acid or aminocaproic acid)
13) Low-molecular weight heparin use within the previous 24 hours
14) Recent (within 90 days) carotid endarterectomy or coronary or cerebrovascular angioplasty or stenting
15) Advanced or terminal illness or any other condition the investigator feels would pose a significant hazard to the patient if rFVIIa were administered
16) Recent (within 30 days) participation in any investigational drug or device trial or earlier participation in any investigational drug or device trial for which the duration of effect is expected to persist until to the time of FASTEST enrollment
17) Planned withdrawal of care or comfort care measures
18) Patient known or suspected of not being able to comply with trial protocol (e.g., due to alcoholism, drug dependency, or psychological disorder)
19) Known or suspected allergy to trial medication(s), excipients, or related products
20) Contraindications to study medication
21) Previous participation in this trial (previously randomized)

22) Females of childbearing potential who are known to be pregnant or within 12 weeks post-partum and/or lactating at time of enrollment

4.7 Intervention

We will randomly assign participants in a 1:1 ratio to intravenous rFVIIa or placebo at a dose of 80 µg/kg (maximum 10,000 µg or 10 mg) and administered intravenously over 2 minutes. All investigators and participants will be blinded throughout the course of the study. Due to the emergency nature of the intervention, a simple randomization scheme will be implemented. There will be no stratification variables. Each drug kit, prepared at the NIH StrokeNet central pharmacy or the central research pharmacies for Canada, Europe, and Japan, will consist of two 5 mg vials of active study drug or matching placebo. Both are supplied by Novo Nordisk A/S. **Enrollment and randomization in the trial will occur upon injection of the study medication** (as was the case in the NINDS t-PA stroke trials). Only these subjects will be considered in the intent-to-treat analysis.

Participants in both arms will receive AHA guideline-supported management of acute ICH. In particular, we will require acute BP management with a target of 140 mm Hg using intravenous medications, as available within a given country. In the U.S., this would include IV nicardipine or IV labetalol. All participants will be managed in an intensive care unit or stroke unit post treatment.

There should not be a need to unblind since rFVIIa is not reversible and has a short half-life, and antithrombotic medications are contraindicated in the setting of ICH. However, when emergency unblinding occurs, the reason, person(s) unblinded, and the date and time of unblinding will be recorded.

4.8 Visit Procedures

All subjects who have an ICH on baseline brain imaging within a participating mobile stroke unit or emergency department are potential FASTEST cases. Investigators will examine the patient, review the baseline imaging, and also calculate the GCS score,[36] NIHSS score,[37] mRS score, ICH volume by ABC/2 method (or by an automated ICH volume imaging software cleared by the FDA in the US or CE Mark in Europe and the UK),[38] and measurement of IVH [39]. If all inclusion and exclusion criteria are met, and country-specific emergency research informed consent procedures are followed, the investigator (or delegated designate) will identify the next study medication kit to be opened and study medication will be prepared. Every effort will be made to consent the relevant responsible person, if available and as applicable, using an abbreviated informed consent form. If the patient or legally responsible representative refuses participation in the trial, the patient will not be enrolled. If the patient or legally responsible representative provides consent, or if consent cannot be obtained within 30 minutes from baseline CT imaging and 120 minutes from stroke onset/last known well (U.S.) and as dictated by country-specific emergency research informed consent regulations, study medication will be administered, and the patient will be considered enrolled in the trial when the study medication is administered.

Participants will have a follow-up NIHSS at 1 hour after treatment and at 24 hours from stroke onset/last known well. Follow-up mRS will be obtained at 30 days remotely or in-person, 90 days remotely or in-person, and 180 days in-person. EQ-5D will be done at 90 days remotely or in-person and 180 days in-person. If the 180 day mRS in-person is not feasible, remote assessment is allowable (video is preferred over telephone). Follow-up CT of the head will be obtained at 24 hours from stroke onset/last known well. **If the participant is taken for surgical intervention, the follow-up CT of the head will be done immediately prior to surgery.** The complete Table of Events is below:

Table of Events

Event	Baseline	1-hour post-dose (±15 minutes)	24-hours from stroke onset/last known well (±6 hours)	Day 4/ Discharge, whichever is sooner	Day 30 (±14 days)	Day 90 (±14 days)	Day 180 (±14 days)

Medical history	**x**						
Physical exam	**x**						
Vitals	**x**	**x**	**x**				
Demographic information	**x**						
NIHSS	**x**	**x**	**x**				
GCS	**x**						
mRS	**x**				**x**	**x**	**x**
EQ-5D						**x**	**x**
CT of head	**x**		**x**				
CTA of head	**x (opt.)**						
EKG	**x**						
Serum troponin	**x**		**x**				
Adverse event assessment		**x**	**x**	**x**	**x**	**x**	**x**

4.9 Assessments for Efficacy

The primary outcome measure is the following distribution of the ordinal mRS at 180 days: 0-2, 3, and 4-6. The Rankin Focused Assessment Tool[40] will be used to obtain mRS scores. The mRS at 180 days will be done by a study investigator in-person talking to the patient and/or primary caregiver, if the patient is not able to provide information. Assessments will include remote or in-person mRS at 30 days and 90 days and EQ-5D at 90 days and in-person at 180 days. Remote (video preferred over telephone) assessment will be allowed if in-person meeting is not feasible. All study investigators will be certified in performance of mRS and NIHSS.

All subjects will have a baseline non-contrast CT of the head and a follow-up non-contrast CT of the head at 24±6 hours from stroke onset/last known well, or, if a surgical intervention is planned prior to 24 hours (e.g., surgical removal of ICH or intraventricular catheter placement), a non-contrast CT scan must be obtained before the procedure. If MRI (instead of CT) is performed routinely, the MRI will be accepted, however, CT is preferable. If CT angiography of the head is done at baseline as part of standard of care, we will collect and analyze these imaging data, but this is not required. Investigators will measure the ICH volume using the ABC/2 method (or by an automated ICH volume imaging software cleared by the FDA in the US or CE Mark in Europe and the UK) and measurement of IVH . All investigators will have completed a certification process online for the ABC/2 method. We will also collect any unscheduled CT scans and MRI of the head (performed as part of standard of care) prior to 24 hours (18-30 hours), including those performed for any neurological deterioration. All images will be stored at an imaging repository at the University of Cincinnati.

Image analysis will be performed at the Imaging Core at the University of Cincinnati. The imaging core will calculate digital measurements of ICH volume, IVH volume, edema, location of ICH and measurement of hypodensities within the areas of ICH on the baseline CT. The imaging core will assess CTA, when available, for the presence of spot sign. The site reading for ICH volume and IVH volume will be used as the determination for entry into the study, but central readings will be used for measurements of ICH and IVH growth.

4.10 Assessments for Safety

The primary safety measure of the study will be life-threatening thromboembolic complications during the first four days after completion of study drug. A significant life-threatening complication will be defined as development of: 1) acute myocardial infarction, 2) acute cerebral infarction, and 3) acute pulmonary embolism, defined as follows. Secondary measures of safety will include mortality at 180 days and mRS of 5-6 at 180 days.

1) Acute myocardial infarction (AMI)
    (a) Troponin greater than the upper limit of normal (99th percentile ULN) ***and either***
    (b) New clinical symptoms consistent with cardiac ischemia ***or***
    (c) EKG manifestation of AMI
        (i) ST Elevation Myocardial Infarction (STEMI)
            (1) ST elevations ≥ 1 mm in two or more contiguous leads
            (2) New LBBB
        (ii) Non-ST Elevation Myocardial Infarction (non-STEMI)
            (1) ST depression ≥ 0.5 mm in two contiguous leads or dynamic T wave changes
        (iii) New Q waves ≥ 0.03 seconds in width and ≥ 1 mm in depth in two or more contiguous leads

2) Acute cerebral infarction

New focal neurological deficits consistent with cerebral ischemia and without alternative explanation lasting > 24 hours. For participants with suspected new cerebral infarction which is not detected on CT scan, MRI is recommended, if clinically feasible.

3) Acute pulmonary embolus (PE)

Clinical findings consistent with PE with confirmatory radiographic findings (CT angiography, catheter angiography, or V/Q scan).

