

STOP-IT STUDY

THE **SPOT** SIGN FOR PREDICTING AND TREATING ICH GROWTH TRIAL CLINICAL PROTOCOL

Phase II, randomized, multicenter, double-blind, placebo-controlled trial comparing rFVIIa to placebo for treatment of subjects with acute ICH and contrast extravasation (the spot sign) identified on CTA.

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Supported By:

**National Institute of Health / National Institute of Neurological Disorders & Stroke
2P50NS044283-06**

Clinical Trial Product Provided By:

Novo Nordisk

Sponsor of IND:

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Original Proposal Submission:	17-December-2007
Revised Proposal Submission:	11-March-2008
Revised Proposal Submission:	07-July 7-2008
Revised Proposal Submission:	18-September-2008 (Post Pre-IND Mtg.)
Amendment 1	23-September-2009
Amendment 1.1	01-July-2010
Amendment 1.2	02-August-2010

TABLE OF CONTENTS

	ACRONYMS	4
1.0	Introduction	5
2.0	Study Objectives	5
3.0	Background and Significance	6
	3.1 Hematoma Growth in the Acute Phase of ICH	6
	3.2 Contrast Extravasation as a Predictor of Hematoma Growth	6-7
	3.3 Utility of CTA for Evaluating ICH	7
	3.3.1 CTA can be Performed Quickly and Easily	7
	3.3.2 CTA is a Diagnostic Tool that can Identify Secondary Causes of ICH	7
	3.3.3 CTA is a Safe Procedure	8
4.0	Supporting Data	8
	4.1 Contrast Extravasation as a Predictor of Hematoma Growth	8
	4.2 Prior Experience with Recombinant Activated Factor VII	8-9
	4.2.1 Efficacy of Recombinant Activated Factor VII	9
	4.2.2 Safety of Recombinant Activated Factor VII	10-11
	4.3 Conclusions from Studies to Date	12
5.0	Research Design and Methods	12
	5.1 Overview	12
	5.2 STOP-IT Study Design	12
	5.2.1 Patient Flow	12-13
	5.2.2 Inclusion Criteria	14
	5.2.3 Exclusion Criteria	15
	5.3 Dose Selection for Recombinant Activated Factor VII	16
	5.4 Drug Storage and Administration	16
	5.5 CT and CTA Methodology	16
	5.5.1 CT and CTA Acquisition	16
	5.5.2 CTA and Standard Care for Acute ICH	16
	5.6 Imaging Analysis	16-17
	5.6.1 Image Data Management	17
	5.6.2 Volume Measurements	17-18
6.0	Measurement of Efficacy Outcomes	18
	6.1 Primary Outcome: Test Performance	18
	6.2 Primary Outcome: Clinical Parameters	18
	6.3 Primary Safety Outcomes	18
	6.3.1 Definitions	18-19
	6.3.2 Primary Safety Measures	19-20
	6.4 Recruitment Procedure and Technique	20
	6.5 Contingency Plan for Lags in Recruitment	20
	6.6 Procedure for Subject Screening	20
	6.7 Competing Ongoing Clinical Trials	20
	6.8 Randomization and Blinding	20-21
	6.9 Drug Distribution and Pharmacy Support	21
7.0	Subject Medical Management	21
8.0	Medical and Laboratory Data Collected	22
	8.1 Schedule of Events	22-23
	8.2 Monitoring for Adverse Events and Assessment of Safety	24-25
	8.3 Stopping Rules for Safety Concerns	25
9.0	Statistical Considerations	26
	9.1 Overview and Patient Entry	26

9.2	Data Forms.....	26
9.3	Manual of Operations	27
9.4	Database Development and Security	27-28
9.5	Data Management, Monitoring and Quality Assurance	28-29
9.6	Sample Size Calculation	29-32
9.7	General Analysis Plan	32
	9.7.1 Objective #1	32-33
	9.7.2 Objective #2	33
	9.7.3 Objective #3	34
9.8	Potential Collaborations and Pooled Analysis	34
10.0	Study Timeline.....	34-35
11.0	Handling of Missing Data	35
12.0	Trial Administrative Structure.....	35
	12.1 National Institute of Neurological Disorders and Stroke (NINDS)	35-36
	Data and Safety Monitoring Board (DSMB)	
	12.2 External Medical Monitor	36
	12.3 Biostatistical Core and Data Management	36
	12.4 Coordinating Clinical Center.....	36-37
	12.5 Imaging Center.....	37
	12.6 Participating Centers	37-38
	12.7 Steering Committee.....	38
	12.8 Drug Distribution and Pharmacy Support.....	38
	12.9 Novo Nordisk.....	38
	12.10 Investigational New Drug (IND) Application	38
	12.11 National Institute of Neurological Disorders and Stroke	38
13.0	Human Subjects	38-39
	13.1 Institutional Review Board (IRB)/Ethics Committee (EC) & Informed Consent.....	39
	13.2 HIPAA/PIPEDA	39
	13.3 Specimens.....	39
	13.4 Recruitment of Minorities and Women	40
	13.5 Inclusion of Children.....	40
	13.6 Potential Risks and Benefits.....	40-41
	13.7 Subject Confidentiality	41
14.0	Vertebrate Animals.....	41
15.0	Select Agent Research	41
16.0	Disclosure of Data.....	41
17.0	Data Sharing Plan.....	41-42
18.0	References	43-45
19.0	Appendices.....	46-65
	Appendix I: National Institute of Health Stroke Scale (NIHSS)	
	Appendix II: Glasgow Coma Scale (GCS)	
	Appendix III: Modified Rankin Scale (mRS)	
	Appendix VI: Barthel Index (BI)	
	Appendix V: Sample Informed Consent Form (For sites where CTA <u>IS NOT</u> standard of care)	
	Appendix VI: Sample Informed Consent Form (For sites where CTA <u>IS</u> standard of care)	

Acronyms

AE	Adverse Event
BI	Barthel Index
BMI	Biomedical Informatics
BSC	Biostatistical Core
CBC	Complete Blood Count
CCC	Clinical Coordinating Center
CCHMC	Cincinnati Children's Hospital Medical Center
CIN	Contrast-induced Nephropathy
CRF	Case Report Form
CT	Computed Tomography
CTA	Computed Tomography Angiography
DMC	Data Management Center
DSA	Digital Subtraction Angiography
DSMB	Data Safety and Monitoring Board
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
ED	Emergency Department
FAST	rFVIIa in Acute Hemorrhagic Stroke Treatment
FDA	Food and Drug Administration
GCS	Glasgow Coma Scale
GERFHS	Genetic and Environmental Risk Factors for Hemorrhagic Stroke
GFR	Glomerular Filtration Rate
GPIIa/IIIb	Platelet Receptor Inhibitors
HIPAA	Health Insurance Portability and Accountability Act
HU	Hounsfield Unit
ICH	Intracerebral Hemorrhage
IDS	Investigational Drug Service
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IS	Ischemic Stroke
ITK	Insight segmentation and Registration Tool Kit
IVH	Intraventricular Hemorrhage
MI	Myocardial Infarction
MOP	Manual of Operating Procedures
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NIH	National Institute of Health
NIHSS	National Institute of Health Stroke Scale
NINDS	National Institute of Neurological Disease and Stroke
NSTEMI Non-ST	Elevation Myocardial Infarctions
PACS	Picture Archiving and Communication System
PE	Pulmonary Embolism
PHI	Personal Health Information
PI	Principal Investigator
PIPEDA	Personal Information, Privacy and Electronics Documents Act
PTT	Partial Thromboplastin Time
RCT	Randomized Controlled Trial
rFVIIa	Recombinant Activated Factor VII (NovoSeven® RT / NiaStase RT®)
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SID	Subject Identification Number
SPORTRIAS	Specialized Program of Translational Research in Acute Stroke
SPOTLIGHT	Spot Sign Selection of ICH to Guide Hemostatic Therapy
STEMI	ST-Elevation Myocardial Infarction
STOP-IT	The Spot Sign for Predicting and Treating ICH Growth Study
V/Q Scan	Ventilation/Perfusion Scan
XML	Extensible Markup Language

1.0 INTRODUCTION

Intracerebral hemorrhage (ICH) is conservatively estimated to affect 67,000 persons in the United States and 5,000 persons in Canada annually and is associated with a 40-50% case-fatality rate.^{1,2} There are no proven treatments for ICH. The demonstration that hematoma growth after ictus is common and associated with neurological decline has spurred research into early hemostatic therapy to potentially improve patient outcomes.³⁻⁵

Recombinant activated factor VII (rFVIIa) was proven to significantly reduce hematoma growth when administered within four hours of symptom onset in two placebo-controlled, blinded, randomized clinical trials.^{6,7} While clinical outcomes were improved in a phase IIb trial, they were not improved in a phase III trial of this drug.^{6,7} Because rFVIIa works to stop bleeding but should not otherwise affect the natural history of ICH, only patients destined to have hematoma growth will benefit from this therapy. Ideally, clinicians will be able to identify patients who will have significant hematoma growth regardless of their time of presentation and administer hemostatic therapy to this group.

CT angiography (CTA) is a widely available, fast, non-invasive tool that has shown promise for predicting hematoma growth.^{8,9} In two recent retrospective case series patients with contrast extravasation within their hematomas (**the spot sign**) had greater risk of subsequent hematoma growth than patients without extravasation.^{8,9}

The next step in this treatment paradigm is to confirm the ability of CTA to predict hematoma growth and to explore the role CTA may play in the administration of hemostatic therapy. Patients presenting within five hours of ICH onset will be eligible for enrollment into one of two study arms in this multicenter phase II study. Patients who have a spot sign on CTA will be randomized to treatment with either rFVIIa or placebo. Patients without a spot sign will be enrolled in a prospective observational arm and their data will be compared to spot-positive patients treated with placebo to determine the sensitivity and specificity of the CTA spot sign for hematoma growth.

2.0 STUDY OBJECTIVES

- Determine the sensitivity and specificity of the CTA spot sign for hematoma growth.
 - Working hypothesis: For patients scanned within five hours of stroke onset, the spot sign will have a high sensitivity and specificity for hematoma growth.
- Determine the feasibility of using CTA to identify ICH patients at high risk of hematoma growth and to select patients for randomization to treatment with rFVIIa or placebo.
 - Working Hypothesis #1: Site investigators will determine the presence or absence of a spot sign in the acute setting with a high degree of accuracy as compared to blinded over-read by a study neuroradiologist.
 - Working Hypothesis #2: Use of CTA to identify candidates for randomization to rFVIIa versus placebo can be done in a time-efficient manner
- Randomize ICH patients who present within five hours of symptom onset and have a spot sign to treatment with rFVIIa versus placebo, in order to (a) determine if rFVIIa is effective at reducing hematoma growth among patients with a spot sign and (b) provide preliminary efficacy data for this treatment paradigm.
 - Working Hypothesis: Spot-positive patients treated with rFVIIa will have less hematoma growth than spot-positive patients treated with placebo.

3.0 BACKGROUND AND SIGNIFICANCE

Intracerebral hemorrhage is a devastating form of stroke.² While ICH was formerly an area of therapeutic nihilism, recent investigations into the surgical and medical management of ICH prove that large-scale clinical trials for this condition are feasible and provide hope that new treatments may improve patient outcomes.^{6, 10} Predictors of outcome after ICH include patient age, Glasgow Coma Scale (GCS) score at presentation, hemorrhage location, anticoagulant use, initial hematoma size, the presence of intraventricular hemorrhage (IVH) and hydrocephalus, and hematoma growth.^{2, 4, 11} Because the majority of deaths from ICH occur within several days of ictus, interventions for improving outcomes must occur early in a patient's clinical course.¹² Among the potentially modifiable determinants of ICH outcome, hematoma growth is a particularly attractive target for intervention. Hematoma growth occurs in the early phase of ICH and is clinically recognized by neurological deterioration, sometimes leading to death.^{3, 4} If hematoma growth can be prevented neurological outcomes may be improved. However, while hematoma growth frequently complicates ICH, until recently little progress was made in identifying markers that can reliably predict this process.

3.1 Hematoma Growth in the Acute Phase of ICH

Hematoma growth in the first few hours after ICH onset is associated with early neurological deterioration and increased mortality.^{3, 4, 13} A recent analysis of ICH outcome found that for each 10% increase in ICH growth the hazard ratio for death was increased by 5% and patients were 16% more likely to have an increase of one point in their modified Rankin Scale (mRS) score at follow-up.⁴ Hematoma growth usually implies active bleeding into the hemorrhage bed. Earlier assumptions that bleeding was self-limited and that neurological decline was invariably due to secondary mass effect and cerebral edema have proven incorrect.⁴ It is estimated that significant early hematoma growth (generally defined as > 33% volume increase) occurs in 18% to 38% of ICH patients scanned within three hours of onset.^{3, 4, 14, 15} Between three and six hours from onset 8-16% of patients show significant hematoma enlargement, implying that this is a time-dependent process.¹⁴⁻¹⁶ Potential predictors of hematoma growth include thalamic location of hemorrhage, larger initial hemorrhage, prior history of stroke, liver disease, hyperglycemia, hypertension, seizures, thrombocytopenia, alcohol use, depressed level of consciousness, irregular hematoma shape, reduced fibrinogen levels and diabetes mellitus.^{6, 15, 17} The dynamic nature of ICH enlargement during the first several hours poses a challenge and an opportunity for intervention; acute hematoma enlargement could be used as a surrogate outcome in clinical trials and to monitor therapy. No reliable radiological variable that predicts hematoma growth has yet been *prospectively* identified.

Table 1. Literature review of the frequency of hematoma growth.

Interval from onset to CT	Brott (1997) ³ (n=103) Prospective	Davis (2006) ⁴ (n=115) Prospective	Fujii (1994) ^{15, 16} (n=627) Retrospective	Fujitsu (1990) ¹⁸ (n=107) Retrospective	Kazui (1996) ¹⁴ (n=204) Retrospective
0 – 3.0 hrs	38% (39/103)	28% (32/115)	18% (78/422)	NA	36% (27/74)
3.1 – 6.0 hrs	NA	NA	8% (8/97)	NA	16% (7/45)
0 – 6.0 hrs	NA	NA	17% (86/519)	21% (23/107)	29% (34/119)
6.1 – 24.0 hrs	NA	NA	2% (2/108)	NA	10% (7/67)

NA = not available.

3.2 Contrast Extravasation as a Predictor of Hematoma Growth

Vascular imaging has revolutionized stroke medicine in the last decade. Patients with ICH often have vascular imaging to exclude a vascular abnormality (arteriovenous malformation, arteriovenous fistula, aneurysm) as a cause of the hemorrhage. Since hematoma growth largely occurs in the hyperacute phase of ICH, vascular imaging may be beneficial in identifying surrogates for active,

ongoing bleeding. One important surrogate for identifying ongoing bleeding is contrast extravasation seen on CTA, MRI, or DSA.

Previous case reports and retrospective studies suggest that contrast extravasation as seen on CT angiography, MRI and DSA in patients with hypertensive ICH correlates with hematoma growth and indicates ongoing bleeding.¹⁹⁻²³ In the first retrospective case series, Murai showed that contrast extravasation on MRI is an indicator of continued hemorrhage in patients with acute ICH.²⁴ In this study, 108 patients with acute hypertensive ICH underwent imaging with enhanced CT, gadolinium-enhanced MR, and conventional cerebral angiography within six hours of hemorrhage onset. A repeat CT scan was obtained within 48 hours to evaluate enlargement of the hematoma. Evidence of contrast extravasation was seen in 39 patients on MRI and cerebral angiography showed extravasation in 17 patients. There was a significant correlation between extravasation on cerebral angiography and MRI and also with hematoma growth on follow-up CT scan. Yamaguchi found that 42% of patients with primary ICH had contrast extravasation during cerebral angiography performed within five hours of symptom onset.²⁵ Becker and colleagues were the first to show that extravasation of radiographic contrast on CTA was an independent predictor of hospital fatality in a large retrospective study.²³ Out of 113 patients studied, contrast extravasation was seen in 46% and the presence of contrast extravasation was associated with increased mortality (63.5%) compared to patients without extravasation (16.4%). The overall mortality rate from ICH was 38% consistent with other studies. Limitations of this study were its retrospective nature, small sample size, no clear protocol or indications for CTA in ICH, and lack of functional outcomes. This study concluded that extravasation of radiographic contrast on CTA is a surrogate for ongoing bleeding.

3.3 Utility of CTA for Evaluating ICH

3.3.1 CTA can be Performed Quickly and Easily

CTA can be performed quickly and easily in any hospital with a CT scanner. CTA images require the injection of iodinated contrast media and can be obtained immediately following the routine non-enhanced CT head scan. The scan time is approximately two minutes. No post-processing of images is required to identify the spot sign. The presence or absence of the spot sign can be determined immediately, often before the patient is taken off the CT scan table. Therefore, use of the CTA spot sign is ideally suited for rapid decision-making and should not introduce significant delay to treatment.

3.3.2 CTA is a Diagnostic Tool that Can Identify Secondary Causes of ICH

CTA is a non-invasive test that provides valuable information about the vascular anatomy of the brain and is emerging as the favored initial diagnostic exam in evaluating patients presenting with spontaneous ICH. In many circumstances it has replaced traditional (invasive) catheter-based cerebral angiography as the method of choice for screening for a variety of vascular anomalies. In addition to potentially identifying patients at risk of hematoma expansion via the spot sign, CTA can provide valuable diagnostic information regarding potential secondary causes of hemorrhage, such as intracranial aneurysms and arteriovenous malformations. Little published data exists on the role of CTA in the context of ICH. Studies of catheter angiography for the detection of secondary causes of ICH are limited by selection bias, however indications for catheter angiography in the setting of ICH have traditionally included subarachnoid hemorrhage, abnormal calcifications, obvious vascular abnormalities, and blood in unusual locations, such as the Sylvian fissure.²⁶ The risk of a secondary cause of ICH is highest in young patients with lobar hemorrhage and patients without hypertension. The performance of CTA as compared to traditional catheter angiography for the detection of vascular anomalies associated with ICH has recently been assessed in a study which found the sensitivity; specificity and accuracy of CTA were 89%, 92% and 91% respectively.²⁷ Subjects with a known or suspected vascular anomaly as a cause of their ICH will be excluded from the STOP-IT study.

3.3.3 CTA is a Safe Procedure

The major concerns for CTA are iodinated contrast media use in the acute setting where renal function or contrast allergy history may be unknown. Contrast-induced nephropathy (CIN) is often defined as a > 25% increase in serum creatinine occurring within several days of contrast administration, without an alternative explanation.²⁸ Chronic renal impairment is the main risk factor for the development of CIN.²⁸ Patients with a normal glomerular filtration rate (GFR) are at extremely low risk of CIN. If the GFR is 30-60 ml/min there is a low to moderate risk of CIN.²⁸ Recent guidelines recommended that where possible patients should be screened for risk factors associated with acute or chronic renal impairment. The guidelines acknowledge that this may not be possible in the acute setting.^{28, 29} In such situations where delay may negatively impact patient outcome, the absence of risk factors effectively eliminates the probability of a given patient having renal impairment.²⁹ A recent study of CTA in patients with acute stroke (ischemic or hemorrhagic) demonstrated a very low incidence of contrast-induced nephropathy (3%) and no patients required dialysis.³⁰ If a risk factor does exist then empiric precautions such as rehydration and choice of contrast agent and osmolarity is suggested. Contrast extravasation into a limb due to failure of intravenous access occurs on rare occasions (0.25-0.6% of contrast-enhanced radiological studies).³¹ Contrast extravasation may result in local tissue damage.³² The radiation dose delivered by a CTA is slightly more than a non-contrast CT study when centered on the intracranial vessels (1.9 mSV vs. 1.7 mSV).³³

4.0 SUPPORTING DATA

4.1 Contrast Extravasation as a Predictor of Hematoma Growth

Two recent studies have spurred further interest in the use of CTA for prediction of ICH growth. In a retrospective study reported by Goldstein, CTAs were reviewed for 104 patients with ICH.⁹ A significant number of patients received their CTA > 24 hour after onset. Contrast was present within the hematoma in 56% of patients, and this finding was the single most powerful predictor of subsequent hematoma expansion. Contrast extravasation was present in 92% of patients who developed hematoma expansion, compared with 51% of those who did not (p=0.006). The sensitivity and specificity of extravasation for predicting hematoma expansion were 93% and 50%, yielding a low positive predictive value (24%) but a striking negative predictive value (98%). The study confirmed a trend towards earlier time to presentation in patients both with contrast extravasation and hematoma expansion. It also confirmed Becker's finding an increased rate of in-hospital mortality in subjects with extravasation (p=0.04). Multivariable analysis demonstrated an independent effect of contrast extravasation on hematoma expansion (OR 18, 95% CI 2.1-162, p=0.009).

A retrospective study coauthored by Drs. Aviv and Gladstone analyzed CTAs from 39 ICH patients scanned within three hours of onset.⁸ Contrast leakage within the hematoma (the spot sign) was identified in 33% of patients and had a sensitivity of 91% and a specificity of 89% for hematoma growth of > 30% or 6 cc. The positive and negative predictive values for growth in this study were 77% and 96%. Hematoma growth was more common in patients with a spot sign than those without (p<0.001). In multiple regression analysis the spot sign (p<0.001) and anticoagulant use (p=0.02) were associated with hematoma enlargement.

4.2 Prior Experience with Recombinant Activated Factor VII

Coagulation factor VII is a naturally occurring initiator of hemostasis; normally, only 1% of factor VII circulates in its active form. Recombinant activated factor VII (rFVIIa, NovoSeven[®]; Novo Nordisk, Bagsvaerd, Denmark) was developed for the treatment of spontaneous and surgical bleeding in patients with hemophilia A or B and inhibitors to factors VIII or IX, respectively.³⁴ rFVIIa binds to the surface of activated platelets where it generates activated Factor X allowing partial restoration of platelet surface thrombin generation.³⁵ Through its action of enhancing local hemostasis after binding to exposed tissue factors, rFVIIa has been shown to be an effective initiator of hemostasis in patients with normal coagulation systems.³⁴⁻³⁶ Moreover, its efficacy has been reported in promoting

hemostasis in central nervous system bleeding in patients with hemophilia.³⁷ The relatively low frequency of systemic activation of coagulation associated with rFVIIa use, together with its rapid action at the site of bleeding and short half-life of 2.5 hours, suggest that rFVIIa may be an ideal agent for use during the earliest stages of ICH.³⁸

4.2.1 Efficacy of Recombinant Activated Factor VII

The effectiveness of rFVIIa for acute ICH has been tested in one dose-escalation trial, one phase IIb trial, and one phase III trial.^{6, 7, 39} Conclusions regarding efficacy of rFVIIa for ICH can be drawn from the phase IIb and phase III trials of this drug. In the phase IIb trial 399 patients (61% male, mean age 66 years) were randomized to treatment within four hours of symptom onset with placebo (n=96) or 40 µg/kg (n=108), 80 µg/kg (n=92), or 160 µg/kg (n=103) of rFVIIa.⁶ Mean ICH volume at baseline was 24 cc, mean interval from symptom onset to baseline CT scan was 114 ± 35 minutes, and mean onset-to-needle time was 167 ± 32 minutes. The mean percentage increase in ICH volume was 29% following placebo treatment, compared with 16%, 14% and 11% in the rFVIIa 40, 80 and 160 µg/kg groups, respectively (p=0.01 for the comparison of the three rFVIIa groups with the placebo group). Mean absolute growth in ICH volume was reduced by 3.3 cc, 4.5 cc and 5.8 cc with the 40, 80, and 160 µg/kg doses of rFVIIa, respectively (p=0.01, rFVIIa combined versus placebo). Notably, the reductions in ICH growth presented are mean values. While 74% of placebo patients had some hematoma growth, only 28% had hematoma growth of > 33%.⁴ Thus, the mean reduction in hematoma growth is lowered considerably by patients who had < 33% hematoma enlargement. If patients destined to have significant hematoma growth can be reliably identified and other patients excluded from treatment, the difference in hematoma growth between placebo and treatment groups is expected to be significantly magnified, and it follows biologically that differences in clinical outcomes should also be magnified. The effect of time to treatment on hematoma growth in the phase IIb trial illustrates this point. Because hematoma growth is most likely within three hours of treatment, the treatment effect is magnified within this window. In the subset of patients who were treated within three hours (n=269), the mean percentage increase in ICH volume was 34% in the placebo group compared with 13% in the rFVIIa groups (p=0.004). The absolute increase in ICH volume in this subset was 10.7 cc for placebo patients and 4.4 cc for rFVIIa patients (p=0.009). There was essentially no difference in mean percent ICH growth between rFVIIa and placebo among patients treated after three hours of onset. The randomized trials of rFVIIa show that treating all ICH patients presenting 3-6 hours after stroke onset with hemostatic therapy is unlikely to produce clinical benefit. In order to treat ICH patients beyond three hours, it is essential that we identify those at highest risk of growth.

The phase III trial of rFVIIa randomized patients to treatment within four hours of symptom onset to placebo (n= 268), rFVIIa 20 µg/kg (n= 276), or rFVIIa 80 µg/kg (n=297).⁷ The biologic effect of rFVIIa on hematoma growth was verified. Patients in the placebo group had a 26% mean increase in hematoma volume compared to 18% in the 20 µg/kg group and 11% in the 80 µg/kg group (p<0.001 for the comparison of placebo and rFVIIa 80 µg/kg). Patients in the rFVIIa 80 µg/kg group had a mean change in ICH volume of 3.8 cc less than placebo patients (p=0.009).⁷ The clinical trial endpoints were discordant in the phase IIb and phase III trials of rFVIIa. In the phase IIb trial, at three months 29% of the placebo treated patients were dead compared to 18% of rFVIIa treated patients, a relative mortality reduction of 38% (p=0.02). Three month scores on the mRS, Barthel Index, and NIHSS all favored rFVIIa treatment. However, in the phase III trial no statistical differences were seen in mortality or functional outcomes as measured by the mRS or Barthel Index at three months. It is not clear why the clinical outcomes of these trials differed but there were important imbalances in baseline patient characteristics.⁷ Placebo subjects in the phase IIb trial were also more likely to have a three-month mRS of 5-6 than placebo subjects in the phase III trial (45% vs. 24%).⁷

4.2.2 Safety of Recombinant Activated Factor VII

The safety profile of rFVIIa for the treatment of acute ICH has been reasonably established by the studies described above. To date, over 800 patients with acute ICH have received rFVIIa in the setting of a blinded, randomized clinical trial. The only safety concern identified for rFVIIa to date is its prothrombotic potential. Because rFVIIa activates the coagulation system, there is concern it may cause an excess of venous (deep venous thrombosis, pulmonary embolism) or arterial (myocardial infarction, ischemic stroke) serious adverse events (SAEs). In the phase IIb trial there was no difference in the overall rate of thromboembolic SAEs between groups (7% in the rFVIIa groups vs. 2% in the placebo group, $p=0.12$) but there was an excess of arterial SAEs in the rFVIIa groups (5% vs. 0%, $p=0.01$).⁶ These SAEs included seven myocardial ischemic events and nine cases of cerebral infarction that occurred within four days of dosing. In the phase III trial there was no difference in the rates of venous thromboembolic SAEs but patients in the 80 µg/kg rFVIIa had a 4% excess of investigator-reported arterial thromboembolic SAEs compared to placebo ($p=0.04$).⁷ Most of the cardiac events were small troponin elevations and non-ST elevation myocardial infarctions (NSTEMIs) with good clinical recovery.^{6, 7} Investigator-reported rates of ST-elevation myocardial infarction (STEMI) in the phase III trial were 1.5% in the placebo group, 0.4% in the 20 µg/kg group, and 2.0% in the 80 µg/kg group. CT evidence of acute ischemic stroke was seen in 2.2% of placebo patients, 3.3% of 20 µg/kg patients, and 4.7% of 80 µg/kg patients.⁷ Investigator-reported event rates are summarized in Table 2.

Table 2. Rates of investigator-reported thromboembolic serious adverse events in rFVIIa trials

Trial	Dose	Patients (n)	Arterial thromboembolic serious adverse events (%)	Venous thromboembolic serious adverse events (%)
Phase IIb ⁶	Placebo	96	0 (0)	2 (2)
	rFVIIa 40 µg/kg	108	6 (6)	1 (1)
	rFVIIa 80 µg/kg	92	2 (2)	2 (2)
	rFVIIa 160 µg/kg	103	8 (8)	2 (2)
	All rFVIIa doses	303	16 (5)	5 (2)
Phase III ⁷	Placebo	268*	11 (4)	11 (4)
	rFVIIa 20 µg/kg	276*	14 (5)	10 (4)
	rFVIIa 80 µg/kg	297*	25 (8)	7 (2)
	Both rFVIIa doses	573*	39 (7)	17 (3)

*Intention-to-treat population. The safety population (patients exposed to a study agent) included 263 patients in the placebo group, 265 patients in the 20 µg/kg group, and 293 patients in the 80 µg/kg group.

For the phase III trial of rFVIIa for ICH, there was an additional, independent safety review to evaluate potential thromboembolic adverse events performed by the Data Monitoring Committee (DMC).⁴⁰ As compared to site investigators, the DMC found higher rates of arterial adverse events, most notably NSTEMIs.⁴⁰ Table 3 compares these differences in the placebo and rFVIIa groups.

A potential explanation for the discrepancy involves troponin monitoring. Troponins were protocol mandated at study enrollment and at 1 hour, 24 hours, 48 hours, and 72 hours after study drug administration. However, these troponins were sent for outside analysis and were not available to investigators in real-time. Patients without clinical symptoms of cardiac ischemia or definite electrocardiographic signs of cardiac ischemia may not have had routine clinical troponins ordered. Without troponins, EKG changes that were considered non-specific by site investigators were not considered indicative of NSTEMIs. All of the 7 additional cerebral infarctions identified by the DMC in the rFVIIa 80 µg/kg group were considered unlikely to be related to study drug (either existing ischemic stroke at the time of randomization, ischemic stroke due to mass effect, or ischemic stroke related to neurosurgical procedures). The DMC review found no excess of venous thromboembolism in the rFVIIa groups.⁴⁰

Table 3. Arterial thromboembolic events in the phase III rFVIIa ICH trial

N (%)	Placebo N = 268		20 µg/kg N = 276		80 µg/kg N = 297		All Events*±		
	Investigator Reported*±	DMC Identified*±	Investigator Reported	DMC Identified	Investigator Reported	DMC Identified	Placebo	20 µg/kg	80 µg/kg
Biochemical Marker Only	—	23 (8.6)	2 (0.7)	13 (4.7)	2 (0.7)	26 (8.8)	23 (8.6)	15 (5.4)	28 (9.4)
NSTEMI	6 (2.2)	7 (2.6)	10 (3.6)	10 (3.6)	9 (3.0)	21 (7.1)	13 (4.9)	20 (7.2)	30 (10.1)
STEMI	2 (0.7)	2 (0.7)	1 (0.4)	—	5 (1.7)	1 (0.3)	4 (1.5)	1 (0.4)	6 (2.0)
Ischemic Stroke	7 (2.6)	2 (1.0)	4 (1.4)	7 (2.5)	10 (3.4)	7 (2.4)	9 (3.4)	11 (4.0)	17 (5.7)
Other Arterial AE	0 (0)	0 (0)	0 (0)	0 (0)	3 (1.0)	0 (0)	0 (0)	0 (0)	3 (1.0)
Total*							26 (9.7)	32 (11.6)	56 (18.9)
(Excluding Biochemical Marker Events)									

* Includes events considered possible or unlikely to be related to study drug by study investigators and DMC

± Excludes isolated biochemical marker abnormalities

In order to mitigate the higher rates of arterial thromboembolism reported by the DMC, particularly NSTEMIs, further subgroup analyses were performed, and STOP-IT Study inclusion and exclusion criteria adjusted accordingly (author's unpublished data). Using the rFVIIa phase III dataset, exclusion of patients with 1) baseline ischemia on EKG or an abnormal baseline troponin 2) any clinical history of thromboembolism and 3) age > 80 years, produced substantially lower rates of arterial thromboembolism in the rFVIIa 80 mcg/kg group (see Table 4). These values are conservative (likely over-reporting actual risk from study drug) because they include events considered both possible and unlikely to be related to study drug.

Table 4. Arterial thromboembolism rates in the rFVIIa phase III trial after exclusion of patients with ischemia at baseline, any clinical history of thromboembolism, and age > 80 years

Events	Placebo N = 202	20 µg/kg N = 196	80 µg/kg N = 214
Biochemical Marker Only*	13 (6.4)	7 (3.6)	17 (7.9)
NSTEMI*	5 (2.5)	7 (3.6)	11 (5.1)
STEMI*	1 (0.5)	0 (0)	3 (1.4)
Ischemic Stroke*	5 (2.5)	5 (2.6)	8 (3.7)
Total±	11 (5.4)	12 (6.1)	22 (10.3)

*Includes events considered possible or unlikely to be related to study drug by study investigators and DMC

±Excluding isolated biochemical marker abnormalities

4.3 Conclusions from Studies to Date

Hematoma growth is an important determinant of outcome after ICH. Hematoma growth is time dependent, occurring in up to 38% of patients imaged within three hours of ictus but in progressively fewer patients presenting at later time periods. Recombinant activated factor VII effectively reduces ongoing bleeding in patients with acute ICH. However, benefit from this therapy in large trials may be diluted by patients who will not have hematoma growth. To date, rFVIIa has only been tested within four hours of ICH onset because the percentage of patients with ICH growth beyond this window is expected to be too small to show improved outcomes among all patients. Clinical results in trials of rFVIIa treating patient in less than four hours have been mixed.

Ideally, a diagnostic and prognostic test exists which reliably identifies ICH patients who will have significant subsequent hematoma growth. Such a test would allow treatments to be tailored to individual patients. Patients presenting early after ICH onset who are not at risk for hematoma expansion would not be subjected to the potential risk and cost of hemostatic therapy. Conversely, patients presenting later who are destined to have hematoma growth would not be excluded from an effective treatment by time of onset. Furthermore, such a test would substantially increase the chance that a clinical trial of hemostatic therapy would show positive results by excluding patients who will not benefit from treatment and need not be exposed to potential thromboembolic risk. Recombinant activated factor VII is biologically effective. It remains to be demonstrated which patients will derive clinical benefit from its use. The STOP-IT study is the next step in identifying these patients and determining whether CT angiography can be used to guide their treatment. The combined use of CTA to predict hematoma growth and rFVIIa to stop hematoma growth is a biologically and clinically elegant and plausible means to improve patient outcome after ICH.

5.0 RESEARCH DESIGN AND METHODS

5.1 Overview

STOP-IT will enroll patients with acute ICH less than five hours from symptom onset. Patients will be included in one of two study arms. The first arm will be a multicenter, randomized, double-blind, placebo-controlled trial comparing rFVIIa to placebo for treatment of patients with acute ICH and a spot sign on CTA. The second arm will be a multicenter, prospective observational study of hematoma growth among patients without a spot sign on CTA. Comparisons will be made between 1) patients with a spot sign randomized to placebo and patients without a spot sign, in order to determine the value of the spot sign for predicting hematoma growth and 2) patients who have a spot sign and are randomized to rFVIIa or placebo in order to determine the effect of study drug upon hematoma growth.

This phase II study will determine whether the spot sign is a reliable predictor of hematoma growth, if site investigators (neurologists and emergency department physicians) can reliably identify the spot sign, whether CTA is a practical tool for making treatment decisions in the acute period, and whether subjects with a spot sign treated with rFVIIa have less hematoma growth than subjects with a spot sign who are treated with placebo. Preliminary data on clinical efficacy will be collected to help determine whether a phase III trial which uses the spot sign to select subjects for hemostatic therapy is warranted. For the STOP-IT study 12 clinical sites will recruit an estimated 184 subjects.

5.2 STOP-IT Study Design

5.2.1 Patient Flow

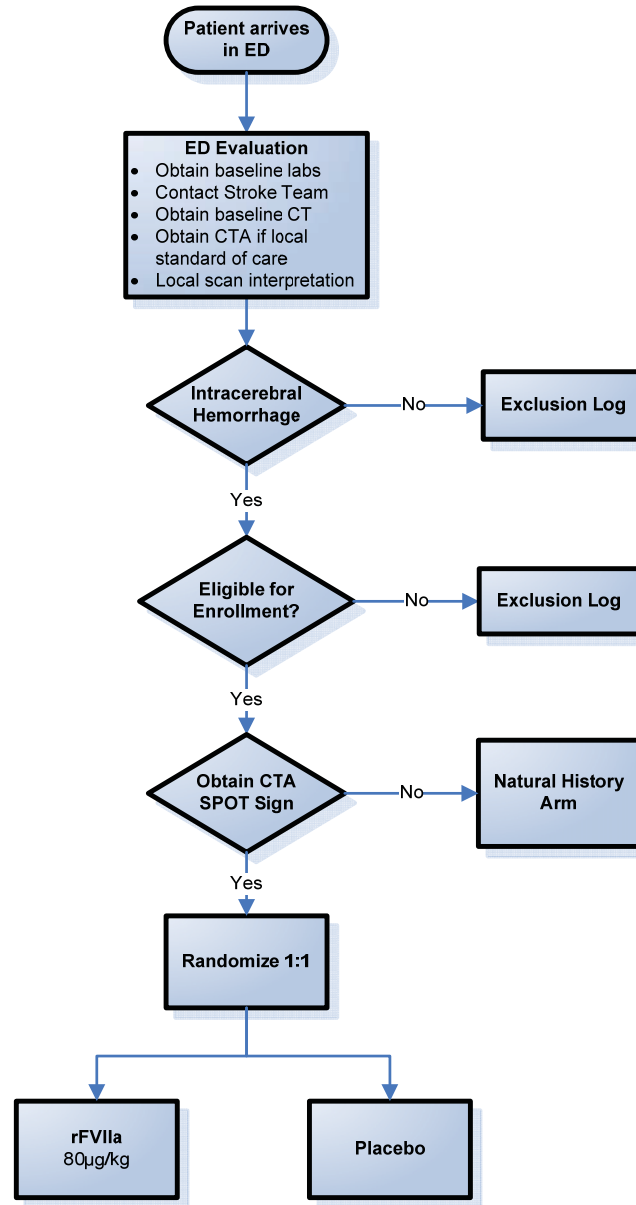
Patients presenting with ICH to participating study centers will be screened for eligibility. Only patients who meet study inclusion criteria, do not meet study exclusion criteria, and have a non-contrast head CT head within five hours of symptom onset will be approached for study participation. After the patient and/or their legally authorized representative has provided informed consent, if not already performed as standard of care (see section 5.5.2) the CTA will be performed. Patients transferred from an outside hospital will also have their non-contrast head CT repeated at the participating study center. The CTA will be reviewed by the local study investigator to determine the

presence or absence of the CTA spot sign. Patient flow will be determined by the local investigator's interpretation of the CTA. One goal of the STOP-IT study is to determine whether local investigators can identify the spot sign with a high degree of accuracy. This will be crucial in generalizing the results of any study based upon the spot sign to widespread clinical use. Patients with a spot sign will be randomized to treatment with rFVIIa 80 µg/kg IV bolus or placebo. Patients without a spot sign will receive standard medical care and be enrolled into the prospective observational arm (Figure 1).