Other AEs potentially related to study drug that will be analyzed separately from the arterial thromboembolic SAEs of acute myocardial infarction, acute cerebral infarction, and pulmonary emboli include:

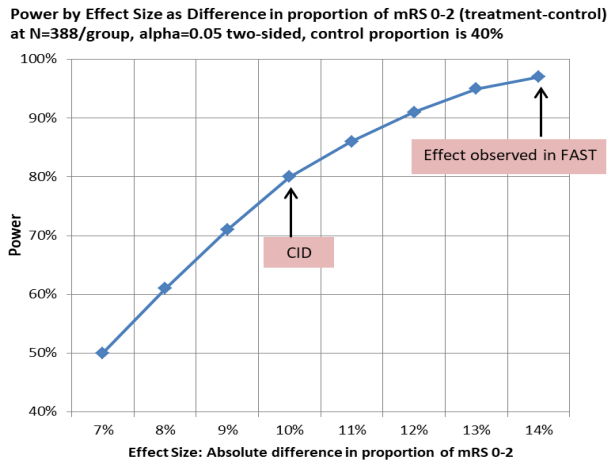
1) Myocardial injury without acute coronary syndrome – “enzyme leak”. Elevated troponin greater than the upper limit of normal at the clinical site in the absence of clinical symptoms or EKG evidence of an acute coronary syndrome.
2) Unstable angina. Clinical symptoms (chest pain, dyspnea) or EKG evidence (ST depression) of reduced myocardial flow without a significant elevation in troponin.
3) Deep venous thrombosis.
4) Other unspecified thromboembolic events.

AEs occurring through the first four days after completion of study drug or discharge, whichever is sooner will be collected and recorded on the Adverse Event form and followed as appropriate. All SAEs during and after hospital discharge until Day 90, whether expected or unexpected, volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test, or other means, will be collected and recorded on the Adverse Event form and followed as appropriate. An independent Medical Safety Monitor will review all serious adverse events and determine their expectedness, severity, and relatedness to the study intervention. The Safety Monitor will adjudicate events while blinded to treatment status. Mortality collected through Day 180 will be collected and recorded on the Adverse Event form.

4.11 Statistical Power and Sample Size Considerations

We chose our primary efficacy measurement at 180 days based upon the recently published MISTIE II, MISTIE III, and iDEF ICH trials which demonstrate continued improvement in ICH patients from 90 to 180 days. However, prior rFVIIa trials only had follow-up to 90 days. Thus, we approximated the sample size via two-sample test of proportions of mRS 0-2 at 90 days (Chi-squared test). From a post-hoc analysis of the FAST

trial shown above in **Table 3** having the characteristics that we plan to enroll (the subset aged ≤ 80 and treated within 2 hours from stroke onset), the proportion of mRS 0-2 at 90 days was 52% in the rFVIIa group and 38% in the placebo group (14% absolute difference in proportions). To detect a smaller but still **clinically important difference (CID) of 10%,** we would need n = 388/group to achieve 80% power at alpha = 0.05 two-sided, when conservatively assuming a slightly better placebo proportion of 40%. However, if the distribution of the mRS scores is exactly as observed in the FAST subset, we will have > 95% power to detect a 14% difference with a sample size of 388/group. The sample size was inflated for 10% lost to follow-up and missing data (conservative assumption), with an additional minor inflation to the sample size for one interim analysis giving a **total n = 860 (430/group)**.



The ordinal logistic regression planned for the primary analysis should have similar power to the binary analysis and may have better power when adjusting for baseline covariates. **If the effect size noted in the preliminary data is the true difference, we could detect a significant clinical benefit at the interim analysis of 430 subjects.**

4.12 Statistical Methods

The primary analysis will be conducted on the intent-to-treat (ITT) analysis population. We will compare the ordinal values of the 180-day mRS by treatment group via an ordinal logistic regression adjusted for age, baseline ICH volume, baseline IVH volume, and pre-stroke mRS. Since the baseline covariates are continuous, we will rely on comparisons of nested models to assess the proportionality assumption. If the proportionality assumption is violated, then the primary analysis would be a partial proportional odds model.[41] For participants who are missing a primary outcome assessment and have not died, the 90-day mRS, or 30-day mRS if the 90-day is not available, will be used to impute the 180-day value using a multiple imputation approach.

A subject is considered to have been enrolled into the FASTEST trial upon start of the infusion of the study medication. All enrolled subjects will be included in the intent-to-treat analysis, regardless of whether they received all of the study drug or met the eligibility criteria. The per-protocol analysis will exclude those subjects' who received less than 1.5 minutes of infusion of the study medication or who did not meet the key eligibility criteria including: did not have a spontaneous ICH, time from stroke onset was > 120 minutes, age was > 80 years old, ICH or IVH volume was out of eligible range, or baseline GCS was less than 8.

Secondary analyses of the mRS outcome at 90 and180 days include the following:

1) Re-analysis of the primary outcome with the per-protocol sample;
2) Ordinal logistic regression analysis of the mRS using all 7 steps of disability;
3) Dichotomous analysis of the mRS (0-2) using a logistic regression with treatment, age, ICH volume, IVH volume, and pre-stroke mRS as covariates (ITT sample);
4) Utility-weighted analysis of mRS (UW-mRS) using the utility weights as defined for the DAWN trial and a linear regression with treatment, age, ICH volume, IVH volume, and pre-stroke mRS as covariates (ITT sample);
5) Analysis for participants ≤ age 70; and,
6) Tests for treatment-by-country interactions and for homogeneity across sites. However, the expected smaller number of subjects per site make testing for treatment-by-center interaction challenging.

Other secondary analyses include EuroQol EQ-5D at 90 days and 180 days, and the change from baseline to 24 hours in ICH volume and ICH+IVH volume (analyzed via linear regression adjusted for the same baseline covariates).

We plan exploratory analyses that examine the differences in mRS between treatment groups by time from onset to treatment (0-90 vs. 90-120 minutes), Ultra-early Hematoma Growth (UHG) categories of ≥ 10 cc/hour or < 10 cc/hour, and volume of ICH (2-30 cc vs. 31-59 cc). The primary analysis will be re-done adjusting for time-to-treatment and UHG categories (≥ or < 10cc/hour), in the ordinal logistic regression.

We will collect baseline CT angiograms done at institutions as standard of care (not required by the trial) and analyze the relationship of positive spot signs (determined by central reviewer) with growth of ICH and ICH+IVH, and the relationship of a positive spot sign with treatment effect. We will also analyze the relationship of hypodensities within the ICH on baseline CT with treatment effect.

Finally, the Data Safety Monitoring Board (DSMB) will closely monitor the following serious adverse safety events: cerebral infarction, myocardial infarction, pulmonary emboli, and all-cause mortality. The frequency and proportion of subjects by treatment group will be provided at both 4 days and 90 days after treatment. Other secondary measures of safety will include mortality at 180 days and mRS of 5-6 at 180 days. The relative risk and the 95% confidence intervals will be provided in each summary table to the DSMB. A composite measure of cerebral infarction, myocardial infarction, and pulmonary emboli will also be used. At the end of the study, the cumulative incidences of these safety events, as well as all AEs, will be compared between the two treatment groups using Fisher's exact test at the two-sided alpha level of 0.05. Kaplan-Meier curves and log-rank tests will be used to compare time to death. We also examine the proportion of mRS of 5-6 per treatment group as an additional safety measure.

4.121 Plan for Subgroup Analysis by Sex, Race, and Ethnicity

All eligible subjects of both genders and all races and ethnic groups will be considered for enrollment in the FASTEST Trial. StrokeNet sites reported that 28% of ICH subjects enrolled in clinical trials are minorities and 45% are female. Metrics on the recruitment and retention of women and minorities will be monitored by the DSMB and provided to the NINDS. Although we do not anticipate differential treatment effects based on sex/gender or race/ethnicity, our analyses will explore clinically important differences due to sex/gender and race/ethnicity. To do so, the primary outcome will be analyzed including indicators of sex, ethnicity, and racial groups and interaction terms with treatment group. Each covariate will be evaluated individually first with a model that includes an interaction effect with the treatment group. A multivariable model that includes covariates that contributed significantly ($p < 0.05$) as treatment modifiers individually may then be constructed. To reduce statistical bias, this subgroup analysis will be performed only at the end of the trial.