For a patient to be enrolled, all of the following must be performed:

1. Time of stroke onset verified.
2. Non-enhanced head CT obtained within five hours of symptom onset. Results determined by investigator to be consistent with primary ICH (i.e. no radiographic features of hemorrhagic cerebral infarction, aneurysmal subarachnoid hemorrhage, traumatic contusion, vascular malformation, tumor, or venous sinus thrombosis).
3. Plans for early (<24 hours) neurosurgical hematoma evacuation excluded. This may require emergent neurosurgical consultation, especially for cerebellar hemorrhages or hemorrhages producing significant mass effect.
4. ECG showing no acute ischemic changes and no clinical history to suggest acute myocardial ischemia (e.g., ST elevation in two contiguous leads, new LBBB, or ST depression). Clinically silent evidence of old ischemia on EKG (Q waves) will not be considered reasons for exclusion.
5. Normal baseline troponin
6. Medical history including current medications obtained to exclude warfarin use, history of thromboembolic event, history of coagulopathy (documentation of normal INR and PTT will be required before enrollment only if the patient has used warfarin or heparin, has a history suggesting coagulopathy, or if accurate medication inventory is not available), or other conditions detailed in study exclusion criteria.
7. Pregnancy ruled out by stat urine pregnancy test in women of childbearing potential.
8. Baseline clinical assessment performed (including vital signs, NIHSS score, mRS and GCS score).
9. For patients with a spot-sign, study drug (rFVIIa or placebo) should be administered as quickly as possible and must be administered within 90 minutes of the baseline non-contrast head CT. Patients transferred from outlying hospitals will have their non-contrast head CT repeated at the participating study site. This must be done within five hours of symptoms onset and will be considered the qualifying CT for both study analyses and study drug administration time limits.

Figure 1. STOP-IT Study Patient Flow



5.2.2 Inclusion Criteria

1. Acute, spontaneous ICH (including bleeding in cerebellum) diagnosed by non-enhanced CT scan within five hours of symptom onset. Time of onset is defined as the last time the patient was witnessed to be at baseline (i.e., subjects who have stroke symptoms upon awakening will be considered to have their onset at beginning of sleep)
2. Age ≥ 18 through 80 years (candidates must have had their 18th birthday, but not had their 81st birthday)
3. For spot positive patients, dosing of study drug within 90 minutes of enrolling CT scan

5.2.3 Exclusion Criteria

1. Time of symptom onset of ICH is unknown or more than five hours prior to baseline CT scan
2. ICH secondary to known or suspected trauma, aneurysm, vascular malformation, hemorrhagic conversion of ischemic stroke, venous sinus thrombosis, thrombolytic treatment of any condition (e.g., myocardial infarction, cerebral infarction, etc.), CNS tumor, or CNS infection
3. Brainstem location of hemorrhage (patients with cerebellar hemorrhage may be enrolled)
4. Serum creatinine > 1.4 mg/dl (123 µmol/L)*
5. Known allergy to iodinated contrast media
6. Intravenous or intra-arterial administration of iodinated contrast media within the previous 24 hours of baseline CT scan
7. Known hereditary (e.g., hemophilia) or acquired hemorrhagic diathesis, coagulation factor deficiency, or anticoagulant therapy with INR > 1.2
8. Known or suspected thrombocytopenia (unless current platelet count documented above 50,000 / µl)
9. Unfractionated heparin use with abnormal PTT
10. Low-molecular weight heparin use within the previous 24 hours
11. GPIIb/IIIa antagonist use in the previous two weeks
12. Glasgow Coma Scale < 8 at time of proposed enrollment
13. Pre-admission modified Rankin Scale score > 2
14. Baseline ICH volume of < 0.5 cc (Hematoma volume will be estimated by local investigators from the baseline CT using the abc / 2 method ⁴¹)
15. Baseline ICH volume of > 90 cc
16. Planned surgical evacuation of ICH within 24 hours of symptom onset (placement of intraventricular catheter is not a contraindication to study enrollment)
17. Evidence of acute or subacute ischemic stroke on baseline qualifying CT scan
18. Clinical history of thromboembolism or ischemic vascular disease, including myocardial infarction, coronary artery bypass surgery, cardiac angina, transient ischemic attack, ischemic stroke, peripheral artery disease (vascular claudication), cerebral bypass surgery, carotid endarterectomy, deep venous thrombosis, pulmonary embolism, or coronary or cerebrovascular angioplasty or stenting. (Clinically silent evidence of old ischemia on EKG (Q waves) or CT scan (silent old infarct) will not be considered reasons for exclusion).
19. Baseline electrocardiogram shows evidence of acute cardiac ischemia (ST elevation in two contiguous leads, new LBBB, or ST depression)
20. Clinical history suggestive of acute cardiac ischemia (e.g. chest pain)
21. Abnormal baseline troponin
22. Females of childbearing potential who are known to be pregnant and / or lactating or who have positive pregnancy tests on admission
23. Advanced or terminal illness or any other condition the investigator feels would pose a significant hazard to the patient if rFVIIa were administered.
24. 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 the time of STOP-IT enrollment
25. Planned withdrawal of care or comfort care measures
26. Patient known or suspected of not being able to comply with trial protocol (e.g., due to alcoholism, drug dependency or psychological disorder)
27. Informed consent cannot be obtained from the patient or legally authorized representative

*For participating sites that do not perform CTA as part of standard of care for evaluation of ICH and will be screening and obtaining informed consent before the CTA. Other sites will follow their standard procedures regarding renal insufficiency

5.3 Dose Selection for Recombinant Activated Factor VII

The dose of rFVIIa chosen for this study is 80 µg/kg (maximum dose volume 10.0 mL, equivalent to maximum weight of 125 kg). This dose was based upon extensive preclinical testing, testing for non-stroke medical indications, dose-escalation studies in ICH, and a phase III clinical trial in ICH.^{6, 7, 39, 42} The safety profile of rFVIIa use for acute ICH was previously discussed above in section 4.4.2.

5.4 Drug Storage and Administration

The Investigator or designated trial staff must ensure the availability of proper storage conditions. The trial product rFVIIa (NovoSeven® RT / NiaStase RT®) is to be refrigerated or stored between 2-25° C / 36-77° F (do not freeze) and can be kept for up to 2 years. The study drug is stable until the expiration date stated on each vial. The investigator or designated trial staff must record the temperature of the trial product storage facility. A temperature log should be kept for the trial product facility.

Once eligibility is confirmed by the Investigator, subjects will be randomized 1:1 to receive rFVIIa (80 µg/kg) or placebo (maximum dose volume 10.0 mL, equivalent to maximum weight 125 kg). Study drug will be reconstituted or placebo drawn up by the site pharmacist and administered by the investigator as a single slow intravenous bolus injection over 2-5 minutes no later than 90 minutes after the enrolling CT scan and no later than 6.5 hours from symptom onset. All investigators, physicians, nurses, and participating subjects are blinded to the content of the study medication. No trial product may be dispensed to any person not enrolled in the trial.

5.5 CT and CTA Methodology

5.5.1 CT and CTA Acquisition

Non-enhanced CT scans are performed at baseline, 24 hours (+/- 3 hours from baseline CT scan) and for change in subject condition (safety CTs). These scans are considered part of standard clinical care for patients with ICH. CTA is performed once at baseline to determine the presence or absence of the CTA spot sign.

5.5.2 CTA and Standard Care for Acute ICH

The use of CTA for the evaluation of acute stroke is not standardized in North America. There is evidence that CTA provides useful diagnostic information for patients with ICH and that it is safe for patients with acute stroke (see section 3.3). However, CTA has not been proven to improve patient outcomes compared to other diagnostic paradigms (such as delayed imaging or imaging with MRI or digital subtraction angiography). Medical standards of care are often not explicitly defined and the legal interpretation of these standards may vary by community, state, and nation.⁴³ Standard imaging for patients with ICH differs at different centers in North America. Some centers routinely perform CTA at the time of the initial head CT for all patients without definite contraindications to contrast administration such as known renal failure or contrast allergy. Other sites do not use CTA as part of their standard diagnostic evaluation. **The design of the STOP-IT study must therefore take this practice variation into consideration.** Sites that have routinely performed CTA as part of their initial, standard evaluation for ICH patients will continue this practice. At these sites, patient consent for participation in the STOP-IT study will occur after the CTA. For sites that do not currently perform CTA as standard initial care for patients with ICH, patient consent for the STOP-IT study must occur before performance of the CTA. All CTAs will be available to local radiologists and clinicians as they may provide additional diagnostic utility beyond the spots sign for detection of occult aneurysms, vascular malformations, etc. All patients will have serial creatinine measurements following the CTA to monitor for the development of contrast-induced nephropathy.

5.6 Imaging Analysis

The local investigator will use the baseline CT as part of the screening process for eligibility. Baseline hematoma volume for study screening will be calculated by the abc/2 method.⁴¹ De-identified baseline and 24-hour CTs will be provided to the University of Calgary via the CCC for

subsequent interpretation by a blinded clinician. Hematoma volumes for study endpoints will be calculated by volumetric analysis. Scans will also be analyzed for the location of hemorrhage, the presence and volume of IVH, the presence or absence of hydrocephalus, edema volume, mass effect, prior infarction(s) (baseline CT) and acute infarction(s).

The CTA spot sign will be defined as one or more foci of contrast enhancement seen within the hematoma on CTA source images. Based upon our prior experience with the spot sign, the following criteria will be used to identify the spot sign:

1. The shape may be spot-like, serpiginous, and/or linear.
2. The location must be within the margin of a parenchymal hematoma.
3. The density (in Hounsfield units) should be greater than that of the background hematoma (site investigators are not required to document the density).
4. There should be no connection to a vessel outside the hematoma margin.

Local investigators will interpret the CTA for the presence or absence of the spot sign in the acute setting. Digital copies of the CTAs will be provided to the Clinical Coordinating Center (CCC) for subsequent interpretation by a blinded neuroradiologist. All CTAs will also be subsequently reviewed for the presence or absence of the spot sign by a blinded study neurologist and a blinded study emergency medicine physician. Measures of inter-rater reliability will be determined among the evaluators, with the neuroradiologist's reading considered the gold-standard. Before study initiation on-line training sessions will be mandatory for study investigators reviewing the abc/2 method of ICH volume calculation and use of CTA source images to identify the spot sign.

5.6.1 CT Image Data Management

All imaging data will be sent to the Clinical Coordinating Center at the University of Cincinnati for standardized archiving and data blinding if needed. De-identified CT image data will then be transferred via a secure file transfer protocol (SFTP) to a research PACS system at the University of Calgary Neuro Imaging Centre and subsequently analyzed, under the direction of Dr. Andrew Demchuk, on a personal workstation using Quantomo software that was developed at the University of Calgary. User-selected parameters used to segment the volumes (i.e., seed-points, HU intensity thresholds, etc.) will be saved in Extensible Markup Language (XML) files to allow retrospective analysis (i.e., reproduce and validate the results from the operators). This cost-effective approach will also allow us to perform future retrospective studies using the same data from the current study. In addition to user-selected parameters, the masked segmented volume and the mean and standard deviation of the volumes will also be saved in the XML files. Statistical analysis will be performed off-line using the data collected in the XML files. De-identified CTA image data will be transferred via a secure transfer protocol to Sunnybrook Health Sciences Centre in Toronto, Canada, where Dr. Richard Aviv, study neuroradiologist, will review scans as the "gold standard" for the presence or absence of the spot sign.

5.6.2 Volume Measurements

Segmented volumes will be obtained with Quantomo software using a user-assisted neighborhood-connected region-growing threshold-segmentation method implemented in the Insight Segmentation and Registration Toolkit (ITK; National Library of Medicine, Bethesda, MD) in conjunction with freehand drawing tools for the ICH, IVH and edema volumes. The operator will be required to place seed-points within the volume of interest and adjust lower and upper intensity HU thresholds until the entire volume is correctly selected. In cases where the ICH volume cannot be differentiated from IVH volume, the operator will use freehand drawing tools in order to remove the IVH volume using their best estimate. In this situation, the IVH will be determined using the original over-segmented volume that includes the combined ICH and IVH volumes, V_{total} , as $IVH = V_{total} - ICH$. This limitation is unavoidable as IVH has the same intensity as ICH and the two volumes often border each another. The volume (ml), mean (HU), standard deviation (HU) and the affected part(s) of the brain will be measured from the segmented volume.

Based on initial experimentation, we anticipate more difficulties in segmenting edema volumes as edema has more subtle HU intensity differences relative to normal tissue. Thus, edema segmentation will likely require more operator effort (i.e., seed-points, freehand tools, etc.) Although initial testing has shown that the current user-assisted technique will be sufficient for this study, we wish to reduce the amount of time operators spend to perform the user-assisted volume segmentations. Thus, we are currently investigating more sophisticated segmentation methods based on level-sets (i.e., shape) in order to further automate the segmentation process

6.0 MEASUREMENT OF EFFICACY OUTCOME

Measuring outcomes for acute stroke trials should be clinically relevant, valid, reproducible, and easy to perform. There is no single accepted clinical endpoint for acute stroke trials since no single endpoint encompasses all of the domains that stroke affects including functional disability, neurological deficit, volume of brain infarction or hemorrhage, and quality of life. It is for this reason that all stroke trials include multiple clinical endpoints.

An NIH Stroke Scale Score and Glasgow Coma Score (GCS) will be performed on every subject (i.e., treatment arm and observational arm) during the initial baseline assessment, at 24 hours +/- 3 hours of baseline enrolling CT scan, and at discharge from hospital +/- 2 days. For subjects in the treatment arm (i.e., spot-positive), an NIHSS score and GCS will be obtained at one hour +/- 10 minutes post study drug administration. In addition, a Modified Rankin Scale (mRS) to indicate the subject's functional status prior to the qualifying intracerebral hemorrhage (pre-event) will be obtained on all subjects at baseline as well as discharge. At 30 days and 90 days, functional outcome will be assessed with a telephone mRS and BI.

All investigators will be certified in the NIHSS score and will receive standardized training regarding the mRS.

6.1 Primary Outcome: Test Performance

A primary outcome of the STOP-IT study will be the sensitivity and specificity of the spot sign for predicting hematoma growth. Secondary outcomes will be the positive and negative predictive value of the spot sign and the accuracy of site investigators for correct identification of the spot sign as compared to a blinded study neuroradiologist.

6.2 Primary Outcome: Clinical Parameters

The primary para-clinical outcome of the STOP-IT study will be the rate of hematoma growth among spot-positive subjects at 24 hours, comparing subjects treated with rFVIIa to those treated with placebo. Hematoma growth will be defined as a > 33% or > 6 cc increase in volume.

Secondary outcome measures will be the rate of total hemorrhage volume growth (hematoma plus IVH) among spot-positive subjects and clinical outcomes among patients treated with rFVIIa vs. those treated with placebo. Analysis will be performed for mortality at 90 days and good (mRS 0-4) versus poor (mRS 5-6) functional outcome.

6.3 Primary Safety Outcomes

6.3.1 Definitions

Adverse events (AE) are defined as any undesirable event involving a study patient, whether or not it is felt to be related to the study drug. This includes events occurring after the patient and/or legally authorized representative has signed the informed consent but before study drug administration through the follow-up period as defined in the study. A serious adverse event (SAE) is a medical event defined as (but not limited to) any experience that is: fatal, life-threatening, permanently disabling, requires or prolongs inpatient hospitalization, overdose, laboratory values or abnormal trends judged to be clinically serious, or a congenital anomaly or birth defect. A non-serious adverse

event (AE) is any adverse event which does not fulfill the above definition of a serious adverse event.

6.3.2 Primary Safety Measures

While all thromboembolic events must be reported expeditiously for the duration of the study period (see section 8.2), the primary safety measures 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 ischemia 2) acute cerebral ischemia and 3) acute pulmonary embolism.

Clinical definitions of significant thromboembolic adverse events:

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. ECG 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 (NSTEMI)
 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 ischemia:

New focal neurological deficits consistent with cerebral ischemia and without alternative explanation lasting > 24 hours. For patients with suspected new cerebral ischemia which is not detected on CT scan, MRI is recommended if clinically feasible. This definition is also satisfied by deficits lasting < 24 hours but associated with signs of new cerebral ischemia on CT or MRI.
3. Acute pulmonary embolus (PE)

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

All other thromboembolic events (i.e., both treatment and observational arm) must be reported expeditiously through 90-day follow-up, regardless of body site or judgment of relatedness to study drug (treatment arm only), but will be analyzed separately from the primary safety measures above. These events include but are not limited to:

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 (e.g., chest pain, dyspnea) or ECG evidence (ST depression) of reduced myocardial flow without a significant elevation in troponin.
3. Deep venous thrombosis.

For a discussion of stopping rules related to arterial thromboembolic SAEs please see section 8.3.

Localization of ischemia:

- The location of each type of ECG change will be classified as follows:
 - Inferior distribution II, III, aVF
 - Anterior distribution V3, V4
 - Septal distribution V1, V2
 - Lateral distribution I, aVL, V5, V6

- Posterior distribution (relevant only for tall R waves, upright T) V1, V2
- Right ventricular V4R

Adverse Event Attribution Categories:

Unrelated	The AE is clearly NOT related to the study drug
Unlikely	The AE is doubtfully related to the study drug
Possible	The AE may be related to the study drug
Probable	The AE is likely related to the study drug
Definite	The AE is clearly related to the study drug

6.4 Recruitment Procedure and Technique

The primary means for recruitment of patients is to ensure rapid identification of potential study candidates at the respective hospitals and to minimize the time for evaluation and treatment with study medication. All of the participating hospitals in the study have an active acute stroke intervention team, and in particular, a strong representation of emergency medicine within those stroke teams. Each of these emergency departments is already equipped to treat stroke as a medical emergency. The systems approach that was used in the FAST trial of rFVIIa will be used in the emergency departments at each of the participating hospitals to identify potential sources of delay and to suggest potential solutions.