4.122 Interim Analysis

Two interim analysis are planned. The first interim analysis is for futility alone and has two components which both must be met: clinical functional outcome as measured by the mRS at 6 months and the mean difference in ICH growth between the two treatment groups. This analysis will occur after 200 randomized subjects have completed 6 months of follow-up. The study will be considered futile and the study stopped if both of the following conditions are met

1.) conditional power is less than 0.20 for the primary outcome <u>AND</u>

2) the 95% upper confidence bound for the observed difference in ICH volume (growth) between the two groups (rFVIIA vs. placebo) exceeds that for a mean difference of -2.5 cc less growth in the rFVIIa group versus control as predicted for FASTEST subgroup from FAST Trial. In the prior rFVIIa trial (FAST), a subset of 53 subjects who met FASTEST inclusion criteria (based on age, IVH & ICH volume, and time to treatment). In these 53 subjects the mean ICH volume difference (rFVIIA – placebo) was -2.7ml (SD=16.7) 95%CI (-11.7, 6.3). This represents a reduction in ICH growth of 2.7ml in favor of the rFVIIA arm, but the 95% CI includes zero. Assuming a sample size of n=200, and given the SD=16.7 observed in the FAST subset, then the 95%CI around a mean difference of -2.5 would be tighter (-7.1, 2.1), but is still expected to include zero. Thus, we have defined our futility rule for ICH volume based upon the upper 95%CI exceeding what would be expected (i.e. > 2.1). In FASTEST when n=200, if we observe in an upper 95%CI of the mean difference which is greater than 2.1 <u>then the mean difference in ICH volume may be less than expected and hence futile.</u>

The second interim analysis of the primary outcome is planned after approximately ½ (n ~ 430) of the total number of randomized subjects have been evaluated for the primary outcome. An alpha spending function with O'Brien and Fleming type stopping boundaries (two-sided) will be used to stop the trial for overwhelming superiority of either group, while maintaining the type I error rate at 0.05. The stopping boundaries to be used under the O'Brien and Fleming method are two-sided p-value ≤ 0.003 for the interim look and two-sided p-value ≤ 0.049 for the final analysis. The trial may also be stopped early for futility if the conditional power is less than 0.20. At the time of the interim analysis, safety data will be summarized by treatment group in DSMB reports using RR and 95% CI. The DSMB may conduct unplanned interim analyses if warranted for safety concerns. This analysis is done by an unblinded statistician at the Medical University of South Carolina (National Data Management and Statistical Center for StrokeNet (NDMC)) in conjunction with an NINDS-appointed independent DSMB. None of this analysis is shared with the study leadership, blinded statistician, or investigators unless the DSMB makes a recommendation to the NINDS to halt the study for efficacy or futility.

4.13 Data Handling and Record Keeping

4.131 Data Management

Data management will be handled by the StrokeNet NDMC, which is housed in the Data Coordination Unit (DCU) of the Department of Public Health Sciences at the Medical University of South Carolina (MUSC). All activities will be conducted in coordination with the study PIs, the StrokeNet NCC, and the clinical study sites. The study data will be managed (including data queries) by the NDMC using the WebDCU™ system. This electronic data management system is used for several federally funded multicenter studies including NINDS-funded projects of the NETT Network (U01NS059041), the ALIAS and IMS III trials (U01NS054630 for both), and all NIH StrokeNet trials (U01NS086872). This user-friendly web-based database system, developed and validated by the NDMC, will be used for regulatory document management, subject enrollment, data entry, data validation, project progress monitoring, subject tracking, user customizable report generation, and secure data transfer. In addition to the study database, the NDMC will provide study site staff access (via password) to a standard set of web-enabled tools, including a subject visit calendar, subject accrual status indicator, case report form completion status indicator, and outstanding data queries pertaining to their respective clinical site.

Once the case report forms (CRFs) are finalized, they will be pilot tested by the NDMC personnel during the database validation phase. In order to provide easy interfaces, the WebDCU™ data capture screens are designed based on individual CRFs. The latest version of each CRF will be available as a PDF file on the study website for use as worksheets and source documents by study personnel. Furthermore, all approved study materials, such as the protocol, 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. This process facilitates version control of all study related documents, particularly since documents may evolve over the course of the study.

4.14 Data and Safety Monitoring Board

The members of the DSMB will be determined by the program staff at the NINDS and will not include any of the PIs or members of the study team. This independent committee will determine at study initiation whether to review blinded or unblinded data, will perform data reviews and analyses at regularly scheduled intervals, and will be responsible for final recommendations to the NINDS of safety and ethical concerns, whether the study should continue, and other concerns. They will also have access to the independent Medical Safety Monitor.

4.15 Study Drugs and Materials

Study Medication(s)

rFVIIa and placebo 5 mg vials will be supplied by Novo Nordisk A/S to respective research pharmacies in participating countries (in the U.S., this is the NIH StrokeNet central pharmacy). Unblinded central research pharmacies would receive boxes that contain two 5 mg vials of rFVIIa or two matching placebo vials from Novo Nordisk A/S. Each box with 2 vials will have a unique seven-digit Dispensing Unit Number (DUN). The same DUN will be on each vial in this box. The research pharmacies will be provided with a list of these DUNs that indicate if the vials contain rFVIIa or placebo. Study diluents (histidine solvent 5.2 mL in 10 mL prefilled syringe

with scale) will be sent in separate boxes that also have a DUN. To summarize, Novo Nordisk A/S will send labelled boxes/vials with placebo (with DUN) and rFVIIa (with DUN), and boxes with histidine diluents (with DUN).

Each research pharmacy in participating countries will combine the boxes into one larger study kit that contains labelled study medication, diluent, and instructions for use (specific for each country). The larger kits will then be separately labelled with study ID numbers supplied by Medical University of South Carolina that is the Data Management and Statistical Center for the NIH StrokeNet. When these kits are completed, the research pharmacy in each country would distribute the study medication to participating sites. Participating research pharmacies include U.S., Canada, Europe (for Germany, Spain, and the U.K.), and Japan.

Packaging and Labelling of Study Medication(s)

All investigators and participants will be blinded throughout the course of the study. Study drug kits will be labeled at the NIH StrokeNet central pharmacy and other central research pharmacies in other countries, using study drug kit IDs and labels supplied by the NDMC. Study medication will be packaged and labelled in accordance with local law and study requirements.

Storage and Drug Accountability of Study Medication(s)

Study medication (rFVIIa and placebo will be stored as per specifications in the NovoSeven®/NiaStase® product information). Temperature requirements will also be maintained during transport of study kits to participating sites.

In the U.S., the StrokeNet central pharmacy will store all study medications prior to preparation of study kits and shipping of kits to study sites in the U.S. The StrokeNet central pharmacy is a distinct research pharmacy licensed by the Ohio State Board of Pharmacy. The current research pharmacy is located in the Holmes Building adjacent to the Medical Sciences Building and University of Cincinnati Medical Center (UCMC). The pharmacy serves only as a research pharmacy and does not dispense medications strictly for clinical care. The UCMC also has separate research and clinical pharmacies. This UCMC clinical pharmacy has an ancillary site also in the Holmes Building. Access to the research pharmacy is restricted to the pharmacist of record and back-up pharmacist only. No other site personnel have access to the pharmacy.

Figure – Floor Plan of Research Pharmacy

The research pharmacy (circled above) has a total of 400 square feet of space divided into the pharmacy proper (Room 1209A) and outer office space (1209). The pharmacy is double-locked with access to the pharmacy proper restricted by key only to certified pharmacists. An inventory accountability log is maintained and kept in the pharmacy at all times. Any time product is dispensed or returned inventory logs are updated in real time. The pharmacist has a personal computer with access to a specifically designed pharmacy program to facilitate production of labels for dispensing study drug. This unique computer program was modified to ensure confidentiality with restricted access only to the research pharmacists.

The pharmacy is fully equipped for maintaining study product. The research pharmacy contains shelving for investigational product and protocols. There is a refrigerator with interior dimensions of 20” wide x 22” deep x 36” high; a -20°C freezer with dimensions 27½” wide x 23½” deep x 57” high; and a -70°C freezer with interior dimensions of 66½” wide x 28½” deep x 40½” high. These are all located within the pharmacy and continuously monitored for temperature excursions. In the event of a temperature excursion, an electronic system notifies the pharmacist of record and the back-up pharmacist by telephone, e-mail, and text message until resolution. There is a secondary continuous temperature monitoring system in place as well. The research has a back-up temperature monitoring system capable of storing temperature readings in the event network issues arise. There is a back-up generator for the building as well with alarms in place if there is a sudden power loss notifying building security. The research pharmacy is equipped with an ISO 5 horizontal flow hood compliant with USP 797 requirements to be utilized for compounding of sterile products.

Refrigerators, freezers, and cleanroom hoods are all connected to an emergency back-up generator that is tested monthly. Drug storage and preparation areas are only accessible to pharmacists and personnel under the direct supervision of pharmacists in accordance with Ohio State Pharmacy Board laws.

The StrokeNet central pharmacy will require the local site pharmacy to store kits at the appropriate treatment site and to provide the pharmacist of record with all relevant information confirming the subject has been enrolled in the trial. The central pharmacy has adequate space for storage of used and unused study medications. Upon receipt, unused study medications are stored separately from used study medications. The unused study medications are stored in bins on shelves physically separated from used study medications with appropriate labeling to identify the drugs and study associated with them. The unused study medications are inventoried on a continuous accountability log when received and dispensed.

The central pharmacy upon receipt records the drug on a continuous study inventory log. When a drug kit is used and study medication is dispensed to a treatment site, this is documented on the continuous inventory log and the subject specific log.

All study medication returned from study sites to the StrokeNet central pharmacy that are expired, damaged, or remaining for any other reason from research studies, will be destructed according to the Ohio State Pharmacy Guidelines. There are two acceptable methods of drug destruction: 1) sites may collect and ship to sponsor all study medication that is expired, unused, or damaged; and, 2) sponsor may request from the pharmacist of record to destroy all drugs, expired, unused, or damaged, per local policy.

In the event study drug needs to be destroyed on site per local policy, the pharmacist of record will ensure the drug is rendered “non-retrievable” in compliance with all applicable Federal, State and local laws. Drug will only be destroyed once the pharmacist of record has permission and approval from the sponsor to destruct the drug on site per local policy. The pharmacist of record will keep a Medication Destruction Log.

The same requirements for kit storage at research sites, drug accountability, and return and destruction policies also apply to the central research pharmacies in the other participating countries.

Study Drug Administration

Study drug will be administered according to the NovoSeven®/NiaStase® product information.

4.16 Safety Assessment and Reporting

The FASTEST trial will comply with all local, legal, regulatory, and Institutional Review Board (IRB) requirements. Dr. Broderick, as the sponsor-investigator, will be responsible to ensure that treating investigators report all AEs, including SAEs, suspected unexpected serious adverse reactions (SUSARs), and serious adverse drug reactions (SADRs), to the competent authority and independent ethics committees/institutional review boards based upon federal regulations and local/IRB policies. Reporting to regulatory authorities and independent ethics committees/institutional review boards in all participating territories will be done according to all applicable national and local regulations. Information about all AEs, whether expected or unexpected, volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test, or other means, will be collected and recorded on the Adverse Event form and followed as appropriate.

In addition, Dr. Broderick, or his designate, will report required SAEs, SUSARs, and SADRs to regulatory authorities, per reporting regulations, within 7 or 15 days from the sponsor-investigator becoming aware of such AEs.

Dr. Broderick, or his designate, will ensure that the treating investigators will collect the following information, at minimum, for AEs:

1) Study name
2) Patient identification (e.g., subject number, initials, sex, age)
3) Event (preferably a diagnosis)
4) Drug (NovoSeven®/NiaStase®)
5) Reporter identification (e.g., name, or initials)
6) Causality
7) Outcome

We will utilize the following definitions as listed below. Details about SAEs relevant to the FASTEST Trial are described under Safety Events above. We will use the FDA Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057.pdf, to evaluate all unexpected events and adverse reactions.

Definitions

Adverse Event (AE):
An AE is any undesirable medical event occurring to a subject in a clinical trial, whether or not related to the trial product(s). This includes events reported from the time of enrollment/randomization and until post-treatment follow-up period, as defined in the protocol. The following should not be recorded as AEs, if recorded as medical history/concomitant illness on the CRF at screening:

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the time of enrollment/randomization
- Pre-existing conditions found as a result of screening procedures

Clinical Laboratory Adverse Event:
A clinical laboratory AE is any clinical laboratory abnormality regarded as clinically significant (i.e., an abnormality that suggests a disease and/or organ toxicity and is of a severity, which requires active management (i.e., change of dose, discontinuation of trial product, more frequent follow-up, or diagnostic investigation).

Serious Adverse Event (SAE):
A serious AE is an experience that at any dose results in any of the following:

- Death
- A life-threatening* experience
- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity

- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening*, or require hospitalization may be considered an SAE when, based upon appropriate medical judgement, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition
- Suspicion of transmission of infectious agents

* The term life-threatening in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

Serious Adverse Drug Reaction (SADR):
An adverse drug reaction (ADR) is an AE for which a causal relationship to the trial product is at least possible (i.e., causal relationship is conceivable and cannot be dismissed). Serious adverse reaction (SAR): AE that fulfills both the criteria for an SAE and the criteria for an Adverse Drug Reaction.

Suspected Unexpected Serious Adverse Reaction (SUSAR):
An SAE that is unexpected and regarded as possibly or probably related to the trial/study product by the investigator.

Adverse Events of Special Interest (AESI):
An AESI is 1) a medication error (e.g., wrong drug administration or wrong route of administration) or 2) a suspected transmission of an infectious agent via the product.

Non-Serious Adverse Event:
A non-serious AE is any AE which does not fulfill the definition of an SAE.

Severity Assessment Definitions:
The severity of all AEs will be reported using the grading system outlined in the NCI Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE). The CTCAE provides a grading (severity) scale for each AE term and AEs are listed alphabetically within categories based on anatomy or pathophysiology. The CTCAE (v5.0) displays Grades 1-5 with unique clinical descriptions of severity for each AE based on this general guidance:

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: Severe or Disabling AE
- Grade 4: Life-threatening AE
- Grade 5: Death related to AE

Relationship to Study Medication Assessment Definitions:

Not Related (must have 1)

- Unreasonable or incompatible temporal relationship to the intervention
- Event is clearly due to extraneous causes (e.g., underlying disease, environment)

Unlikely (must have 2)

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

Reasonable Possibility (must have 2)

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

Definitely (must have 4)

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

Outcome Categories and Definitions:
Any AE that is not resolved must be followed until resolution or until subject has reached end of study:
- Resolved
- Resolved with sequelae
- Continuing (follow-up is required)
- Continuing at end of study (no follow-up is required)
- Continuing at time of death
- Unknown

Collection, Recording, and Reporting of Adverse Events:
All events meeting the definition of an AE must be collected and reported from the time of enrollment/randomization and until the following time points:
- For AEs, through Day 4 or discharge, whichever comes first
- For SAEs, through Day 90
- For mortality, through Day 180

Follow-Up of Adverse Events:
The FASTEST Trial investigators will provide adequate medical care to the study subject for any study-related AEs, including clinically significant laboratory values related to the study. This medical care for study subjects will be provided regardless of their insurance status.

All AEs classified as serious or severe or possibly/probably related to the trial product will be followed until resolution, stabilization, the event is otherwise explained (e.g., chronic condition), or the subject is lost to follow-up, and after all queries have been resolved. Recurrent episodes or progression of the same AE/SAE must be reported as a follow-up of the initial AE/SAE. For cases of chronic conditions, follow-up until the outcome category is "recovered" is not required, as these cases can be closed with an outcome of "recovering" or "not recovered". All other AEs must be followed until the outcome of the event is "recovering" (for chronic conditions) or "recovered" or until the end of the post-treatment follow-up stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved.

Precautions/Over-Dosage:
The maximum dosage is 10 mg. We will record as protocol violations any participants who receive greater than the maximum dose as calculated by weight.