6.5 Contingency Plan for Lags in Recruitment

Based upon recruitment in the FAST trial of rFVIIa, we expect that we will be able to reach our goal of 184 patients at the study centers. We will recruit 2-4 more participating centers should recruitment lag behind our expectations.

6.6 Procedure for Subject Screening

For the purpose of documenting the emergency department and hospital population from which the patients in this trial are drawn, each clinical center will maintain a study screening log. All patients with spontaneous intracerebral hemorrhage who are admitted to the participating hospitals within five hours of onset during the accrual phase of the study, whether eligible or not, will be recorded in the study screening log. A reason for exclusion for each patient not entered into the trial will be recorded. Each participating performance site will enter the information on its Stroke Log in the STOP-IT Study web site on a monthly basis. This information will be used when planning the recruitment of patients for the potential, future Phase III trial. The number of patients enrolled per center as well as the number of screened patients along with a tabulation of reasons for exclusion will be included in the monthly accrual report to the steering committee.

6.7 Competing Ongoing Clinical Trials

At this time there are few competing clinical trials for patients with intracerebral hemorrhage. Should other trials compete with STOP-IT in the future, a planned stratification of enrollment must be put into place in those hospitals actively enrolling patients in multiple studies, thereby preventing preferential enrollment into any one trial. Centers that have more than one ongoing ICH trial within the five hour time window must submit their assignment system of patient allocation into the various trials to the Clinical Coordinating Center.

6.8 Randomization and Blinding

In order to reduce bias, the treatment arm of this study will be conducted as a double-blind, placebo-controlled trial. The randomization will be performed with equal allocation between treatment arms. Neither the treating physicians nor the patients will know to which treatment arm the patient is randomized. In order to avoid a situation of bias with respect to important covariates a system of adaptive randomization will be used. In general, the process of adaptive randomization determines the allocation of the participant into one of the groups based on the composition of the groups at the time of randomization. The process described below will provide a tighter balance of time from

symptom onset to CT and baseline hematoma volume in the two groups than using stratified randomization. The implementation of this process involves the examination of the marginal totals for each level of each covariate. Given the time and hematoma volume for the patient to be randomized, the imbalance will be calculated if the person is assigned to the rFVIIa arm and also for assignment to the placebo arm. The assignment that results in the smaller imbalance will be chosen. Although this is not strictly a pure randomization scheme, the data are treated as if they were assigned randomly. The variables considered in the adaptive randomization scheme will be time from symptom onset to baseline CT scan (dichotomized as 0 to 3 hours vs. > 3 hours to 5 hours) and baseline hemorrhage volume (trichotomized as < 30 cc, 30 to 60 cc, and > 60 to 90 cc). Periodically, study biostatisticians will review the distributions of the two variables and decide if an adjustment to the categorization is warranted.

Assignment to a treatment group will be done centrally. The local study investigator enrolling a patient will access a web-based program to determine the randomization number. If for some reason the web system cannot be accessed there will be a back-up emergency phone system to provide a randomization number. Pharmacies at the study sites will have a list of randomization numbers and when given the assigned number for the study subject will know which trial product to mix.

To maintain the blinding of the Investigator and designated study staff an equal volume/kg body weight (BW) of the trial product (i.e., rFVIIa or placebo) will be administered to all eligible spot-positive subjects independent of the treatment group assignment.

It is not anticipated that it will be necessary to unblind the study for an individual patient. Any adverse event related to rFVIIa will be treated according to routine standards of care. However, blinding may be broken in a medical emergency, if deemed necessary by the treating physician, if knowing the treatment allocation would influence the medical management of the subject. If the study site needs to break the randomization code, the Clinical Coordinating Center should, if possible, be contacted prior to breaking the code. In all cases, the CCC must be notified within 24 hours after the randomization code has been broken. When unblinding has been performed, the time, date, and reason must be recorded on the source documents and the CRF.

6.9 Drug Distribution and Pharmacy Support

The Department of Pharmacy Services at The University Hospital (TUH) at the University of Cincinnati has 20 years experience in industry and NIH funded pharmaceutical research. The TUH Pharmacy-Coordinated Investigational Drug Service (IDS) has successfully facilitated, dispensed and provided accountability and control of medications used in multiple acute stroke drug studies including the NIH funded rt-PA dose escalation trial, the randomized NINDS rt-PA Stroke Study, and the EMS, IMS I, IMS II, IMS III and CLEAR Trials. The IDS, under the direction of Caron Sue, PharmD, PhD, is staffed by both investigational drug pharmacists and pharmacy technicians.

Foothills Medical Centre Pharmacy IDS at the University of Calgary will act as the drug distribution center for Canada. As a member of the Canadian Stroke Consortium, the University of Calgary has already acted as the drug distribution center for Canada in the IMS I, II, and III trials.

7.0 SUBJECT MEDICAL MANAGEMENT

Management of ICH after study entry will be determined by local clinicians who will be encouraged to follow published guidelines where applicable.²⁶ It is anticipated that almost all patients will be admitted to an intensive care unit for at least 24 hours. Planned hematoma evacuation within 24 hours of stroke onset is a study exclusion criterion. However, it is recognized that some patients will experience clinical deterioration and may require emergent surgical treatment at the discretion of their treating clinicians prior to the 24-hour CT scan. In these cases a repeat head CT should be performed before surgical intervention. This scan will be used as the follow-up CT to assess hematoma growth. In addition, patients who experience significant clinical deterioration before 24

hours in whom withdrawal of care is contemplated should also have a repeat head CT performed, at the discretion of the treating physician, which will be used as the follow-up CT for hemorrhage volume analysis if a 24 hour head CT is not performed.

8.0 MEDICAL AND LABORATORY DATA COLLECTED

Data collected will differ slightly based upon whether subjects are enrolled in the observational arm (spot negative) or the treatment arm (spot positive). Subjects in the treatment arm of the study will have additional troponin levels and electrocardiograms performed for real-time safety monitoring. The troponin values will be processed locally and immediately available to local investigators.

8.1 Schedule of Events

Table 5a. Summary of Data Collection: Treatment Arm – All Spot-Positive Subjects

Event	Baseline	1 hour post dose (± 10 min)	Day 1 24 hours (± 3 hrs) after baseline CT	Day 2 48 hours (± 6 hrs) after baseline CT	Day 3 72 hours (± 6 hrs) after baseline CT	Day 15 (± 2 days) or Discharge \pm	Day 30* (± 7 Days)	Day 90* (± 7 Days)
Informed consent	X							
Medical history	X							
Physical exam	X							
Vital signs	X	X	X	X	X	X		
Demographic information	X							
Creatinine	X		X		X	X		
Pregnancy test \ddagger	X							
INR + PTT	X							
Complete blood count (CBC)	X							
GCS Score	X	X	X			X		
NIHSS score	X	X	X			X		
Barthel Index (BI)						X	X	X
mRS score	X					X	X	X
CT scan of head	X		X					
CT angiography of head	X							
Electrocardiogram	X		X	X	X			
Serum troponin	X		X	X	X			
Adverse event assessment	X	X	X	X	X	X	X	X

- NIHSS = National Institutes of Health Stroke Scale, INR = international normalized ratio, PTT = partial thromboplastin time, GCS = Glasgow Coma Scale, mRS = modified Rankin Scale
- *30-day and 90-day follow-ups will be via telephone

- ‡Women of childbearing potential
- ‡Whichever is earlier

Table 5b. Summary of Data Collection: Observation Arm - All Spot-Negative Subjects

Event	Baseline	Day 1 24 hours (± 3 hrs) after baseline CT	Day 2 48 hours (± 6 hrs) after baseline CT	Day 3 72 hours (± 6 hrs) after baseline CT	Day 15 (± 2 days) or Discharge‡	Day 30* (±7 Days)	Day 90* (±7 Days)
Informed consent	X						
Medical history	X						
Physical exam	X						
Vital signs	X	X	X	X	X		
Demographic information	X						
Creatinine	X	X		X	X		
Pregnancy test‡	X						
INR + PTT	X						
Complete blood count (CBC)	X						
GCS Score	X	X			X		
NIHSS score	X	X			X		
Barthel Index (BI)					X	X	X
mRS score	X				X	X	X
CT scan of head	X	X					
CT angiography of head	X						
Electrocardiogram	X						
Serum troponin	X						
Adverse event assessment	X	X	X	X	X	X	X

- NIHSS = National Institutes of Health Stroke Scale, INR = international normalized ratio, PTT = partial thromboplastin time, GCS = Glasgow Coma Scale, mRS = modified Rankin Scale
- *30-day and 90-day follow ups will be via telephone
- ‡Women of childbearing potential
- ‡Whichever is earlier

8.2 Monitoring for Adverse Events and Assessment of Safety

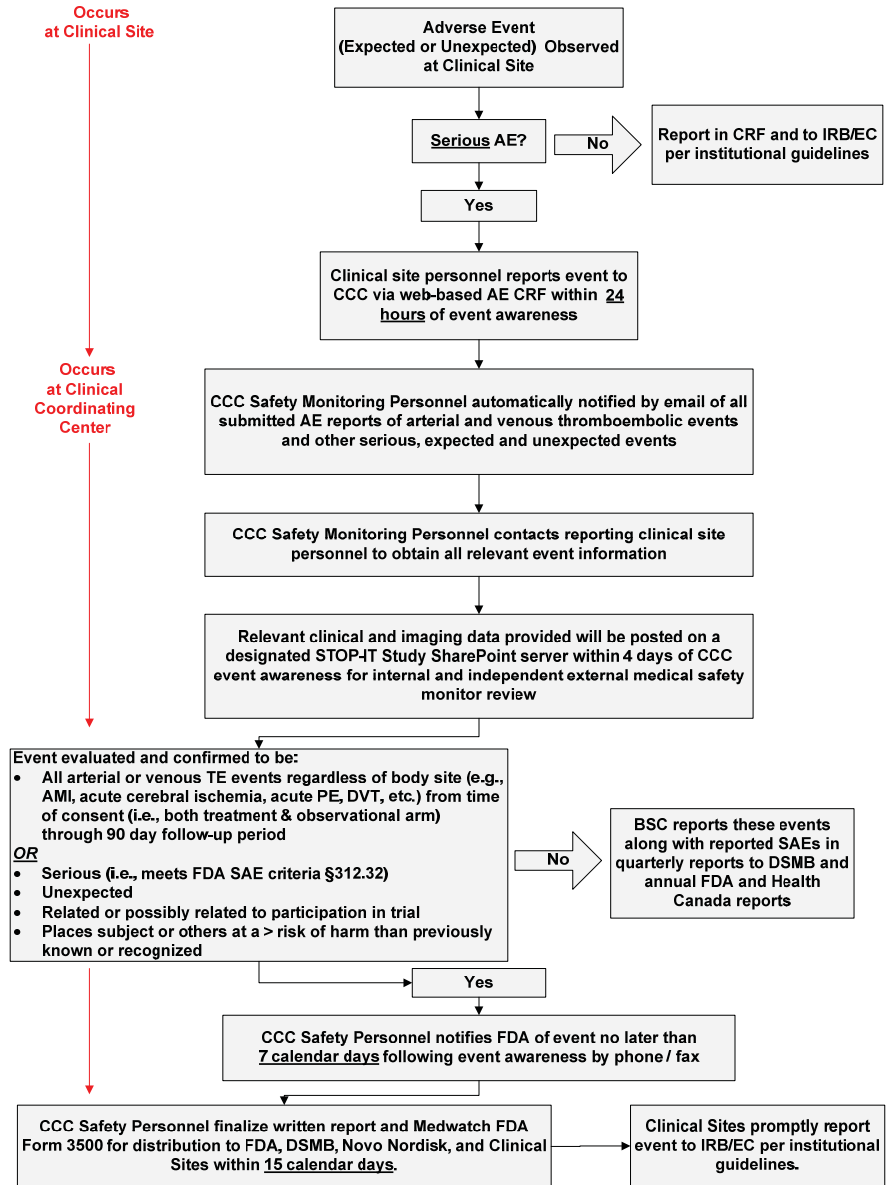
Figure 2

Safety assessments will consist of ongoing monitoring and reporting of adverse events (AEs) and serious adverse events (SAEs); both anticipated and unanticipated that are considered to be associated with the use of the study drug, CTA, participation in the trial, and the disease itself. Reporting will be in compliance with both the FDA and HHS defined Code of Federal Regulations (CFR) for the protection of human research subjects, the procedures and requirements governing the use of investigational new drugs, and the monitoring of serious adverse events (21 CFR Part 312 and 45 CFR Part 46). The primary safety measurement of this study will be any life threatening arterial and venous thromboembolic (TE) complication defined as acute myocardial infarction, acute cerebral ischemia and acute pulmonary embolism during the first 96 hours after rFVIIa / placebo administration (Spot Positive - Treatment Arm).

Serious adverse experience is defined as, but not limited to, any experience that results in any of the following outcomes: death, is life-threatening, requires inpatient hospitalization or prolongs existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, or is considered a significant medical event by the investigator based on appropriate medical judgment and may jeopardize the subject's health outcome or may require medical or surgical intervention to prevent permanent impairment or damage or one of the outcomes listed in this definition. Unexpected adverse experience is defined as any adverse experience that is not identified in nature, severity, or frequency in the current Investigator's Brochure.

Clinical site investigator's are responsible for the identification of all possible study-related adverse events and instructed to report all arterial and venous thromboembolic events, deaths, serious, unexpected events, and events related to study product in the Biostatistical Core Database System within 24 hours of their becoming aware of the event.

Upon event notification, the Internal Medical Safety Monitors and the project manager in



collaboration with the independent external medical safety monitors, Dr. Claude Hemphill (Neurologist) and Dr. David Gregg, IV (Cardiologist), will investigate the event. If there is any disagreement of the event classification between the treating investigator and the Internal Medical Safety Monitor, Dr. Hemphill and/or Dr. Gregg will provide the final adjudication that will be used for reporting of the event to the regulatory agencies. The decision to file an expedited IND safety report will be based on the reporting criteria described in the STOP-IT SAE Reporting Algorithm (see Figure 2) and further detailed in the STOP-IT Manual of Procedures AE Reporting Guidelines.

An IND safety report will be expeditiously filed if the event is determined to be unexpected (not previously observed), related to trial participation (study drug, CTA) and meets FDA criteria as a serious event, or if the event is any venous or arterial thromboembolic event regardless of body site (i.e., both treatment and observational arm) through 90 day follow-up. The CCC will notify the FDA as soon as possible but no later than 7 calendar days after initial receipt of the information by telephone or fax transmission. The final written report describing the results of the event analysis will be submitted to the FDA, DSMB, Novo Nordisk, and Clinical Site Investigators as soon as possible, but no later than 15 calendar days after the determination is made. Each Clinical Site Investigator is responsible for promptly informing his/her IRB / EC of these events per their institutional guidelines.

All reported adverse events determined *not* to be related to trial participation (study drug, CTA), are not unexpected, or meet FDA criteria as a serious event will be included along with the listing of individual SAEs in the interim DSMB safety reports. The initial DSMB meeting will tentatively occur following randomization of the first 20 subjects (Spot Positive – Treatment Arm) or as needed prior to this milestone if there is any concern about event occurrence, potentially emerging safety problems, or if important new information external to the trial arises.

The BSC will also provide the Internal and External MSM with safety monitoring statistics on the primary safety variables (i.e., AMI, acute cerebral ischemia and acute PE) and all other arterial and venous TE events which will be viewed on an ongoing basis.

Expanded policies and procedures for monitoring the safety of participating subjects are provided in the STOP-IT Study Manual of Procedures Adverse Event Reporting Guidelines.

8.3 Stopping Rules for Safety Concerns

The only serious safety concern identified in prior studies of rFVIIa for intracerebral hemorrhage is an excess risk of arterial thromboembolic serious adverse events (SAEs) with rFVIIa treatment compared to placebo. These SAEs were primarily NSTEMIs and ischemic strokes, but also included individual cases of renal artery thrombosis, intracardiac thrombus, and retinal artery occlusion.^{6,7} In the STOP-IT Study we anticipate randomizing 42 subjects to rFVIIa treatment. This number is considerably smaller than the previous phase IIb and phase III trials of rFVIIa for intracerebral hemorrhage and so it is unlikely the STOP-IT Study will reveal additional, statistically robust information on arterial thromboembolic SAE risk. However, a stopping rule for excess arterial thromboembolic SAEs in the active treatment arm of the study will be followed.

The entry criteria of the STOP-IT Study have been chosen to exclude patients at highest risk of thromboembolism. Anticipated rates of arterial thromboembolism are those adjudicated by the phase III rFVIIa study DMC after excluding select high risk subjects (see section 4.2.2, Table 4, and section 5.2). For this investigation, the stopping rules are based upon the 10.3% rate of arterial thromboembolic SAEs observed in the applicable subject subset treated with 80 µg/kg of rFVIIa in the phase III trial (Table 4).⁷ The corresponding placebo subset in that trial had a 5.4% risk of arterial thromboembolic SAEs. Thus we will consider the expected rate of arterial SAEs for patients treated with rFVIIa in the STOP-IT Study to be 10.3%. If the rate is significantly greater than 10.3%, the treatment arm of the STOP-IT Study will be put on voluntary hold pending DSMB review. For the purposes of these stopping rules, arterial SAEs occurring more than 4 days after drug dosage,

myocardial injury without acute coronary syndrome (“enzyme leak”) and unstable angina without evidence of infarction (see section 6.2.3) will NOT be counted toward the number of arterial thromboembolic SAEs needed to place the treatment arm on hold.

Using the binomial observed event rate, the associated lower 90% confidence interval was calculated for the observed event, as we were only interested in looking at that part of the distribution. The decision is based on when the assumed true event rate, 10.3%, falls below the lower 90% confidence interval for the observed rate which is dependent upon the number of subjects accrued. **All arterial thromboembolic SAEs will be monitored on a continuous basis, in real time, by an unblinded study biostatistician.**

In summary, the treatment arm of the study is placed on voluntary hold if there are:

- 2 arterial SAEs within the first 5 subjects treated with rFVIIa
- 3 arterial SAEs within the first 10 subjects treated with rFVIIa
- 4 arterial SAEs within the first 15 subjects treated with rFVIIa
- 5 arterial SAEs within the first 20 subjects treated with rFVIIa
- 6 arterial SAEs within the first 25 subjects treated with rFVIIa
- 6 arterial SAEs within the first 30 subjects treated with rFVIIa
- 7 arterial SAEs within the first 35 subjects treated with rFVIIa

This means that the treatment arm of the study will be placed on voluntary hold pending DSMB review if there are two arterial thromboembolic SAEs within the first five subjects treated with rFVIIa, three arterial thromboembolic SAEs within the first ten subjects treated with rFVIIa, etc. Clinical sites that perform CTA as part of routine standard of care can continue to enroll spot-negative subjects into the observational arm.