4.17 Concomitant Illnesses and Medications

Definitions
Concomitant illness: any illness that is present at the start of the trial (i.e., at the first visit).

Concomitant medication: any medication other than the trial product(s) that is being taken at the time of study enrollment during the trial, including the screening period.

We will record details of concomitant illnesses and medications at trial entry (i.e., at the time of enrollment/randomization, defined as injection of study medication). We are only giving one dose of study medication over 2 minutes upon entry into the trial.

4.18 Human Subject Protection

4.181 Institutional Review Board

The Advarra IRB will serve as the National Central Institutional Review Board for all participating sites. The Central Institutional Review Board (CIRB) for multicenter protocols is the single IRB of record. It has regulatory responsibility for assuring the protection of the rights and welfare of research participants in accordance with all Standard Operating Procedures of the Advarra IRB. The National Institute of Neurological Disorders and Stroke (NINDS) selected the Advarra IRB to serve as the CIRB for the FASTEST Trial.

Only CIRB reviewed and approved protocols may subsequently be submitted for review and approval by the regulatory authorities and IRBs/ECs in the other participating countries in line with all applicable national, regional, and local regulations.

4.182 Recruitment of Human Subjects

Subjects for the FASTEST Trial will be recruited from all subjects with acute ICH admitted to participating hospitals or evaluated by mobile stroke units. Specific inclusion and exclusion criteria are provided in the study plan and clinical protocol. Given that time from onset to treatment with rFVIIa is critical, the FASTEST Trial will utilize exception from informed consent (in the U.S.) or emergency research procedures (in Canada, Germany, Spain, the U,K., and Japan), as described below.

In the U.S., this study proposes 2 approaches to informed consent for patients with spontaneous ICH: 1) if the patient is alert and oriented, or without capacity to consent but with a family member/legally authorized representative (LAR) present, within the first 120 minutes of stroke onset/last known well and within 30 minutes of baseline CT imaging, delegated research personnel will approach the patient/LAR and obtain prospective informed consent, either in-person or remotely (as per StrokeNet Standard Operating Procedures), followed by paper or electronic documentation; and 2) if the patient is without capacity to consent and a family member/LAR is not present within the given therapeutic window (following repeated attempts by research and clinical staff to contact the LAR), the patient will be enrolled/randomized under HHS regulation 21 CFR 50.24, Exception from Informed Consent in Certain Emergency Research. The attempted consent process for each enrolled subject will be documented by the treating investigator in the WebDCU™.

4.183 Exception from Informed Consent

This is the first trial of ICH to use Exception from Informed Consent (EFIC). FASTEST requires CT imaging to document ICH and eligibility criteria for the trial. Thus, enrollment, randomization, and treatment can only be done after brain imaging. Per EFIC requirements as detailed by the FDA Guidance Document, investigators will attempt to obtain consent from patients, legal representatives, or family members, if available and as applicable, but this should be done within 30 minutes of baseline CT imaging and 120 minutes of stroke onset/last known well. Although we previously held an IND for rFVIIa for ICH, we submitted a new IND, as per FDA requirements for EFIC trials.

The primary IRB of record in the U.S. for the FASTEST Trial is the Advarra IRB. They will work with the local IRBs to meet the EFIC requirements for FASTEST for U.S. sites. We have outlined below how FASTEST meets the requirements for EFIC:

FDA Guidance for EFIC

"The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following":

1) **The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.**

Answer: Intracerebral hemorrhage (ICH) accounts for more than 10% of all strokes worldwide or about 1,700,000 cases per year. It is the deadliest type of stroke with a mortality of more than 40% at 1 month and only 20% of survivors are functionally independent at 6 months. There is no scientifically proven effective treatment for ICH.

2) **Obtaining informed consent is not feasible because:**

(i) **The subjects will not be able to give their informed consent as a result of their medical condition;**

Answer: Stroke patients have significant limitations in providing informed consent in the acute setting.[42] In the NINDS t-PA stroke trials investigating tissue plasminogen activator (t-PA) for acute ischemic stroke, surrogate consent was used to enroll 439 of 624 (70%) of subjects.[43] These trials included subjects with very mild strokes (0-5 on NIHSS) which would be highly unlikely in the FASTEST Trial of ICH. Compared to NINDS t-PA Trial subjects who provided their own consent, those enrolled by surrogate consent generally were about 5 years older, with higher NIH stroke scale (NIHSS) scores (median 17 versus 9, $p < 0.001$), and less likely to have a good recovery (26% versus 53% had a modified Rankin score of 0-1 at 90 days, $p < 0.001$).

(ii) **The intervention under investigation must be administered before consent from the subjects' LARs is feasible; and**

Answer: The major issue here is the therapeutic window for rFVIIa. Minimization of time from onset to treatment with rFVIIa is critical given the small time window for stopping or slowing growth of ICH that trial data demonstrate is smaller than that for IV t-PA. In the SPOTLIGHT Trial, subjects with a positive "spot sign" on CT angiography indicating ongoing bleeding had imaging at baseline, immediately after start of study medication, and 24 hours (Table 1). *Almost all additional bleeding occurred between the baseline CT imaging and the CT scan immediately after treatment during when informed consent and randomization occurred*. Thus, there was little opportunity for rFVIIa to biologically modify ongoing bleeding.

(iii) **There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.**

Answer: There is no way to identify subjects in the general population who will likely develop ICH. There are certain risk factors that increase risk of ICH (older age, hypertension, genetics) but these are not helpful in identification of eligible patients within a large population.

3) **Participation in the research holds out the prospect of direct benefit to the subjects because:**

(i) **Subjects are facing a life-threatening situation that necessitates intervention;**

Answer: See above.

(ii) **Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects;**

Answer: While there is not a preclinical model of spontaneous ICH, the post-hoc data from the FAST Trial, and replicated in the rFVIIa IIb Trial, indicate a high likelihood of potential benefit, as noted earlier in the protocol

(iii) **Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.**

Answer: ICH is a disease with high morbidity (only 20% of survivors are independent) and mortality (> 40%). rFVIIa is associated with an absolute increase of thrombotic events (myocardial infarction, ischemic stroke, and

pulmonary embolus) of about 5% in the prior trials, the majority of which are not fatal. For comparison, t-PA use in ischemic stroke is associated with a 6% risk of symptomatic ICH, of which 50% are fatal.

4) **The clinical investigation could not practicably be carried out without the waiver.**

Answer: Clinical assessment, imaging of the brain, and treatment with study medication within 120 minutes, with an expected ½ of participants within 90 minutes, is not feasible without a waiver. The process of informed consent generally takes an additional 45 minutes to 1 hour particularly when one includes the time to identify legal representatives and family members. In the SPOTLIGHT Trial, the time from baseline CT scan to start of treatment was 1.6 hours, much of which was related to the process of consent and identification of legal representatives and family members.

5) **The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a LAR for each subject within that window of time and, if feasible, to asking the LAR contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact LARs and make this information available to the IRB at the time of continuing review.**

Answer: For discussion of therapeutic window, see above. The FASTEST Trial commits to identifying the LAR/family member within 30 minutes of baseline CT imaging and 120 minutes from stroke onset/last known well. We will also train investigators regarding methods to identify these individuals.

6) **The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with those outlined in regulations. These procedures and the informed consent document are to be used with subjects or their LARs in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.**

Answer: The FASTEST Trial commits to identifying the LAR and family member as soon as possible after treatment is initiated, if not done prior to treatment. We have outlined procedures to halt a study subject participation in the trial if a family member objects to participation.

7) **Additional protections of the rights and welfare of the subjects will be provided, including, at least:**

(i) **Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;**

Answer: The Advarra IRB is the reviewing IRB for human subject research for the FASTEST Trial. Each participating network institution signs a reliance agreement with the Advarra IRB that delegates the responsibility of human subject protection review to the Advarra IRB.

Per FDA guidance, emergency research may be reviewed using a centralized IRB process. The guidance recommends when a centralized IRB process is used that either:

- The central IRB may be responsible for reviewing all aspects of the study, including local issues; or,
- Review may be shared by a local IRB and central IRB who cooperate in the review of emergency research studies.

For example, the central IRB may agree to be responsible for the scientific review of the study and the informed consent document; the local IRB may agree to be responsible for evaluating plans for community consultation and public disclosure. However, the guidance also indicates that IRBs should not review the study protocol separately from the community consultation and public disclosure plans and states that the “FDA does not recommend reviewing the protocol separately from the other plans. Because the protocol and plans for community consultation and public disclosure can all influence each other, IRBs should review the study

protocol and community consultation and public disclosure plans as a package.". Since the reviewing IRB for StrokeNet studies is a CIRB, it would reduce the efficiency gained by the CIRB process to require that the local IRBs also review the protocol in order to evaluate the community consultation and public disclosure plans.

To meet the FDA guidance that "The IRB that is responsible for finding and documenting that community consultation and public disclosure will take place (as required by 21 CFR 50.24(a)(7)) should be knowledgeable about local conditions in order to evaluate the community consultation and public disclosure plan," the Advarra IRB will work with the National Clinical Coordinating Center, the Regional Coordinating Centers (RCCs), the protocol principal investigator (PPI), the local investigators, and local IRBs to develop community consultation and public disclosure plans for the geographic areas in which the research will take place, and the Advarra IRB will ensure that the study is in compliance with state or local laws and regulations. Whenever possible plans will be developed that could be used by multiple institutions with a region. The Advarra IRB must review the plans for community consultation and public disclosure before the plans are implemented. The local investigators, possibly in conjunction with the local RCCs, will execute the plans. The Advarra IRB, in consultation with the local IRBs, will consider the concerns and objections raised during community consultation activities when the IRB deliberates on whether to approve, require modifications (to secure approval), or disapprove the clinical study. The Advarra IRB must be approve the plans prior to initiation of the clinical study.

(ii) **Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;**

Answer: The goals of community consultation are the following:

1) To ensure that all relevant communities have opportunity for input into the IRB's decision-making process before initiation of the study;
2) To present information so that community members understand the proposed investigation, understand its risks and benefits; and,
3) To be sure community members understand that the investigation will take place without informed consent.

Community consultation does not necessarily imply that there will be community consent for the trial to take place. If community consultation were viewed as community consent, this would imply that the input came from a large proportion or essentially all the members of the community as opposed to representatives of the community. The process is meant to solicit input from the community regarding the study. The IRB makes the final determination as to study approval based on information obtained from the community consultation. For the purposes of EFIC, the definition of community includes "the community in which the research will take place" and "the community from which subjects will be drawn". In other words, the community includes the geographical area from which participants will be drawn and the group of patients with, or at risk for, the disease of interest. See Model for Community Consultation and Disclosure.

The content of community consultation will inform the community participants that informed consent may not be obtained for any research subjects prior to enrollment. Specifically, the goal will be to:

- Inform the community about all relevant aspects of the study including its risks and expected benefits;
- Hear the perspective of the community on the proposed research; and,
- Provide information about ways in which individuals wishing to be excluded may indicate this preference.

The type and frequency of community consultation will:

- Provide opportunities for broad community discussion;
- Ensure that representatives from the communities involved in the research participate in the consultation process;
- Use the most appropriate ways to provide for effective community consultation; and,
- Be based on numerous factors, including the size of the communities, the languages spoken within those communities, the targeted research population, and the heterogeneity of the population.

(iii) **Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;**

Answer: Public disclosure is defined as the "dissemination of information about the research sufficient to allow a reasonable assumption that communities are aware of the plans for the investigation, its risks and expected benefits, and the fact that the study will be conducted". It also includes "dissemination of information after the investigation is completed so that communities and scientific researchers are aware of the study's results". See Model Community Consultation and Disclosure, and Informed Consent.

Appropriate public disclosure includes:

- Clear statement that informed consent may not be obtained for any subjects
- Information about the study medications use, including a balanced description of the risks and benefits
- Synopsis of the research protocol and study design
- How potential study subjects will be identified
- Participating sites/institutions
- Description of the attempts to contact an LAR
- Suggestions for opting-out of the study

(iv) **Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;**

Answer: See 7)(iii) above.

(v) **Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and**

Answer: The DSMB appointed by the NINDS for NIH StrokeNet trials fulfills this role.

(vi) **If obtaining informed consent is not feasible and a LAR is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a LAR, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members.**

Answer: A procedure for prospective informed consent has been developed, as is required by the regulations, in the unlikely event that an LAR can be identified within the presumed short therapeutic time window for the intervention and is able to provide a meaningful prospective surrogate consent for patient enrollment. In circumstances in which is it impossible to identify an LAR within the therapeutic time frame, EFIC will be applied.

Prior to enrolling an eligible patient into the proposed trial with EFIC, the emergency/MSU physician will see if the eligible patient has refused study participation by checking if the patient has a card with the phrase "FASTEST declined". If the words "FASTEST declined" are listed on the card, the patient will not be enrolled in the clinical investigation. If no "opt-out" is identified, the patient will be entered into the study.

Subjects who are enrolled in FASTEST with EFIC or by their LAR/family will be informed of their inclusion in the clinical investigation at the earliest possible opportunity. This will be done in-person, after the patient is hospitalized. A study team member will speak with the senior clinician to determine the stability of the subject and the appropriate time for speaking with the subject, or if not alert or capable of making informed decisions (and the subject was enrolled with EFIC and not by an LAR/family), an LAR or family member. A delegated study team member will approach the subject (or LAR/family) to notify the subject or LAR/family about the subject's enrollment, provide information about the study, about the subject's rights, the responsibilities of the investigators, and answer any questions about the study. At that time, the subject or the LAR will be asked to

provide consent for continued participation in the study. An informed consent document, either in paper form or electronic, will be used to document the subject's (or LAR/family's) decision to either continue in the study or to not participate any further, with the process conducted either in-person or remotely (as per FASTEST Trial Standard Operating Procedures). A copy of this form will be provided to the subject and another copy will be placed in the subject's research record. Subjects who do not wish to continue to participate will be excluded from all further aspects of the study except for the collection of data required by federal agencies and permitted by the IRB to determine safety and efficacy.

If the subject is unable to comprehend a request for continued participation after EFIC enrollment, or the subject dies after enrollment, the investigator will attempt to inform the LAR/family members. Since ICH is associated with a 30-day mortality of > 40%, investigators anticipate the majority of their efforts will be attempting to contact LARs or family members.

For enrolled subjects who die in the ED/MSU or the hospital, investigators will first attempt to notify an LAR of the subject. If such a representative is not reasonably available, a family member will be notified of the subject's inclusion and the details and other pertinent information regarding the study.

Notification will occur either by attempting up to two phone calls to the subject's family or sending two letters to the subject's address (e.g., as listed on the EMS run report form, hospital chart information, or telephone directory). Research team members will document all efforts to contact subjects and their family members and maintain records according to the same process followed for all other record keeping during the study. Telephone discussions and letters will fully inform the subject's representatives of the nature of the research project, the goals and objectives, the study protocols, the details of the EFIC regulations, and the information on the community consultation and public notification that occurred. Subject notification in each case will be documented and will become a permanent part of the study record.

For subjects who appear to have no relatives or persons responsible (e.g., homeless), investigators will make every reasonable effort, including working with the County Medical Examiner, law enforcement, and hospital personnel to help identify a next-of-kin for unidentified deceased subjects so that they may be notified.

The attempted consent process for each enrolled subject will be documented by the treating investigator in the WebDCU™.

The consenting process for emergency treatment in participating countries other than the U.S. for the FASTEST Trial is described below:

Germany

The study investigator physician decides if the patient is eligible for the trial. If the patient can provide consent, the patient is consented prior to enrollment. If the patient cannot, the legal representative (LAR) of the patient can provide consent for the patient in this emergency setting. This may be done by using an abbreviated but ethically approved patient/LAR information sheet. If there is no legal representative, then the study investigator physician directly calls the specified independent physician (who is specifically trained for this role) to confirm if the patient should be randomized. If so, the patient is enrolled/randomized. If the patient regains the ability to give informed consent at a later time, he or she will be asked to confirm consent at that time by signing the full version of the ethically approved information sheet. In the case a patient does not regain the ability to give informed consent, a legal representative needs to be appointed in a reasonable time, and will be asked to confirm consent at that time by signing the full version of the ethically approved information sheet.