9.0. STATISTICAL CONSIDERATIONS

9.1 Overview and Patient Entry

The Biostatistical Core (BSC) and the Clinical Coordinating Center (CCC) at the University of Cincinnati SPOTRIAS Center will be responsible for the data management activities. All drafts of the protocol will be dated and cataloged on the study website and in the study library so that material development is documented. If a new version of the protocol is developed, a list of changes since the last version will also be available on the website. Case report forms and a manual of operating procedures (MOP) will be developed for and maintained during the course of the trial. The manual will detail the specific steps that must be taken from the initial presentation of a potentially eligible patient to the completion and close-out of the study. The manual will also address each data form item on a question-by-question basis. An orderly discussion of each question contained on the data forms will be incorporated into the case report form as well as the manual. The BSC will prepare for this manual content describing, in detail, standard operating procedures of the BSC such as the organizational structure of the BSC, the data management system, computer edit specifications, data flow, and quality control procedures. The directors of the BSC and the personnel of the Clinical Coordinating Center will be involved in the decision making process concerning any changes in the trial.

All patients enrolled in the study will be registered and entered into the study database by identification number only. Only the personnel at the clinical site where the patient is receiving care will have personal identifiers. No names or birth dates or other information that can identify a patient will be entered on the website and/or sent to the BSC. Each clinical site will either access the assigned web site or if the web site is not accessible call the dedicated emergency phone line to receive a randomization designation by means of a unique study randomization number when an eligible patient is identified. This number will be study website accessed or verbally passed along to the site pharmacist who will have the randomization list to interpret and prepare the appropriate study product. The web site will automatically update the randomization number according to a pre-defined scheme. The phone will also be monitored 24 hours a day and seven days a week and updated as appropriate. The site will then either enter information at the web site or fax if web access is temporarily not available, within 24 hours, a completed eligibility form after enrolling the patient. If a form is sent, it will be reviewed and the information compiled into the accrual database. The clinical site will receive a confirmation that the patient is entered into the accrual database. If a patient is found not to meet the inclusion criteria, the BSC will immediately notify the clinical site of this decision and the reason why. The patient will continue to be monitored and information gathered on them.

A table will be created that is the master list of all patients entered into the trial. From this table a monthly recruitment report will be generated and sent to the Steering Committee and all key personnel. Each clinical site will maintain a STOP-IT Stroke Patient Screen Failure Log on the web site. Full reports will be generated for the Data Safety and Monitoring Committee and for the trials Steering Committee, as required. These reports will include details of enrollment, demographic and medical description of patients enrolled, efficacy and safety outcomes, and adverse events.

9.2 Data Forms

The data forms used in the STOP-IT Study will be easy to read and unambiguous. Each clinical site will use a unique identification convention for their study subjects; this number will also be recorded on the form. This will ensure proper compliance with HIPAA / PIPEDA regulations. Data entry screens on the web will follow the flow that has been created on the forms. Although we will use web based entry, the CRFs will be available on the web site for a clinical site to use as a worksheet, if desired. Instructions on completing the data forms will be addressed in detail in the Manual of Operations.

9.3 Manual of Operations

The Manual of Operations will be a document containing detailed instructions on the recruitment process, study procedures, and data collection. The document is used primarily by the clinical sites for day-to-day operations. The manual will be maintained on the web site.

The manual will detail the specific steps that must be taken from the initial presentation of a potentially eligible patient to the completion and close-out of the study. The steps will be arranged in chronological order with appropriate references to subsequent sections. This manual will cover many of the same topics as the protocol but in greater detail.

The operations of the BSC will be described in this manual. Topics such as the organizational structure of the Clinical Coordinating Center, BSC, complete safety assessment and AE/SAE reporting procedures, the data management system, computer edit specifications, data flow, and quality control procedures will be included. Revisions to the Manual of Operations will be made as necessary. All versions of the manual of operations will be dated and archived in the study library.

9.4 Database Development and Security

The Biostatistical Core and the Clinical Coordinating Center will be located at the University of Cincinnati and Cincinnati Children's Hospital Medical Center (CCHMC). The Biostatistical Core and Clinical Coordinating Center will ensure the completeness and accuracy of the collected data while maintaining subject confidentiality, as well as providing the operational infrastructure to facilitate cooperation and communication among the clinical sites, FDA, NIH personnel, and BSC personnel. Each site will be expected to designate a contact person (research coordinator) who will communicate with the BSC concerning data management issues and will be responsible for the collection of data and entry of data into the web-based system. Necessary qualifications of this person include knowledge of the day-to-day site-specific data collection activities and email capabilities. This person will also be responsible for communicating with BSC personnel with regards to data queries.

The approach to data management will be a web-based data entry system using Microsoft (MS) Infopath 2007. Microsoft Infopath 2007 allows users to create electronic forms or questionnaires of varying complexity. These forms can contain workflow logic, data validation, and conditional formatting or controls based on user responses. With MS Infopath, the forms will be created from the pre-existing Word documents. When coupled with Microsoft Sharepoint, these forms will be placed on the Internet (or corporate Intranet) and subsequently be accessed by the appropriate personnel at the study sites using proper authorization. MS Infopath allows the creation of "browser-compatible" forms that are published in Extensible Markup Language (XML), which makes them viewable in any modern web browser. Furthermore, all data entered are stored in a Microsoft SQL Server database and can then be exported into SAS for analysis.

The Division of Biomedical Informatics (BMI) at Cincinnati Children's Hospital Medical Center has significant experience with Infopath/Sharepoint based web-enabled forms and data capture and is committed to supporting the work proposed here. BMI will provide expertise in the use of Infopath and Sharepoint, including (and in particular) for the addition of custom code to implement the randomization algorithm that assigns patients to trial arms. BMI will collaborate closely with Drs. Bean and Khoury to update the randomization assignments if deemed necessary. Furthermore, BMI staff will provide training for local and remote users of the web forms.

BMI will support and host the web server as well as the database on a server that resides in the CCHMC corporate network behind the corporate firewall. HIPAA compliance will be ensured by assigning unique usernames and secure passwords to each authorized user. Furthermore, all data will be incrementally backed up nightly, with full backups occurring weekly. Access to the web-based data entry forms for external (non-CCHMC) study personnel will be granted (in coordination with the

CCHMC corporate Department of Information Services) through the CCHMC Extranet portal. Remote users will first authenticate through the CCHMC firewall and then be granted access to a web page, which in turn will let them authenticate themselves as study investigators/coordinators/personnel. Finally, access to the data obtained as part of proposed study will be given only to the BSC personnel, who will monitor enrollment and provide analyses.

Security measures will be established to prevent the ability of any unauthorized personnel from accessing the data for any patient enrolled into this trial. Confidentiality of data maintained by the BSC is of the utmost priority. Standard Operating Procedures provide for confidentiality of all information. The designated person at each site, the research coordinator will be given security clearance in order to enter data via the website onto a CCHMC server. Data can only be entered under a login with the system attributing all entry and changes to that person. The password to the system will be changed at established intervals. When the database is exited it will be locked. The data will then be transferred to another server by the data manager at CCHMC. At that time the data will undergo further consistency and completeness checks from which the data queries will be generated. Access to the file will be under the control of the director of the Biostatistical Core (BSC) at the CCHMC SPOTRIAS Center. The Data backup on this server is performed daily with a complete backup once every week. A monthly back up is stored in an off campus facility. A virus package is used to detect viruses. All computers are updated monthly and are continuously monitored.

9.5 Data Management, Monitoring and Quality Assurance

To ensure the highest possible quality of data collected, the BSC will establish standard operating procedures. The essential features in having high quality data for analyses are excellent documentation, control over data flow, communication, and training. A major responsibility of the BSC is to ensure the completeness and accuracy of the data collected.

The BSC will work closely with the project manager and clinical coordinator of the CCC to perform the monitoring functions. Data sheets, equivalent to case report forms, generated by the BSC will be compared to the appropriate source documents to check for accuracy and completeness. If corrections are to be made, a form designed for this purpose will be completed and brought back to the BSC.

Site visits will be conducted to inspect study data, subjects' medical records, and CRFs in accordance with current U.S. Good Clinical Practice guidelines and the respective local and national government regulations and guidelines. Authorized Agents of the United States Food and Drug Administration, the University of Cincinnati, the National Institute of Neurological Diseases and Stroke, Novo Nordisk (manufacturer of the study drug recombinant activated factor VII), and respective national or local health and IRB / EC authorities will be allowed to inspect the medical and research records related to this study.

Prior to starting the study, the STOP-IT project manager will visit each site to verify that the site can conduct the trial by the operating procedures outlined in the Manual of Operations. An evaluation checklist will be designed and completed at the time of the site visit. At this time the project manager will instruct the site personnel on procedures specific to this trial. The BSC, in collaboration with the project manager, will develop a PowerPoint presentation to review the steps with each site.

During the trial, the BSC will monitor the activities of each site in order to identify any problems. Areas to be reviewed include rate of subject recruitment, rate of ineligible subject recruitment, entering data in a timely manner, rate of missing or incomplete data, ability of locating the documents pertaining to each individual in the trial, and rate of aberrant data.

The research coordinator at each site is responsible for all the data collected in the study and oversight of the data entry. The process of standardization will be achieved through the Manual of Operating Procedures, the site visit prior to the start of the study, and the ongoing communications between the coordinator and BSC and CCC staff.

A designated data entry person at the site will enter the data into the database. Pop up menus will be provided for valid values for variables. Skip patterns will be built into the data entry system. Fields will have range and/or validity checks built into the system. If disagreement is found, a Data Discrepancy Report will be generated, and posted on the web for the site to access. This report will note the discrepancy and will require documentation of the resolution of the problem, as well as correction of the error. Data edits will be performed to identify missing, out of range, and inconsistent/erroneous data in the database and reports generated to allow correction of these problems.

The procedure at the BSC will be:

1. The data manager of the BSC will review the file from the center; this will reside on a secured server at CCHMC.
2. The data items will undergo edit checks, more stringent than the gross range checks that will be ongoing during data entry. Consistency checks, both within and across forms, will be made at this time.
3. A query will automatically go back to the research coordinator at the originating site for any out-of-range or inconsistent data. The queries will be maintained at the website.

Upon resolution, via an electronic response, the data will be combined into the master database, maintained in SAS format ready for analysis. Data that are determined to be correct, but still fail edit checks, will be flagged rather than be removed from the data files. Repeated flagging of data points indicates the need to modify data collection and/or edit specifications.

The BSC will do computer runs to check the data for patterns of errors not detected by simple range checks. These runs allow the BSC to determine if one question is causing problems across the sites or if one site is having continuing problems. The Steering Committee will have the responsibility for deciding if changes need to be made to the case report forms.

9.6 Sample Size Calculation

The statistical center for the STOP-IT study will be at Cincinnati Children's Hospital Medical Center (study statisticians Judy Bean, PhD and Jane Khoury, PhD). For all analyses the definition of hematoma growth will be an increase in hematoma volume from baseline CT to 24-hour CT of >33% or >6 cc. Secondary analyses will involve any amount of hematoma growth, using growth in absolute terms and as a percentage of hematoma volume. Because of the time necessary for potential study drug dosing after baseline head CT for spot-positive subjects, the maximal time from symptom onset to baseline head CT was set at five hours (rather than the six hour limit reported in several retrospective series of ICH growth). To ensure similarity in spot-negative and spot-positive subjects, this time limit will be applied to both groups. Data on hematoma growth in the 3-5 hour window is not available; therefore data was extrapolated based upon the 3-6 hour window from previous studies.

The first objective of the STOP-IT study is to prospectively determine the sensitivity and specificity of the spot sign for prediction of hematoma growth. Thus, sample size calculations were based upon this analysis rather than calculations regarding preliminary efficacy of rFVIIa vs. placebo as described below for objective #3.

Several estimates regarding the characteristics of the ICH patient population and the performance of the spot sign were required to determine our sample size (see Table 6 below). We attempted to

harmonize the best available data for each item but acknowledge that information is sometimes limited. We were able to estimate the percentage of ICH patients arriving in the 0-3 hour and 3-5 hour strata using population-based data from the Genetic and Environmental Risk Factors for Hemorrhagic Stroke (GERFHS) Study.⁴⁴ As part of the GERFHS study we attempted to ascertain all patients with ICH presenting to an emergency department or hospital in the Greater Cincinnati area between 1998 and 2003. Within this population, using inclusion and exclusion criteria approximating the STOP-IT study criteria, among patients presenting within five hours of ICH onset, approximately 66% presented in the 0-3 hour window while approximately 34% presented in the 3-6 hour window (authors' unpublished data).

Table 6. Variables considered in sample-size calculations (extrapolations from the literature).

Time window hours	Subjects arriving (%)	ICH growth, all patients* (%)	Spot sign prevalence (%)	Spot sign sensitivity	Spot sign specificity
0-3	66	33	34	0.91	0.94
3-5	34	13	34	0.77	0.72
0-5	100	26	34	0.88	0.85

*Overall ICH growth rates among all patients within the specified time windows, without regard to spot sign status.

Based upon a prior prospective study in Greater Cincinnati, 30-40% of ICH patients presenting within three hours will have subsequent hematoma growth by our criteria. There are no prospective data on the rate of hematoma growth in the 3-5 hour window. Retrospective studies indicate the range may be 8-16% (see Table 1). For the purposes of STOP-IT we estimate the overall ICH growth rate (0-5 hour window) to be 26%. For patients in the 0-3 hour strata the growth rate is assumed to be 33%. For patients in the 3-5 hour strata the growth rate is assumed to be 13%. Estimates of the prevalence of the spot sign among ICH patients were obtained from the studies of Becker, Wada, and Goldstein.^{8, 9, 23} For patients presenting within three hours, Wada found that 33% had a spot sign. The prevalence of the spot sign in the 3-5 hour window is more speculative, especially since definitions of the spot sign and contrast extravasation differed between studies. We conservatively estimated that 34% of patients in the 3-5 hour window will have a spot sign. Prior retrospective studies suggest the CTA spot sign has a sensitivity of approximately 90% for ICH growth. The specificity appears high within the first three hours but likely declines somewhat thereafter.^{8, 9, 23}

Taking into consideration the percentage of patients arriving in each time window, the prevalence of the spot sign, our estimated ICH growth rates, and the available literature, we estimate the spot sign will have 91% sensitivity and 94% specificity within the first three hours. Between 3-5 hours we predict 77% sensitivity and 72% specificity. For the overall 0-5 window we therefore predict a sensitivity of 88% and a specificity of 85%.

Using these values we can construct a 2 x 2 table (see Table 7) based upon 100 hypothetical subjects enrolled in the STOP-IT study. For each 100 subject enrolled in the 0-5 hour window, 34 will have a spot sign and 66 will not have a spot sign. ICH growth will occur in 26/100 patients and will not occur in 74/100 patients. Among spot-positive subjects (who are not treated with a hemostatic agent), 23 of 34 (68%) will have hematoma growth.

Table 7. Expected ICH growth characteristics for every 100 subjects enrolled in the STOP-IT study between 0-5 hours of stroke onset.

	ICH growth occurs	ICH growth does not occur	
Spot-sign positive	23	11	34
Spot-sign negative	3	63	66
	26	74	100

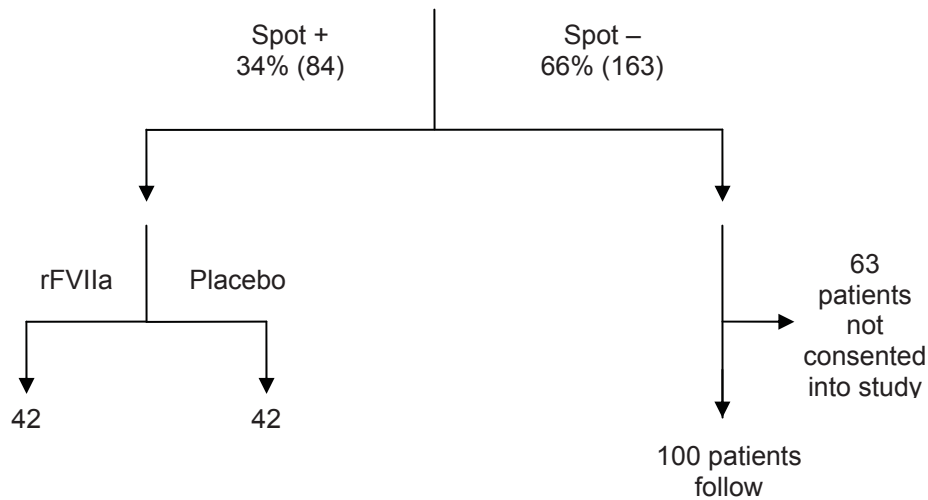
The sample sizes required for a 95% confidence interval of a given width for sensitivity and a 95% confidence interval of a given width for specificity were computed using the approach of Fenn.⁴⁵ This paper describes how to incorporate the prevalence of disease (or in our case ICH growth rates) into computations of the total sample size for sensitivity or specificity. The larger of the two sample sizes calculated is the one required.

The sample of subjects to be used for estimation of sensitivity and specificity of the spot sign is drawn from those who are spot-positive and randomized to the placebo group as well as those who are spot-negative. The method of sample size estimation was the following: the number of true positives plus the number of false negatives is equal to the squared value from the standard normal table times the variance of the sensitivity divided by the width of the confidence interval squared. The variance of sensitivity is the sensitivity times one minus the sensitivity. To obtain the total number required the number calculated from the equation is divided by the growth rate. For the combined group (0-5 hours) the sample size of patients required for a 95% confidence interval of 0.14 are 80 for a sensitivity of 0.88. For the specificity, the variance of the specificity is used and then the number of true negatives plus the number of false negatives is divided by one minus the growth rate. For a specificity of 0.85 and allowing the width of the confidence interval to be 0.14, the sample size is 58. Therefore, the sample size of subjects required is 80 (the larger of the two numbers), composed of 40 spot-positive subjects randomized to placebo and 40 spot-negative subjects. Because spot-positive subjects will be randomized 1:1 to rFVIIa or placebo, a total of 80 spot-positive subjects will be required.

Given that 34% of patients have a spot sign, the number to screen is $80/0.34 = 235$. We believe that our selection criteria should minimize drop-outs during the first 24 hours; however we will increase our total sample size by 5% to account for this possibility. Based upon these numbers, we will need to screen 247 eligible patients with CTA within 0-5 hours of ICH onset in order to verify the sensitivity and specificity of the spot sign with a 95% confidence interval of 0.14. Patients with a spot sign will be randomized to rFVIIa 80 µg/kg (42 patients) or placebo (42 patients). The remaining patients will not have a spot sign. **Forty-two spot-negative subjects will be needed to determine the sensitivity and specificity of the spot sign for hematoma growth (forty subjects completing the 24-hour CT plus two drop-outs). Once we reach this number, sites that perform CTA as standard care (and therefore perform CTA before patient consent) will stop enrolling subjects without a spot sign.** Sites that have not performed CTA as standard care and require consent before the CTA will continue to enroll both spot-negative and spot-positive subjects (see section 5.5.2 for the discussion of CTA as standard practice). Because many of our sites will consent patients before the CTA and therefore enroll twice as many spot-negative subjects as spot-positive subjects, we conservatively estimate that 100 spot-negative patients will ultimately be enrolled, although it is possible the number will be less. See the figure 3 below for patient flow.

Figure 3

247 patients eligible and screened



The effect of rFVIIa on hematoma growth among spot-positive patients will be determined by comparing subjects randomized to rFVIIa vs. placebo. A one-sided alpha is appropriate in this circumstance as all research to date indicates rFVIIa stops bleeding and there is no reason to believe it will increase hematoma size. We anticipate the rate of hematoma growth in the spot-positive placebo arm will be 68%. Given 40 subjects in each treatment arm (42 enrolled minus two drop-outs), using a one-sided alpha of 0.05 we will have 82% power to detect a 30% absolute reduction in the number of subjects with growth in the rFVIIa arm or 71% power to detect a 26% absolute reduction in the number of subjects with growth in the rFVIIa arm. Table 7 summarized our power calculations for hematoma growth.

Table 8. Power calculations for hematoma growth in spot-positive subjects, rFVIIa vs. placebo, n=40* in each group, one-sided alpha.

Percentage in rFVIIa group with growth	38%	42%
Percentage in placebo group with growth	68%	68%
Power	82%	71%

*Original n of 42 in each group minus 5% drop-outs

9.7 General Analysis Plan

The primary statistical package used will be SAS, version 9.1. Prior to any analysis, means, ranges, standard deviations and descriptive measures will be computed for each continuous variable as well as frequencies for categorical variables. Plots and statistics will be used to determine if a continuous variable is not normally distributed; when necessary an appropriate transformation will be performed and analyses will be done with transformed values.

9.7.1 Objective #1: Determine the sensitivity and specificity of the CTA spot sign for hematoma growth.

The first step in analysis will be to calculate estimates of the sensitivity and specificity of the CTA spot sign for hematoma growth (defined as > 33% increase in volume or 6 cc from baseline to 24 hour CT scan). The estimates will utilize the data from those patients who had a spot sign and were randomized to placebo and patients without a spot sign. The next step will be to calculate the 95% confidence intervals. The method developed by Agresti and Coull will be used.⁴⁶ Additionally, positive and negative predictive values and a likelihood ratio for hematoma growth based upon the presence of the spot sign will be calculated, along with 95% confidence intervals.

Next, categorization of subgroups of the patients will be examined. It is conceivable that variables which are important in stroke survival and outcome will be predictors of hematoma growth. Therefore, logistic regression modeling will be performed using the variables age, gender, race, baseline hematoma volume, time from onset to CTA, baseline GCS, baseline blood pressure, baseline antiplatelet drug use, and presence or absence of the spot sign. Variables will be examined for association with either the outcome of hematoma growth or spot sign prior to entry into a model due to sample size considerations and modeling will be considered exploratory. Those variables either reported in the literature to be associated with hematoma growth or statistically associated at $p < 0.25$ will be potentially entered into the multiple logistic regression model.

9.7.2 Objective #2: Determine the feasibility of using CTA to identify ICH patients at high risk of hematoma growth and select patients for randomization to treatment with rFVIIa or placebo.

In order for the spot sign to be a practical, widely applicable test that informs immediate treatment decisions, it is paramount that clinicians are able to accurately determine the presence or absence of the spot sign in an emergency setting. Site investigators will interpret the CTA locally in the acute setting to determine whether the patient is enrolled in the treatment (spot-positive) arm or observation (spot-negative) arm of the study. The scan will later be over-read in a blinded fashion by the study neuroradiologist (Dr. Aviv) who will represent the gold standard for diagnostic accuracy. In order to assess the agreement between the gold standard and the site investigators, intraclass correlation will be estimated using a mixed model design as each investigator will read a different number of scans depending upon recruitment. The mixed model will allow us to account for this potential additional correlation which may exist between scans. A secondary analysis will determine whether interrater reliability improves for sites as the study progresses and more experience is gained by local investigators in identifying the spot sign, by including time in the model.

Additionally, at a later time each scan will be blindly read for the presence or absence of the spot sign by a study neurologist (Drs. Demchuk or Flaherty or designate) and a study emergency physician (Drs. Jauch or Goldstein or designate). Each scan will be randomly allocated to one of the physicians in each group. A Kappa statistic will be computed for agreement between the study neurologist, the study emergency physician, and the study neuroradiologist. Both individual Kappas and a mean of the Kappas will be reported.

The time required for obtaining and interpreting CTAs as well as randomization and study drug administration for patients in the treatment arm will be determined by calculating mean intervals from baseline head CT to CTA and for baseline head CT to study drug administration. Time intervals for patients from sites which currently perform CTA as standard care (and obtain informed consent after the CTA) will be compared to times for patients at sites who obtain informed consent before the CTA. Time values will be assessed for normality. Because these values are often badly skewed, it is anticipated a non-parametric test will be used for comparisons.

9.7.3 Objective #3: Randomize ICH patients who present within five hours of onset and have a spot sign to treatment with rFVIIa versus placebo, in order to a) determine if rFVIIa is effective at reducing hematoma growth among patients with a spot sign and b) provide preliminary efficacy data for this treatment paradigm.

The primary approach will be a Chi-square analysis of spot-positive patients comparing the rate of growth (increase in hematoma size of >33% or 6cc from baseline) between the group treated with rFVIIa and the placebo group. There should be 42 subjects entered into each arm of the study, with an anticipated drop-out of 5%, to give a sample size of 40 evaluable subjects in each arm of the study, with enough power to detect a 30% absolute difference in growth rate. The adaptive randomization scheme will allow a balance of time from symptom onset and initial hematoma size between the two arms of the study. However analysis will involve assessment of differences between the study groups of these variables and other potential factors that may effect hematoma growth. Bivariate analysis will be done in a systematic way to compare demographic and potential risk factors for hematoma growth between the groups. Variables that are associated with growth at $p < 0.25$ or thought clinically important will be included in a multiple logistic regression model to assess the independent effect of rFVIIa on hematoma growth. Another approach, which may be more powerful, will be to use a multiple linear regression model with percent growth as the dependent variable. The advantage to this would be a potential increase in power; however the dependent variable would have to be transformed as percentage growth would violate the assumption of normality. Appropriate transformations will be tried and the residuals will be assessed to ensure validity of interpretation.

A secondary analysis will consider rates of total hemorrhage growth (hematoma plus IVH) in spot-positive subjects treated with rFVIIa vs. placebo. The STOP-IT Study is not powered to detect differences in clinical outcomes among subjects in the treatment arm. However, in an additional secondary analysis clinical outcomes among spot-positive patients treated with rFVIIa and those treated with placebo will be compared using multiple logistic regression analysis as described for hematoma growth, with consideration of covariates. Analysis will be performed for mortality at 90 days and also good (mRS 0-4) versus poor (mRS 5-6) functional outcome. An exploratory analysis will consider differences in outcome for the two groups when defining good outcome as mRS 0-3 and also over the entire range of the mRS using a cumulative logit model with adjustments for important baseline variables such as age, baseline hemorrhage volume, baseline GCS, the presence of IVH, and ICH location. Hematoma growth, mortality, and functional outcome will also be compared for patients with a spot sign randomized to placebo and patients without a spot sign.

9.8 Potential Collaborations and Pooled Analyses

Two participating STOP-IT sites are Canadian (University of Calgary and Sunnybrook Medical Centre). Canadian investigators have received funding through Canadian public sources for a parallel trial called the “**Spot Sign Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT) Study**” which will be conducted at other Canadian centers. It is anticipated that this study will have a similar protocol to the NINDS-funded STOP-IT Study. Data from SPOTLIGHT will be pooled with data from STOP-IT as a pre-specified part of all primary and secondary analyses. Additional patient recruitment via this mechanism will allow greater power to show differences in hematoma growth and clinical outcomes between subjects randomized to rFVIIa vs. placebo.

10.0 STUDY TIMELINE

The University of Cincinnati and other enrolling sites in the STOP-IT study have extensive experience in research involving subjects with acute ICH and have a proven track record of patient enrollment in ICH studies. In addition to treating patients who arrive directly to the study institutions, most of our sites serve as tertiary referral centers for ICH and receive patients in transfer from other hospitals. Each enrolling site in the STOP-IT study participated in the FAST trial of rFVIIa for intracerebral hemorrhage.⁷ Because of new safety data from the phase III rFVIIa trial that was

made available to investigators in late spring 2009 (and considered in the protocol amendment), as well as delay in supply of study drug by Novo Nordisk, initial recruitment was delayed.⁴⁰ Every effort will be made to maximize recruitment to compensate for delays in study initiation. The recruitment goals we have set for STOP-IT are presented in Tables 9 and 10.

Table 9. STOP-IT/SPOTRIAS Timeline

Year 1	Year 2	Year 3	Year 4	Year 5	
0-12 months	12-24 months	24-36 months	36-48 months	48-54 months	54-60 months
Study initiation	Patient enrollment				Data analysis and study close-out
					Planning and submission of NIH R01 or industry-sponsored phase III study

Table 10. STOP-IT/SPOTRIAS Anticipated Patient Enrollment

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
University of Cincinnati	0	0	10	10	8	28
University of California at San Diego	0	0	11	11	8	30
Other sites	0	0	47	47	32	126
Total	0	0	68	68	48	184

11.0 HANDLING OF MISSING DATA

Based upon our trial design, it is anticipated that there will be minimal loss to follow up for the 24-hour CT scan for hematoma growth or the 90-day assessment of clinical outcome. Nevertheless, some missing data will be inevitable. For patients who require emergency surgery before 24 hours, a CT scan should be obtained before surgery if possible. The presence or absence of hematoma growth will be determined from this scan. The number, timing, and reasons for early scans will be tracked and reported. For patients without 24-hour CT scans, the baseline scan results will be carried forward (patient will be assigned no hematoma growth). If a substantial number of subjects have no follow-up scans or have early scans without subsequent 24-hour scans, an additional analysis using only the study population with 24-hour scans will be performed. Patients lost to follow-up after hospital dismissal will be assigned the worst possible outcomes (short of death) on the mRS and Barthel Index. These assumptions are consistent with the handling of missing outcome data in the NINDS rt-PA Stroke Study.⁴⁷ In addition, all analyses will be repeated excluding the cases with missing data to check for potential bias.

Missing covariate data will be imputed using the multiple imputation, regression method, or hot-decking. If imputation is needed the specific method will be decided at the time of analysis, using SOLAS®.

12.0 TRIAL ADMINISTRATIVE STRUCTURE

12.1 National Institute of Neurological Disorders and Stroke (NINDS) Data and Safety Monitoring Board (DSMB)

A NINDS appointed independent Data and Safety Monitoring Board will act in an advisory capacity to monitor participant safety, data quality and evaluate the progress of the study. The DSMB is responsible for assuring the NINDS that study participants are not exposed to unnecessary or unreasonable risks and that the study is being conducted according to high scientific and ethical standards. Specifically, the DSMB will:

- protect the safety of the study participants;
- review the research protocol, informed consent documents, amendments, and plans for data safety and monitoring;
- evaluate the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, performance of the trial sites, and other factors that may potentially affect study outcome;
- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator;
- report to NINDS on the safety and progress of the trial;
- make recommendations to the NINDS, the Principal Investigator, and, if required, to the Food and Drug Administration (FDA) concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- ensure the confidentiality of the study data and the results of monitoring; and,
- advise the NINDS and the study investigators as to whether the protocol should continue as scheduled or undergo a modification due to a finding from the monitoring process.

For a detailed description of the DSMB monitoring guidelines, go to the following website: http://www.ninds.nih.gov/funding/research/clinical_research/policies/data_safety_monitoring.htm

12.2 External Medical Safety Monitor

Dr. Claude Hemphill, Neurologist from the University of California San Francisco, and Dr. David Gregg, IV, Cardiologist from the Medical University of South Carolina, will serve as independent external Medical Safety Monitors. They will be responsible for the ongoing monitoring of reports of SAEs submitted by clinical sites to ensure good clinical practice and to quickly identify safety concerns.

12.3 Biostatistical Core and Data Management (BSC)

The University of Cincinnati and Cincinnati Children's Hospital Medical Center will provide the data management and analysis for this study. Judy Bean, PhD, and Jane Khoury, PhD, experienced biostatisticians, will lead this center. This center will be responsible for providing the case report forms, procedure manual, clinical monitoring and source document review, data entry and programming and reports for the NINDS, the DSMB, SPOTRIAS, Novo Nordisk, and participating centers. In addition, Dr. Matthew Flaherty is the sponsor of the IND for the study and will be responsible for timely and appropriate reporting of adverse drug experiences to the Food and Drug Administration (FDA), the NINDS, the DSMB, and the enrolling centers.

12.4. Coordinating Clinical Center

The Clinical Coordinating Center (CCC) will provide overall clinical guidance and leadership for the execution of the STOP-IT Study. The overall Principal Investigators, Drs. Flaherty and Jauch, will be responsible for oversight of the conduct of the trial, recruitment of centers, and management of day-to-day issues.

The Clinical Coordinating Center physicians and overall project manager will be available to discuss any treatment issues that arise at a given center. Sites will be instructed to contact the Clinical Coordinating Center prior to deviating from the protocol.

The Clinical Coordinating Center will be responsible for coordinating the response to regulatory agencies by communicating with any center in the preparation and submission of all NINDS, DSMB, and FDA IND safety reports (Medwatch), and to all corporate partners and the clinical centers. The

coordinating site will maintain a record of all safety correspondence with these entities.

The Clinical Coordinating Center staff will be responsible for training and verifying the training of the investigator and staff at the clinical centers. Specifically this will include standardized training for the trial's major clinical measures: spot sign identification training, the NIHSS, and the modified Rankin Scale. All training will require verification of participation.

The Clinical Coordinating Center will coordinate and supervise site recruitment. They will monitor site performance and make decisions regarding the dropping of poorly performing clinical centers and the screening and addition of new clinical centers. Intermittently, CCC personnel will make site visits to re-evaluate a site or to assist a center in developing a more effective recruitment strategy. The Coordinating Center in Cincinnati will create and maintain the trials central regulatory document file and coordinate communication regarding verification of these documents at the centers with the site monitoring staff.

The data-monitoring plan will be developed by the Clinical Coordinating Center with guidance provided by the Biostatistical Core. The data monitoring staff will be supervised and managed by Clinical Coordinating staff. All monitoring trip assignments will be made by the Coordinating Center Clinical staff.

12.5 Imaging Center

Primary imaging analyses will be provided by the investigators at the University of Calgary and Sunnybrook Health Sciences Centre, Toronto. Image analysis will be led by Drs. Demchuk and Aviv in a standard manner, blinded to clinical data.

12.6 Participating Centers

The participating centers in this trial are comprised of one or more Principal Investigators (either neurology or emergency medicine), co-investigators, research coordinators, radiologists, and other necessary staff who will be responsible for enrolling the patients and collecting the data for this trial. The Principal Investigator at each participating center is responsible for the overall conduct and performance of the clinical center. A participating center may have one or more participating performance sites. All participating centers and its performance sites must demonstrate clear involvement and leadership within the emergency medicine department, as the emergency department is where initial contact with most patients is made and the early diagnostic and treatment activities occur. The clinical coordinator will be responsible for such critical matters as completing exclusion logs, tracking and performing telephone follow-up visits, coordinating and verifying the completion and web-based entering of case report forms and regulatory documents, and arranging the shipment of CT and CTA data to the Clinical Coordinating Center. The storage and documentation of study medication will be the responsibility of the hospital pharmacy.

Each clinical center is expected to provide all applicable regulatory documents deemed necessary by the Clinical Coordinating Center for the initiation of a clinical research protocol at each of its clinical performance sites. All sites will be expected to comply with state and federal requirements for the initiation and ongoing performance of a clinical trial and adherence to its local IRB / EC requirements for obtaining subject consent, reporting of protocol defined SAEs and the storage and accountability of study medication. Each site is expected to screen all acute ICH patients at IRB / EC approved performance sites for inclusion into the STOP-IT Study and enter the information on its Stroke Screen Failure Log in the STOP-IT Study web site on a monthly basis. Sites will identify and recruit appropriate study candidates as defined by the trial's inclusion and exclusion criteria. All performance sites will observe trial defined imaging and imaging acquisition protocols as well as other protocol-defined procedures. Clinical Centers are expected to provide clinical and imaging data in a time frame consistent with those defined in the Manual of Procedures. All centers must permit inspection of site regulatory documents and monitoring of CRF source documents by trial

representatives and/or representatives of local or federal regulatory agencies. Each clinical center in the STOP-IT Study will provide a site representative at all required investigator meetings and trial conference calls.

Enrollment and compliance with all protocols will be reviewed periodically by the research coordinator. If serious protocol breaks or decreased enrollment occur, the center may be dropped from the study at the discretion of Dr. Flaherty or Dr. Jauch. The clinical coordinator at each participating center will be responsible for such critical matters as checking emergency department logs, follow-up calls, checking the completeness of forms and arranging the shipment of imaging data to the Coordinating Center.

12.7 Steering Committee

The steering committee will be comprised of the Co-Principal Investigators for this project (Drs. Matthew Flaherty and Edward Jauch), the overall Principal Investigator for the University of Cincinnati SPOTRIAS site (Dr. Joseph Broderick), Dr. Joshua Goldstein (Harvard University), Dr. Stephan Mayer (Columbia), Drs. Richard Aviv and David Gladstone (Sunnybrook Health Sciences Centre, Toronto), and Drs. Andrew Demchuk and Michael Hill (University of Calgary). The Steering Committee will advise and assist the Clinical Coordinating Center on operational matters, monitor the performance of the clinical centers, receive requests for any proposed ancillary studies, and establish publication policies for the pilot trial. The Steering Committee will also report major problems and recommend changes in the protocol to the NINDS Project Officer and the Data and Safety Monitoring Board. Beyond providing study guidance, the Steering Committee also provides the forum for Principal Investigators to serve as study collaborators. Members of the steering committee will be responsible for overseeing publications which result from the STOP-IT Study.

12.8 Drug Distribution and Pharmacy Support

The Department of Pharmacy Services at The University Hospital (TUH) at the University of Cincinnati has 20 years experience in industry and NIH funded pharmaceutical research. The TUH Pharmacy-Coordinated Investigational Drug Service (IDS) has successfully facilitated, dispensed and provided accountability and control of medications used in multiple acute stroke drug studies including the NIH funded rt-PA dose escalation trial, the randomized NINDS rt-PA Stroke Trial, the EMS, IMS I, IMS II, and IMS III trials, and the CLEAR trial as part of the previous SPOTRIAS funding period. IDS, under the direction of Caron Sue, PharmD, Ph.D, is staffed by both an investigational drug pharmacist and pharmacy technician.

Foothills Medical Centre Pharmacy IDS at the University of Calgary will act as the drug distribution center for Canada. As a member of the Canadian Stroke Consortium, the University of Calgary has already acted as the drug distribution center for Canada in the IMS I, II, and III trials.

12.9 Novo Nordisk

Novo Nordisk manufactures rFVIIa (NovoSeven® RT [US], NiaStase RT® [Canada]) and will be responsible for providing study drug, rFVIIa, to the participating centers via the University of Cincinnati and University of Calgary drug distribution centers.

12.10 Investigational New Drug (IND) Application

With the cooperation of Novo Nordisk an IND was approved by the US Food and Drug Administration for use of rFVIIa in this trial.