Spain

The study investigator physician decides if the patient is eligible for the trial. If the patient can provide consent, the patient is consented prior to enrollment. If the patient cannot, a family member or legal representative for the patient can provide consent for the patient in this emergency setting. If there is no family member or legal representative, then the study investigator physician directly calls the specified independent physician to confirm if the patient should be enrolled/randomized. If so, the patient is enrolled/randomized. If the patient regains the ability to give informed consent at a later time, he or she will be asked to confirm consent at that time. In the case a patient does not regain ability to give informed consent, a legal representative or family

member will be asked to confirm consent at that time.

United Kingdom

The study investigator physician decides if the patient is eligible for the trial. If the patient can provide consent, the patient is consented prior to enrollment. This is done using a brief but ethically approved information sheet. If the patient cannot, then the study investigator physician can take proxy consent from a close relative or friend, if they know the person well enough to know what they would want. If no friend or relative is available, an independent physician (who is **not** specifically trained for this role) can confirm if the patient should be enrolled/randomized. If so, the patient is enrolled/randomized. If a relative/friend then appears later, they can give proxy consent. The patient's views will always override the relative/friend/independent decision. If the patient regains the ability to give informed consent at later time, he or she will be asked to confirm consent at that time.

Canada

Canada has a national standard in the TCPS-2, section 3.8. This standard is observed in all Canadian jurisdictions except Quebec where the Civil Law code forbids the application of this particular section. The application of this section means that one has to make a special application to the Research Ethics Board (REB) of record and justify and meet all 6 criteria listed below. If the REB judges that these criteria can be met, then deferral of consent/waiver of consent can be granted. It is always necessary to seek consent from a relative first and it is always necessary to obtain regained capacity consent in Canada.

Language from the relevant section is below:
Article 3.8: Subject to all applicable legal and regulatory requirements, research involving medical emergencies shall be conducted only if it addresses the emergency needs of the individuals involved, and then only in accordance with criteria established in advance of such research by the REB. The REB may allow research that involves medical emergencies to be carried out without the consent of participants, or of their authorized third party, if all of the following apply:

(a) a serious threat to the prospective participant requires immediate intervention;
(b) either no standard efficacious care exists or the research offers a realistic possibility of direct benefit to the participant in comparison with standard care;
(c) either the risk is not greater than that involved in standard efficacious care, or it is clearly justified by the prospect for direct benefits to the participant;
(d) the prospective participant is unconscious or lacks capacity to understand the risks, methods, and purposes of the research project;
(e) third party authorization cannot be secured in sufficient time, despite diligent and documented efforts to do so; and;
(f) no relevant prior directive by the participant is known to exist.

When a previously incapacitated participant regains capacity, or when an authorized third party is found, consent shall be sought promptly for continuation in the project, and for subsequent examinations or tests related to the research project.

Japan

In the Japanese Guideline for Good Clinical Practice (GCP), it is described that subjects can be enrolled in trials without informed consent (IC) of patients/relatives in case that:

1) subjects fall in emergent and life-threatening risk;
2) currently approved therapeutic strategies are not effective enough against the risk;
3) trial drugs have high possibility to resolve the risk;
4) disadvantages of the trial drugs to subjects are minimum; and,
5) it is impossible to communicate with relatives (representatives) quickly.

However, exception from informed consent has never been applied for a stroke trial per local investigators. Even if FASTEST cannot obtain exception from informed consent, Japanese ICH patients arrive at the ED very quickly as compared to other countries. According to reports from the Japan Stroke Data Bank, 51.9% of total hypertensive ICH patients (n ≥ 14,000) visited the ED within 2 hours and 23.4% between 2 hours and 6 hours.

4.184 Potential Risks

The primary risks to subjects in the FASTEST Trial are thromboembolic complications. These include: 1) acute myocardial infarction; 2) acute cerebral infarction; and, 3) acute pulmonary embolism. These events were usually non-fatal in prior trials, but can lead to death. All information concerning subjects will be kept confidential. Subjects will be assigned a study ID number. No personal identifying information will be used in presentation or publication of data from this study.

4.185 Protections Against Risk

Safety Management Plan

Safety Outcomes and Interim Safety Monitoring: Active monitoring for all AEs will occur throughout the study, as described in the clinical protocol. An independent Medical Safety Monitor will be notified using an automated notification system triggered when SAEs are entered into the study database by study investigators. The independent Medical Safety Monitor will adjudicate the event for seriousness, relationship to the study intervention, and expectedness. If the independent Medical Safety Monitor determines the event to be serious, unexpected, and related, a MedWatch report will be generated in WebDCU™ with information about the subject and event. The Safety Monitor will work with the site to complete the MedWatch Report. The report will then be submitted to the FDA and CIRB within the required reporting requirements.

A DSMB will be appointed by the NINDS. The DSMB members will not be involved in the conduct of the study and will act in an expert, independent advisory capacity to monitor participant safety, study conduct, and trial quality. A Safety Monitoring Plan (SMP) will be established in collaboration with the NDMC and the FASTEST Executive Committee. The NDMC statisticians will generate DSMB Reports semiannually or more frequently, as needed. This review will aid in identifying any safety issues that may need to be addressed. All AEs occurring within 4 days of treatment or discharge, whichever comes first, and all SAEs occurring through Day 90 will be collected in the study database. Mortality will be collected through Day 180. The independent Medical Safety Monitor will be notified in real time (automatic e-mail notification upon data entry at the site) of all SAEs and will be required to provide a timely review of relatedness and expectedness of the specific SAE. AEs (including SAEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The rate of expected AEs by treatment group and by age group will be included in each DSMB report. All MedDRA coded AEs and SAEs will be summarized in terms of frequency of the event, number of subjects having the event, and severity and relatedness to treatment. The independent Medical Safety Monitor assessment of the SAE will be included in both the open and closed DSMB reports. Although unexpected to differ by gender, race, and ethnicity, safety outcomes will be compared by demographic characteristics at the end of the trial.

In addition to AEs/SAEs, each semiannual DSMB report will include cumulative summary statistics on enrollment and retention, baseline characteristics, protocol violations, and data management/quality information (e.g., timeliness and completeness of data entry by the clinical sites and number of data queries generated and resolved). The DSMB may issue recommendations regarding study conduct when concerns arise that may threaten participant safety or study integrity. In addition, the NDMC will generate Interim Monitoring Reports according to the planned interim analyses for the DSMB to review. The DSMB will follow the trial stopping rules for efficacy or futility, as described in the FASTEST study design. The NDMC statisticians will generate two versions of the DSMB report. The statistics for the **'**Closed Session**'** DSMB reports are provided by treatment group (partially blinded as group A and B), and will be made available to the DSMB only. The 'Open Session' DSMB report contains aggregated statistics only (i.e., not by treatment group), and is made available to the FASTEST Executive Committee.

Health Insurance Portability and Accountability (HIPAA/PIPED)

Under U.S. federal law, researchers who use information about the health of their research participants are required, except in specific circumstances, to get written permission to use their participant's protected health information (PHI) for the research study. For the FASTEST Trial, that involves exception from informed consent, we have requested a HIPAA waiver for the reasons listed below, as per published guideline, since

the research could not practicably be conducted without the requested waiver or alteration:

FASTEST meets the following criteria:
1) The research could not practicably be conducted without access to and use of the PHI;
2) The PHI use or disclosure involves no more than minimal risk to the privacy of individuals based on at least the presence of:
    (a) an adequate plan to protect PHI identifiers from improper use and disclosure (every subject will be assigned a study ID number and all associated data is de-identified within a protected study database – see Statistical Protocol);
    (b) an adequate plan to destroy those identifiers at the earliest opportunity, consistent with the research, absent a health or research justification for retaining the identifiers or if retention is otherwise required by law (all study identifiers will be destroyed at earliest opportunity and prior to any public use database); and,
    (c) adequate written assurances that the PHI will not be reused or disclosed to any other person or entity except (a) as required by law, (b) for authorized oversight of the research study, or (c) for other research for which the use or disclosure of the PHI is permitted by the Privacy Rule.