12.11 National Institute of Neurological Disorders and Stroke

The NINDS will provide funding for all aspects of this trial other than cost of study drug, via the SPOTRIAS consortium. Scott Janis, Ph.D, will be the Program Scientific Officer. Dr. Janis will have substantial scientific-programmatic involvement during the conduct of this phase II trial.

13.0 HUMAN SUBJECTS

This study will be conducted in accordance with current US Food and Drug Administration Good Clinical Practice and local ethical and legal requirements. Subjects for this trial will be recruited from all subjects with suspected acute ICH admitted to participating performance sites. All subjects with acute ICH, whether eligible or not, who are admitted to the participating site within five hours of onset during the accrual phase of the study will be recorded in a Stroke Log. Informed consent from the patient, or if the patient is aphasic or confused, the legal representative of that patient will be required prior to enrollment / randomization.

It is ethical to conduct this randomized controlled trial (RCT) because clinical equipoise currently exists: there is uncertainty whether or not rFVIIa can produce a clinically meaningful benefit to patients. The drug is available but is currently not approved for the indication of ICH treatment by Health Canada or the United States FDA. Only a properly conducted RCT will provide the evidence base necessary for clinical decision making. Because rFVIIa is a prothrombotic drug, its use in the ICH population is associated with an increase in the incidence of arterial thromboembolic complications, as detailed previously. This is considered an acceptable low risk, particularly given the fact that it is being administered for a life-threatening emergency. Study patients will continue to receive routine clinical stroke care that is standard practice at each of the participating centers. This is an investigator-initiated, academic trial.

13.1 Institutional Review Board (IRB) / Ethics Committee (EC) and Informed Consent

This protocol, the informed consent document, and relevant supporting information must be submitted to local IRBs / ECs for review and approval before the study is initiated. The principal investigator at each clinical site is responsible for keeping the local IRB / EC apprised of the progress of the study and of any changes made to the study protocol, as well as any serious adverse events.

The final IRB/EC approved document will be provided to the Clinical Coordinating Center. Prior to participation/randomization in the study, the IRB/EC approved informed consent statement must be obtained from a competent subject and/or subject's legally authorized representative. The process for obtaining consent of the subject (i.e., from the subject and/or legal representative) must be in compliance with the local performance site's IRB/EC guidelines and policies for obtaining informed consent for research participation. Waiver of consent (exception of informed consent) will not be allowed in this study and a subject will not be enrolled if consent cannot be obtained from the subject themselves or their legally authorized surrogate. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

13.2 HIPAA / PIPEDA

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. Each participating U.S. clinical center is expected to comply with its individual performance site's requirements established for compliance of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) affecting the research process with respect to subject PHI. The CCC will require the authorization include that subject PHI may be disclosed to specific agencies or persons for their use with regard to the STOP-IT Study. The document will be provided to the CCC for final approval.

Under Canadian federal legislation effective early 2004, all Canadian centers will be expected to comply with the Personal Information, Privacy and Electronic Documents act (PIPEDA).

13.3 Specimens

Blood tests that are routinely obtained on patients with ICH will be recorded. Troponin levels will be obtained at baseline, 24, and 48 hours for subjects in the treatment arm. A baseline troponin will be obtained for subjects in the observational arm. Serum creatinine will be obtained for subjects in the treatment and observational arm at baseline, 24 hours, 72 hours, and day 15 or discharge (whichever is sooner). No genetic testing will be performed on obtained blood samples and no blood samples will be stored for research purposes as part of this study.

13.4 Recruitment of Minorities and Women

This study will encourage enrollment of all eligible subjects regardless of gender, race, or ethnicity. Any gender, racial or ethnic disparity in recruitment detected will be the result of differences in the pattern of referral to the participating institutions. Pregnant women are excluded from this protocol because of potential risk to the fetus.

Table 11. Targeted/planned enrollment

Ethnic Categories	Sex		
	Female	Male	Total
○ Hispanic or Latino	4	4	8
○ Not Hispanic or Latino	88	88	176
Total	92	92	184
Racial Categories			
○ American Indian/Alaska Native	0	0	0
○ Asian	2	2	4
○ Native Hawaiian or Other Pacific Islander	0	0	0
○ Black or African American	13	13	26
○ White	77	77	154
Total	92	92	184

13.5 Inclusion of Children

Only persons 18 years and older will be enrolled in the study. ICH in the neonatal period is a different disease process than ICH in adults and is not appropriate for inclusion in this study. Spontaneous ICH is otherwise extremely rare in children and is often due to vascular malformations or aneurysms.

13.6 Potential Risks and Benefits

Intracerebral hemorrhage is the most devastating form of stroke with overall 30-day mortality ranging from, 30-50%. While many patients arrive in the emergency department significantly impaired by the hemorrhage, others arrive with modest deficits which rapidly worsen due to hemorrhage expansion. No targeted intervention currently exists to mitigate the clinical effect of the hemorrhage and hemorrhage expansion. While phase II studies suggested clinical benefit from hemostatic therapy, a recently completed phase III trial left uncertainty as to optimal patient selection to minimize the potential thromboembolic side effects of hemostatic therapy while maximizing potential hemostatic benefit. Adequate protections against excessive risk of thromboembolism are in place by conservative patient selection criteria. The major risk associated with participation in this study is serious arterial thromboembolic events (e.g., acute myocardial ischemia and ischemic stroke) associated with rFVIIa administration. Treatment with rFVIIa in the STOP-IT Study is expected to produce an approximately 5% excess risk of arterial thromboembolic events compared to placebo (see Table 4).^{6,7} There appears to be no difference in the rate of venous thromboembolic events in rFVIIa-treated subjects versus placebo-treated subjects^{6,7} (see section 4.2.2 for further discussion of the safety profile of rFVIIa). Aggressive clinical and laboratory monitoring are essential components

of this study to monitor for and address this risk.

An additional risk from participating in this trial is associated with the use of intravenous contrast medium for the CTA. Radiographic iodinated contrast agents are used extensively in health care. As discussed in section 5.5.2, CTA is already used as a standard method of evaluation for patients with acute ICH at some centers in North America. Allergic reactions are a real but relatively rare occurrence with modern contrast agents; mild allergic reactions occur in 2% of patients receiving intravenous contrast dye, severe reactions to contrast media occur in roughly 0.1% of patients. Contrast extravasation into a limb due to failure of the intravenous access may occur in 0.25-0.6% of injections.³¹ Contrast extravasation may result in local tissue damage.³² Based upon clinical literature, reported deaths from the administration of iodinated contrast agents range from 6.6 per million (0.00066%) to 1 in 10,000 (0.01%).⁴⁸ An additional risk with the use of iodinated radiographic contrast medium is contrast-induced nephropathy.²⁸ A recent study of CTA in patients with acute stroke demonstrated a very low incidence of contrast-induced nephropathy (3%) and no patients required dialysis.³⁰ This risk is greatest in patients with chronic kidney disease and is proportional to the amount of agent administered.²⁸ Our patient selection includes a conservative serum creatinine level for inclusion among patients entered at sites that do not perform CTA as standard care for patients with ICH. Centers that do perform CTA as standard acute care for patients with ICH also have protocols in place to exclude patients with significant renal insufficiency.³⁰ Only a single administration of contrast medium will be associated with this study. Serial monitoring for elevations in serum creatinine will be performed to identify any increase in creatinine as a sign of contrast-induced nephropathy.

The CT scans and CT angiography used in this study involve exposure to a small amount of radiation in addition to the usual x-ray studies done in patients with intracerebral hemorrhage. The radiation dose delivered by a CTA is slightly more than a non-contrast CT study when centered on the intracranial vessels (1.9 mSV vs. 1.7 mSV).³³ There is a very small chance of skin or hair damage.

13.7 Subject Confidentiality

All information concerning subjects (e.g., imaging and laboratory data, evaluation forms, CRFs, etc.) will be identified only by the assigned Subject Identification Number (SID) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using SIDs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB/EC, the FDA, or NINDS, the study's sponsor. No personal identifying information will be used in presentation or publication of data from this study.

14.0 VERTEBRATE ANIMALS

No vertebrate animals will be used in this study.

15.0 SELECT AGENT RESEARCH

Not applicable.

16.0 DISCLOSURE OF DATA

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited. Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Data generated by this study must be available for inspection upon request by Authorized Agents of the United States Food and Drug Administration, national and local health authorities, the University of Cincinnati, the National Institute of Neurological Disorders and Stroke, Novo Nordisk (manufacturer of the study drug recombinant activate factor VII), and respective IRB/EC authorities.

17.0 DATA SHARING PLAN

The BSC will be responsible for constructing a redacted file for this trial that will be released to the general public in compliance the NIH Data Sharing Policy. After completion and finalization of the data base and publication of study results, the data base will be made available to clinical investigators as has been done for the NINDS rt-PA Stroke Trial through the NINDS. The public use database will be stripped of any and all personal identifiers.

The public use database will consists of several data files: 1) baseline data file; 2) outcome assessments file; 3) CT and/or CTA data file; 4) concomitant medications file 5) procedures file; and 6) adverse events file. Each data file will be made available as a formatted SAS® dataset or as a MS Excel or Access data file. The data files will be distributed, along with the data dictionary. Anyone wishing access to the data may do so by completing a data request form and submitting it to the Trial Steering Committee. The data files can be distributed on CD or via email on password protected zip file. Limited information for the trial subjects will be available through the SPOTRIAS shared database.

18.0 REFERENCES

1. Kissela B, Schneider A, Kleindorfer D, et al. Stroke in a biracial population: The excess burden of stroke among blacks. *Stroke*. 2004; 35:426-431.
2. Flaherty ML, Haverbusch M, Sekar P, et al. Long-term mortality after intracerebral hemorrhage. *Neurology*. 2006; 66:1182-1186.
3. Brott T, Broderick J, Kothari R, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke*. 1997;28:1-5.
4. Davis SM, Broderick J, Hennerici M, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology*. 2006;66:1175-1181.
5. Mayer SA. Ultra-early hemostatic therapy for intracerebral hemorrhage. *Stroke*. 2003;34:224-229.
6. Mayer SA, Brun NC, Begtrup K, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2005;352:777-785.
7. Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2008;358:2127-2137.
8. Wada R, Aviv RI, Fox AJ, et al. CT angiography "spot sign" predicts hematoma expansion in acute intracerebral hemorrhage. *Stroke*. 2007;38:1257-1262.
9. Goldstein JN, Fazen LE, Snider R, et al. Contrast extravasation on CT angiography predicts hematoma expansion in intracerebral hemorrhage. *Neurology*. 2007;68:889-894.
10. Mendelow A, Gregson B, Fernandes H, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the international surgical trial in intracerebral haemorrhage (STICH): A randomized trial. *Lancet*. 2005;365:387-397.
11. Hemphill JC,III, Bonovich DC, Besmertis L, Manley GT, Johnston SC, Tuhim S. The ICH score: A simple, reliable grading scale for intracerebral hemorrhage editorial comment: A simple, reliable grading scale for intracerebral hemorrhage. *Stroke*. 2001;32:891-897.
12. Broderick J, Brott T, Tomsick T, Tew J, Duldner J, Huster G. Management of intracerebral hemorrhage in a large metropolitan population. *Neurosurgery*. 1994;34:882-887.
13. Leira R, Davalos A, Silva Y, et al. Early neurologic deterioration in intracerebral hemorrhage: Predictors and associated factors. *Neurology*. 2004;63:461-467.
14. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage: Incidence and time course. *Stroke*. 1996;27:1783-1787.
15. Fujii Y, Takeuchi S, Sasaki O, Minakawa T, Tanaka R. Multivariate analysis of predictors of hematoma enlargement in spontaneous intracerebral hemorrhage. *Stroke*. 1998;29:1160-1166.
16. Cheung RTF, Fujii Y, Tanaka R. Predictors of hematoma growth? ò response. *Stroke*. 1998;29:2442-2443.
17. Kazui S, Minematsu K, Yamamoto H, Sawada T, Yamaguchi T. Predisposing factors to enlargement of spontaneous intracerebral hematoma. *Stroke*. 1997;28:2370-2375.
18. Fujitsu K, Muramoto M, Ikeda Y, Inada Y, Kim I, Kuwabara T. Indications for surgical treatment of putaminal hemorrhage. *J Neurosurg*. 1990;73:518-525.
19. Yamaki T, Yoshino E, Higuchi T. Extravasation of contrast medium during both computed tomography and cerebral angiography. *Surg Neurol*. 1983;19:247-250.
20. Yamamoto T, Muraki M, Oishi H, Uemura K. Contrast-enhanced MRI of hypertensive intracerebral hemorrhage in the hyperacute stage--extravasation of contrast medium as detector of growing hematoma. *Nippon Rinsho*. 1993;51 (Suppl):48-54.
21. Wolpert SM, Schatzki SC. Extravasation of contrast material in the intracerebral basal ganglia. *Radiology*. 1972;102:83-85.
22. Huckman MS, Weinberg PE, Kim KS, Davis DO. Angiographic and clinico-pathologic correlates in basal ganglionic hemorrhage. *Radiology*. 1970;95:79-92.
23. Becker KJ, Baxter AB, Bybee HM, Tirschwell DL, Abouelsaad T, Cohen WA. Extravasation of radiographic contrast is an independent predictor of death in primary intracerebral hemorrhage. *Stroke*. 1999;30:2025-2032.

24. Murai Y, Ikeda Y, Teramoto A, Tsuji Y. Magnetic resonance imaging documented extravasation as an indicator of acute hypertensive intracerebral hemorrhage. *J Neurosurg.* 1998;88:650-655.
25. Yamaguchi K, Uemura K, Takahashi H, Kowada M, Kutsuzawa T. Extravasation of contrast media in hypertensive cerebral hemorrhage. *Rinsho Hoshasen.* 1972;17:257-263.
26. Broderick J, Connolly S, Feldmann E, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: A guideline from the American heart association/American stroke association stroke council, high blood pressure research council, and the quality of care and outcomes in research interdisciplinary working group: The American academy of neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke.* 2007;38:2001-2023.
27. Yeung R, Ahmad T, Aviv RI, Noel de Tilly L, Fox AJ, Aymons SP. Comparison of CTA to DSA in determining the etiology of spontaneous intracerebral hemorrhage. *Canadian Journal of Neurological Sciences.* 2009;37:176-180.
28. Benko A, Fraser-Hill M, Magner P, et al. Canadian association of radiologists: Consensus guidelines for the prevention of contrast-induced nephropathy. *Can Assoc Radiol J.* 2007;58:79.
29. Rudnick MR, Goldfarb S, Wexler L, et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: A randomized trial. *Kidney Int.* 1995;47:254-261.
30. Krol AL, Dzialowski I, Roy J, et al. Incidence of radiocontrast nephropathy in patients undergoing acute stroke computed tomography angiography. *Stroke.* 2007;38:2364-2366.
31. Cochran ST, Bomyea K, Sayre JW. Trends in adverse events after IV administration of contrast media. *Am J Roentgenol.* 2001;176:1385-1388.
32. Bellin MF, Jakobsen JA, Tomassin I, Thomsen HS, Morcos SK, and members of the Contrast Safety Committee of the European Society of Urogenital Radiology (ESUR). Contrast medium extravasation injury: Guidelines for prevention and management. *Eur Radiol.* 2002;12:2807-2812.
33. Cohnen M, Wittsack H-, Assadi S, et al. Radiation exposure of patients in comprehensive computed tomography of the head in acute stroke. *Am J Neuroradiol.* 2006;27:1741-1745.
34. Hedner U. Recombinant activated factor VII as a universal haemostatic agent. *Blood Coagul Fibrinolysis.* 1998;9 (Suppl 1):S147-152.
35. Hedner U, Ingerslev J. Clinical use of recombinant FVIIa (rFVIIa). *Transfus Sci.* 1998;19:163-176.
36. Friederich P, Henny C, Messelink E, et al. Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: A double-blind placebo-controlled randomised trial. *Lancet.* 2003;361:201-205.
37. Rice KM, Savidge GF. Novoseven (recombinant factor VIIa) in central nervous system bleeds. *Haemostasis.* 1996;26 (Suppl 1):131-134.
38. Fewel M, Park P. The emerging role of recombinant-activated factor VII in neurocritical care. *Neurocritical Care.* 2004;1:19-29.
39. Mayer SA, Brun NC, Broderick J, et al. Safety and feasibility of recombinant factor VIIa for acute intracerebral hemorrhage. *Stroke.* 2005;36:74-79.
40. Diringer MN, Skolnick BE, Mayer SA, et al. Thromboembolic events with recombinant activated factor VII in spontaneous intracerebral hemorrhage: Results from the factor seven for acute hemorrhagic stroke (FAST) trial. *Stroke.* 2010;41:48-53.
41. Kothari RU, Brott T, Broderick JP, et al. The ABCs of measuring intracerebral hemorrhage volumes. *Stroke.* 1996;27:1304-1305.
42. Roberts HR, Monroe DM, White GC. The use of recombinant factor VIIa in the treatment of bleeding disorders. *Blood.* 2004;104:3858-3864.
43. Lewis MH, Gohagan JK, Merenstein DJ. The locality rule and the physician's dilemma: Local medical practices vs the national standard of care. *JAMA.* 2007;297:2633-2637.
44. Flaherty ML, Woo D, Haverbusch M, et al. Potential applicability of recombinant factor VIIa for intracerebral hemorrhage. *Stroke.* 2005;36:2660-2664.

45. Fenn-Buderer NM. Statistical methodology: Incorporating the prevalence of disease into the sample size calculation for sensitivity and specificity. *Acad Emerg Med.* 1996;3:895-900.
46. Agresti A, Coull B. Approximate is preferred over "exact" for interval estimation of binomial proportions. *Am Stat.* 1998;52:119-126.
47. NINDS . Effect of intravenous recombinant tissue plasminogen activator on ischemic stroke lesion size measured by computed tomography. *Stroke.* 2000;31:2912-2919.
48. GE Healthcare Inc. Visipaque (iodixanol) injection package insert. 2006.