Potential Benefits of the Proposed Research to Human Subjects and Others
There may not be a direct medical benefit to participants in the proposed research. However, we hope the information learned from this research study will inform treatment of acute ICH and future trials of acute stroke therapies. Potential benefits may include greater efficacy of rFVIIa in slowing the bleeding of ICH and improving outcome, as noted in the preliminary studies.

Importance of Knowledge to be Gained
The FASTEST Trial seeks to determine whether rFVIIa improves outcomes in participants with ICH as compared to placebo. Given that there is currently no scientifically approved treatment for acute ICH, knowledge gained from this trial will significantly inform the acute treatment of stroke.

In summary, the study will be conducted in accordance with the Declaration of Helsinki and with the International Conference on Harmonisation (ICH) GCP guidelines. We will comply with all applicable regulatory and legal requirements, ICH GCP guidelines, and the Declaration of Helsinki in obtaining and documenting informed consent and HIPAA, and meeting the requirements for EFIC for U.S. sites, and meeting the participating countries' requirements for emergency research consenting procedures and subject data protection in clinical trials.

4.186 Recruitment of Minorities and Women

The individual age, race, and gender of each participant will be transferred to the NINDS at fixed intervals per the NINDS "Standard Operating Procedure of E-mail Recruitment Enrollment". The proposed study will take place in communities where there are diverse populations.

Inclusion of Women
All eligible patients of both genders will be approached to participate in the FASTEST Trial. Based upon earlier acute trials of ICH, we expect approximately 39% of participants to be women. Further, while we do not anticipate differential treatment effects based on gender, our analyses will explore clinically important differences due to gender.

Inclusion of Minorities
All eligible patients of all races and ethnic groups will be approached to participate in FASTEST. Based upon prior rFVIIa trials, the NINDS-funded ATACH and ATACH-2 Trials, the TICH-2 Trial, the NINDS-funded IMS III Trial that took place in 5 of the 6 countries that are also participants in the FASTEST Trial, we expect the demographics of this study to be approximately: Non-Hispanic White (70%), Black (12%), Hispanic White (8%), Asian (10%), Male (61%), and Female (39%), Median Age: 64 years. In addition, the incidence rates of ICH are higher in blacks than whites. Thus, these factors should facilitate adequate representation of minorities enrolled.

4.187 Subject Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and other information generated will be held in strict confidence. No information about the study or data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, and representatives of the NCC, NDMC, CIRB, and/or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for the duration specified by the StrokeNet Standard Operating Procedure (SOP) or longer as dictated by CIRB and local institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored for the duration of the study and analysis at the NDMC. The study data entry and study management systems used by clinical sites and by the NDMC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and a Public Use Dataset (PUDS) will be archived with NINDS.

4.188 Study Modification/Discontinuation

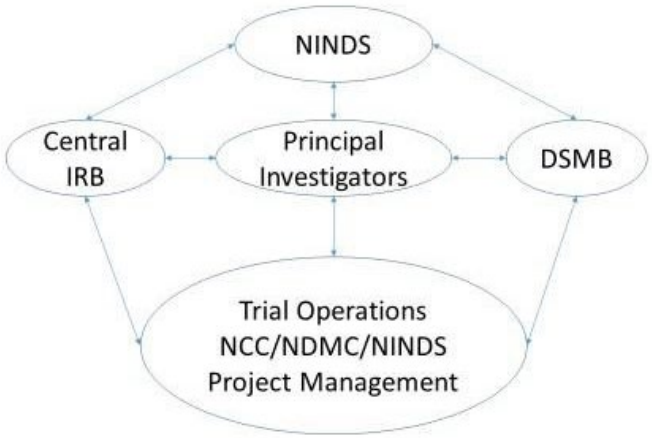
The study may be modified or discontinued at any time by the CIRB, the NINDS, the sponsor, the Office for Human Research Protections (OHRP), the FDA, or other government agencies, as part of their duties to ensure that research subjects are protected.

4.19 Study Schedule

Task	Year 1				Year 2				Year 3				Year 4				Year 5				Year 6	
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2-Q4
Start of study	■																					
First enrollment				■																		
Recruitment period				■	■	■	■	■	■	■	■	■	■	■	■	■	■					
Last patient follow-up primary endpoint				■															■			
Data cleaning, analysis																	■	■	■	■		
Primary publication																	■	■	■	■	■	
Planned completion of final study report																						■

5.0 FASTEST ADMINISTRATIVE STRUCTURE

5.1 Organizational Structure



5.2 StrokeNet National Coordinating Center and National Data Management Center

The clinical coordination of the FASTEST Trial operations will be centralized through the following:

NIH StrokeNet National Coordinating Center (NCC)
University of Cincinnati
260 Stetson Street, Suite 2300
Cincinnati, Ohio 45267-0525

A Project Manager at the NCC will be assigned to coordinate the following study oversight: trial

communication, required training activities, site assessment and/or initiation visits, collection of trial related regulatory documents, recruitment performance tracking and performance analysis.

The data coordination and analysis of the FASTEST Trial will be centralized through the following:

NIH StrokeNet National Data Management Center (NDMC)
Medical University of South Carolina
135 Cannon Street
Charleston, South Carolina 29425-8350

The study data will be managed (including data queries) by the NDMC using the WebDCU™ system. This user-friendly web-based database system, developed and validated by the NDMC, 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.

5.3 Global Trial Management

The overall PIs of FASTEST, the NCC, and NDMC will oversee all trial operations including start of trial, site start-up, patient randomization and enrollment, etc. However, specific trial operations in other participating countries (research pharmacy labelling and distribution of study medications, human subjects, regulatory issues, site start-up and monitoring, etc.) will be managed by specific research organizations in each country and overseen by a principal investigator (PI) in each country.

5.4 Data Safety and Monitoring Board (DSMB) for trial

FASTEST will have an independent DSMB appointed by the NIH to oversee study safety. The DSMB may put the study on hold at any point for safety concerns. The DSMB will specify the content and frequency of data reports to be generated by the NDMC.

5.5 Independent Medical Safety Monitor (IMSM)

An independent Medical Safety Monitor (IMSM) will review all serious adverse ischemic events and determine their expectedness, severity, and relatedness to the study intervention. The IMSM will adjudicate events while blinded to treatment status. He/she also will be responsible for ongoing monitoring of reports of SAEs submitted by the clinical centers in real time to ensure GCP and to identify safety concerns quickly. In the event of unexpected SAEs or an unduly high rate of SAEs, the IMSM will promptly contact the lead PI and the NINDS Program Official who will notify the DSMB Chair.

5.6 Executive Committee

The Executive Committee will provide overall clinical guidance and leadership for the execution of the FASTEST Trial. This committee will provide a means of partnership between the investigators, the NINDS, and the sponsors. The committee will meet monthly by phone (1 hour/month) for the full duration of the study. Responsibilities include oversight of the overall conduct of the study with regard to protocol compliance and modifications/amendments, recruitment, study progress, and problem-solving. The lead PI will chair the Executive Committee.

5.7 National Institute of Neurological Disorders and Stroke (NINDS)

Except for study medication that will be supplied by Novo Nordisk A/S, the NINDS will provide funding for all aspects of this trial via the NIH StrokeNet. An identified Program Official will be responsible for oversight of this trial.

6.0 PUBLICATION PLAN

The primary presentation of the study results is planned to be within 6 months of completion of last primary endpoint follow-up. Ideally, a concomitant publication would be published at the same time but, if not, within the next 6 months. The publication committee of the FASTEST Trial will develop guidelines for the authorship of the primary publication as well as all secondary publications. The FASTEST Trial will be registered at clinicaltrials.gov, and we will plan to share the data generated by the trial on clinicaltrials.gov and as per NINDS requirements.

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FASTEST

AGREEMENT ON THE PROTOCOL

By signing below, I confirm that:

1. I have read this protocol and it contains all necessary details for conducting this study.

AND

2. I agree to conduct the trial in compliance with this protocol and to adhere to all regulations that govern the conduct of the study.

_____

Principal Investigator's Printed Name

_____ _____

Principal Investigator's Signature **Date**

_____

Clinical Performance Site Name