19.0 APPENDICES

Appendix I

STOP-IT | | | | | Subject # | | | | | - | | | | | - | | | | | Consent Date | | | | | - | | | | | - | | | | | (Page 1 of 3)
 NIHSS Worksheet

NIH STROKE SCALE WORKSHEET

<input type="checkbox"/> BASELINE <input type="checkbox"/> 24 Hour + 3 Hours (Blinded)		<input type="checkbox"/> 1 Hour (+/- 10 Minutes) – Required For Treatment Arm Subjects Only <input type="checkbox"/> Discharge + 2 Days (Blinded)		<input type="checkbox"/> Other	
Was stroke scale rating done?		1 <input type="checkbox"/> Yes	2 <input type="checkbox"/> No	Date	Time
				DD / MMM / YYYY	24 hr. clock
Is patient intubated and paralyzed?		1 <input type="checkbox"/> Yes	2 <input type="checkbox"/> No	(IF YES, score as unexaminable using all 9s)	
Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).					
IF ANY ITEM IS LEFT UNTESTED, A DETAILED EXPLANATION MUST BE CLEARLY WRITTEN ON THE FORM. ALL UNTESTED ITEMS WILL BE REVIEWED BY THE MEDICAL MONITOR, AND DISCUSSED WITH THE EXAMINER BY TELEPHONE.					
Instructions	Scale Definition	Score			
1a. Level of Consciousness: The investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation. <i>* Use coma scoring detailed on instruction page for patients scoring a "3" on this item</i>	0 = Alert; keenly responsive 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond 2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped) *3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, areflexic	_____			
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = Answers both questions correctly 1 = Answers one question correctly 2 = Answers neither question correctly	_____			
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to them (pantomime) and score the result (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly	_____			
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored but calorice testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI) score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness or other disorder of visual acuity or fields should be tested with reflexive movements and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = Normal 1 = Partial gaze palsy. This score is given when gaze is abnormal in one or both eyes, but where forced deviation or total gaze paresis are not present 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver	_____			
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat as appropriate. Patient must be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia is found. If patient is blind from any cause score 3. Double simultaneous stimulation is performed at this point. If there is extinction patient receives a 1 and the results are used to answer question 11.	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia (blind including cortical blindness)	_____			

STOP-IT
NIHSS Worksheet

Subject # [] - [] - [] - [] - [] Consent Date [] - [] - [] (Page 2 of 3)

NIH STROKE SCALE WORKSHEET *continued*

<input type="checkbox"/> BASELINE <input type="checkbox"/> 24 Hour ± 3 Hours (Blinded)		<input type="checkbox"/> 1 Hour (+/- 10 Minutes) – Required For Treatment Arm Subjects Only <input type="checkbox"/> Discharge ± 2 Days (Blinded)		<input type="checkbox"/> Other	
Instructions	Scale Definition	Score			
<p>4. Facial Palsy: Ask, or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barrier obscures the face, these should be removed to the extent possible.</p>	<p>0 = Normal symmetrical movement 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling) 2 = Partial paralysis (total or near total paralysis of lower face) 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)</p>	_____			
<p>5 & 6. Motor Arm and Leg: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder or hip may the score be "9" and the examiner must clearly write the explanation for scoring as a "9".</p> <p style="text-align: center;">* SCORE BOTH SIDES</p>	<p>0 = No drift, limb holds 90 (or 45) degrees for full 10 seconds 1 = Drift, limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support 2 = Some effort against gravity, limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity, limb falls 4 = No movement 9 = Amputation, joint fusion explain: _____</p> <p style="text-align: right;">5a. Left Arm 5b. Right Arm</p>	_____ _____			
	<p>0 = No drift, leg holds 30 degrees position for full 5 seconds. 1 = Drift, leg falls by the end of the 5 second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity, leg falls to bed immediately. 4 = No movement 9 = Amputation, joint fusion explain: _____</p> <p style="text-align: right;">6a. Left Leg 6b. Right Leg</p>	_____ _____			
<p>7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, insure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion may the item be scored "9", and the examiner must clearly write the explanation for not scoring. In case of blindness test by touching nose from extended arm position.</p>	<p>0 = Absent 1 = Present in one limb 2 = Present in two limbs</p> <p>If present, is ataxia in:</p> <p>Right arm 1=Yes 2=No 9=amputation or joint fusion explain _____ Left arm 1=Yes 2=No 9=amputation or joint fusion explain _____ Right leg 1=Yes 2=No 9=amputation or joint fusion explain _____ Left leg 1=Yes 2=No 9=amputation or joint fusion explain _____</p>	_____ _____ _____ _____ _____			

STOP-IT
NIHSS Worksheet

Subject # _____ - _____ - _____ Consent Date _____ - _____ - _____
(Page 3 of 3)

NIH STROKE SCALE WORKSHEET *continued*

<input type="checkbox"/> BASELINE	<input type="checkbox"/> 1 Hour (+/- 10 Minutes) – Required For Treatment Arm Subjects Only	
<input type="checkbox"/> 24 Hour ± 3 Hours (Blinded)	<input type="checkbox"/> Discharge ± 2 Days (Blinded)	<input type="checkbox"/> Other
Instructions	Scale Definition	Score
<p>8. Sensory: Sensation or grimace to pin prick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas [arms (not hands), legs, trunk, face] as needed to accurately check for hemisensory loss. A score of 2, "severe or total," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will therefore probably score 1 or 0. The patient with brain stem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic score 2. Patients in coma (item 1a=3) are arbitrarily given a 2 on this item.</p>	<p>0 = Normal; no sensory loss. 1 = Mild to moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick but patient is aware he/she is being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.</p>	_____
<p>9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. The patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences. Comprehension is judged from responses here as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in coma (question 1a=3) will arbitrarily score 3 on this item. The examiner must choose a score in the patient with stupor or limited cooperation but a score of 3 should be used only if the patient is mute and follows no one step commands.</p>	<p>0 = No aphasia, normal 1 = Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided material difficult or impossible. For example in conversation about provided materials examiner can identify picture or naming card from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.</p>	_____
<p>10. Dysarthria: If patient is thought to be normal an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barrier to producing speech, may the item be scored "0", and the examiner must clearly write an explanation for not scoring. Do not tell the patient why he/she is being tested.</p>	<p>0 = Normal 1 = Mild to moderate; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. 0 = Intubated or other physical barrier, explain</p>	_____
<p>11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.</p>	<p>0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space.</p>	_____
<p>FOR THIS EVALUATION, WAS THE PATIENT SEDATED?</p>		<p>1 <input type="checkbox"/> YES 2 <input type="checkbox"/> NO</p>
<p>If yes, did the sedation effect the score?</p>		<p>1 <input type="checkbox"/> YES 2 <input type="checkbox"/> NO</p>

Signature (Site Investigator): _____

Date _____
DD / MMM / YYYY (ie - 01 / JAN / 1901)

Print Name (Last, First): _____

Appendix II

Confidential

Appendix II: Glasgow Coma Scale

GLASGOW COMA SCALE	
Points:	Best Eye Response
4	• Eyes opening spontaneously
3	• Eyes opening to speech
2	• Eyes opening in response to pain
1	• No eye opening
	Best Verbal Response
5	• Oriented (Patient responds coherently and appropriately to questions)
4	• Confused (Patient responds to questions coherently but there is some disorientation)
3	• Inappropriate words (Random articulated speech, but no conversational exchange)
2	• Incomprehensible sounds (Moaning but no words)
1	• No verbal response
	Best Motor Response
6	• Obeys commands
5	• Localized to pain (Purposeful movements towards painful stimuli)
4	• Flexion / withdrawal to pain
3	• Abnormal flexion to pain (Decorticate response)
2	• Abnormal extension to pain (Decerebrate response)
1	• No motor response
	GCS Score
_____	Total from above (15 – 3)

Confidential

Appendix III: Modified Rankin Scale

MODIFIED RANKIN SCALE (mRS)	
Total Score (0–6):	
0 = No symptoms at all	
1 = No significant disability despite symptoms; able to carry out all usual duties and activities	
2 = Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance	
3 = Moderate disability; requiring some help, but able to walk without assistance	_____
4 = Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance	
5 = Severe disability; bedridden, incontinent and requiring constant nursing care and attention	
6 = Dead	

Confidential

Appendix IV: Barthel Index

Feeding	0 = Unable 5 = Needs help cutting, spreading butter, or requires modified diet 10 = Independent
Transfer (bed to chair and back)	0 = Unable, no sitting balance 5 = Major help (one or two people; physical), can sit 10 = Minor help (verbal or physical) 15 = Independent
Grooming	0 = Needs help with personal care 5 = Independent face/hair/teeth/shaving (implements provided)
Toilet Use	0 = Dependent 5 = Needs some help, but can do something alone 10 = Independent (on and off, dressing, wiping)
Bathing	0 = Dependent 5 = Independent (or in shower)
Mobility (on level surface)	0 = Immobile or < 50 yards 5 = Wheelchair independent, including corners, > 50 yards 10 = Walks with help of one person (verbal or physical) > 50 yards 15 = Independent (but may use aid, e.g., cane) > 50 yards
Stairs	0 = Unable 5 = Needs help (verbal, physical, carrying aid) 10 = Independent
Dressing	0 = Dependent 5 = Needs help but can do about half unaided 10 = Independent (including buttons, zips, laces, etc.)
Bowels	0 = Incontinent (or needs to be given enemas) 5 = Occasional accident 10 = Continent
Bladder	0 = Incontinent, or catheterized and unable to manage alone 5 = Occasional accident 10 = Independent

Consent if CTA IS NOT Standard of Care
PATIENT CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Spot Sign for Predicting and Treating ICH Growth Study (STOP-IT Study)

Funding Source: NIH / NINDS

Funding Source #: 2P50NS044283-06

INTRODUCTION:

If you are acting as a representative to give consent for another person to participate in this study, “you” throughout this consent form refers to that individual.

Your obligation is to try to determine what the individual would do if competent, or if the subject’s wishes cannot be determined, what you think is in the person’s best interest. If possible, an attempt should be made to obtain permission from the individual. Some persons may resist participating in a research protocol that has been approved by their representatives. Under no circumstances may individuals be forced to participate.

Before you agree to participate in this research study, it is important that you be told the purpose, procedures, benefits, risks, discomforts, and precautions of the research. You should also be told what alternative procedures are available to you if you do not participate in the research study.

Your participation in this research study is entirely voluntary. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from the study at any time without penalty. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time without unfairness to you or your medical care. We do not promise that you will receive any benefits from this study.

This informed consent document is a brief written summary of what your study doctor is telling you. Be sure to ask questions while you read this if there is anything that you do not understand.

WHY IS THIS RESEARCH BEING DONE?

The purposes of this research study are:

1. To find out if a special x-ray test called a computed tomography angiogram (CTA) can help doctors predict which patients that have suffered an intracerebral hemorrhage or breakage of a blood vessel with bleeding into the brain will experience significant growth in the size of the hemorrhage or bleed. Growth or increase in the size of the hemorrhage can cause additional injury to the brain and has been associated with a worse outcome for patients.
2. For patients considered to be at high risk for hemorrhage growth based on the results of the CTA, to compare the effects (good or bad) of the study medication called recombinant activated factor seven (NovoSeven® RT, NiaStase RT®) with a placebo (inactive medication) on reducing intracerebral hemorrhage growth to see which is better. You may or may not receive the study drug.

CT angiography is a common imaging tool used for stroke patients. The use of CTA to predict hemorrhage growth and its potential role in the treatment of intracerebral hemorrhage is experimental. Recombinant activated factor VII (NovoSeven® RT, NiaStase RT®) has been approved by the Food and Drug Administration (FDA) and Health Canada *[Insert for Canadian sites]* for treatment of bleeding in some patients with a type of bleeding disorder in which blood does not clot normally called hemophilia. Recombinant activated factor VII is not FDA approved for treatment of intracerebral hemorrhage and its use for this condition is experimental.

WHY HAVE YOU BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in this research study because you are between the ages of 18 and 80 years of age and you have been diagnosed with a type of stroke called an acute intracerebral hemorrhage or hemorrhagic stroke.

HOW LONG WILL YOU BE IN THE RESEARCH STUDY?

You will be in the research study for approximately 3 months from the time of treatment for your hemorrhagic stroke. After discharge from the hospital, you will receive follow-up telephone calls at 1 month and again at three months by study staff to evaluate your condition at that time.

The researcher may decide to take you off this research study at any time. If you experience any of the side effects described in the “Risks and Discomforts” section or if you become ill during the research, you may have to drop out, even if you would like to continue. In addition, the National Institute of Health (NIH) and National Institute of Neurological Disorders and Stroke (NINDS), the study’s funding source, and the IRB / EC has the right to terminate the study or the Principal Investigator’s participation in the study at any time. Novo Nordisk A/S, the study drug manufacturer has the right to terminate their participation in the study at any time.

You may withdraw from the study at any time. If you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first so that stopping can be done safely. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful to you.

WHO IS CONDUCTING THE RESEARCH STUDY?

This study is funded by the National Institute of Health (NIH) and National Institute of Neurological Disorders and Stroke (NINDS).

The study is directed by and under the medical supervision of *[Insert name of your site PI]*, the researcher at the *[Insert name of your participating institution]*.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

About *[Insert number of subjects projected to be enrolled at your site]* people will take part in this study at *[Insert name of your participating institution]*. Approximately 184 people will take part across the United States and Canada.

WHAT IS INVOLVED IN THE RESEARCH STUDY?

If you take part in this study, you will have the following tests and procedures:

1. You will receive the same standard of care given to all hemorrhagic stroke patients.
2. An intravenous line will be started for the administration of fluids and X-ray dye.
3. An electrocardiogram (EKG), which measures the electrical activity of your heartbeat, will be obtained to assess the functioning of your heart. Access to your prior EKGs, if you have ever had one and if available, may be necessary to compare with this EKG to determine if you are eligible to participate.
4. To determine your initial condition, you will be examined by a physician who will perform a few simple tests to look for problems with your brain (for example, your ability to move your arms and legs, to talk and understand speech and to see in all directions). A CT scan, a special type of brain x-ray, will be done to determine that you have a stroke from a breakage of a blood vessel with bleeding into your brain.
5. Routine blood samples will be drawn as in all stroke patients. The blood samples (about 2 tablespoons) will be taken from a vein in your arm for laboratory testing. No genetic testing will be performed on these samples.
6. You will also receive a CT angiography (CTA), as part of the study, which is a special x-ray of the brain that will check to see if there is a “spot sign” present within the blood or hemorrhage in

your brain tissue. This sign, if present, may predict a higher risk that the hemorrhage in your brain will get bigger in the next few hours. The CTA follows the regular CT scan (or you will be returned to the scanner if the CT scan has already been performed). For this test X-ray dye will be given through an IV in your arm before the test can be performed.

7. If the Spot Sign is present on the CTA:

- You will be “randomized” into one of two study groups described below. Randomization means that you are put into a group completely by chance. It is like flipping a coin. Neither you nor the researcher conducting this study will choose what group you will be in. You have an equal chance of being placed in either group. However, in the event of an emergency, your study doctor will be able to find out what treatment you are receiving.
- You will receive either an active study medication called recombinant activated factor VII, or you will receive a placebo or an inactive study medication through the IV in your arm.
- Additional blood samples (approximately 2 tablespoons total) will also be drawn at baseline, day 1, 2, 3 following treatment and at discharge as part of the study as a safety precaution to monitor your heart and kidney function.
- EKG’s will also be performed as part of the study on day 1, 2 and 3 to continue to assess the functioning of your heart.
- You will have a CT scan (a special x-ray of the brain) between 21 and 27 hours after you receive study drug as a safety check to evaluate the size of your hemorrhage.
- If you were to have any deterioration in your condition during the first 24 hours, or at any other time, a CT scan will be obtained immediately.
- You will be visited throughout your stay in the hospital by a stroke team physician or study nurse to evaluate your current condition.
- After discharge from the hospital, you will have follow-up phone calls at one and three months after your hemorrhagic stroke. During these calls, you will be asked questions about your quality of life at that time.

8. If the Spot Sign is not present on the CTA:

- You will not be randomized to receive any study medication; however you will continue to be part of the study.
- You will continue to receive the standard of care given to all hemorrhagic stroke patients. Part of this care will include a CT scan at between 21 and 27 hours after your CTA as a safety check to evaluate the size of your hemorrhage.
- Blood samples (approximately 1 tablespoon total) will be drawn as part of the study on day 1, 3 and discharge to monitor kidney function and a sample at baseline to monitor your heart function.
- You will be visited throughout your stay in the hospital by a stroke team physician or study nurse to evaluate your current condition.
- After discharge from the hospital, you will have follow-up phone calls at one and three months after your hemorrhagic stroke. During these calls, you will be asked questions about your quality of life at that time.

The following procedures/test articles are considered to be experimental: The use of the CT angiography “spot sign” to identify intracerebral hemorrhage (ICH) patients at high risk of hematoma growth and as a criterion to select patients for randomization to treatment with recombinant activated factor VII or placebo is experimental. Recombinant activated factor VII (NovoSeven® RT; NiaStase RT®) has been approved by the Food and Drug Administration (FDA) and Health Canada [*Insert for Canadian sites*] for treatment of bleeding in some patients with a bleeding disorder called hemophilia. Recombinant activated factor VII is not FDA or Health Canada [*Insert for Canadian sites*] approved for treatment of intracerebral hemorrhage and its use for this condition is experimental.

WHAT ARE THE RISKS AND DISCOMFORTS OF THE RESEARCH STUDY?

You have been told that the study described above may involve the following risks and/or discomforts and safeguards and or precautions to avoid them.

Participation in this study may involve some risk. Like all medications recombinant activated factor VII (rFVIIa) may have side effects if you are randomized to that group. Because rFVIIa helps prevent bleeding, there is a potential risk of life-threatening blood clots developing in arteries which could lead to a heart attack or stroke. Life-threatening blood clots could also develop in veins of the legs or lungs which could cause a serious clot in the lungs called a pulmonary embolism. Based upon this study's inclusion / exclusion criteria and prior studies of rFVIIa for intracerebral hemorrhage, it is anticipated that the risk of heart attack or stroke may be 5% higher in patients receiving the rFVIIa compared to patients receiving the placebo or inactive medication. Prior studies have not shown a difference in the risk of having a blood clot in the legs or lungs between patients receiving rFVIIa or placebo.

As with any drug, there is some chance of allergic reaction. There have been very rare reports (less than 1 event per 10,000 standard doses) of allergic reactions to recombinant activated factor VII including rash, fever, nausea, headache, and vomiting.

Mild allergic reactions to x-ray dye that will be administered through your IV for the CTA may occur in up to 2 to 4% (2 to 4 out of 100) of patients having CT angiography. Severe reactions to x-ray dye occur in 1 person in 1000. You will be monitored for all possible allergic responses during the procedure. There is also a risk of kidney problems or kidney failure after receiving x-ray dye. As with any patient having this procedure, your kidney function and your individual risk factors will be evaluated before and after the CT angiogram. On rare occasions (2 to 6 people out of 1000), X-ray dye may leak out of the vein into the surrounding arm tissue.

The CT scans of your brain done at baseline and at 21 to 27 hours are generally part of standard intracerebral hemorrhage patient care and involve exposure to only a small amount of radiation. The CTA that will be done at baseline as part of the study will also involve exposure to a small amount of radiation. There is a small chance that your skin or hair may be damaged. This has yet to happen as a result of studies for stroke treatments.

Collecting blood samples requires venipuncture (drawing blood from a vein in the forearm or hand). The risk of simple venipuncture commonly includes: discomfort and/or bruising at the site of the puncture, and less commonly, an infection at the site of the puncture, the formation of a small blood clot or swelling of the vein and surrounding tissue and bleeding from the puncture site.

Your skin may be slightly irritated from the sticky electrodes placed on your skin in order to perform the electrocardiogram (EKG).

There also may be risks and discomforts which are not yet known.

WHAT ARE THE REPRODUCTION RISKS?

If you are a woman able to have children, you must not be pregnant or nursing when you enter the study. You also must not become pregnant or cause a pregnancy during the study. This study could seriously harm your fetus if you are pregnant, become pregnant or suspect you caused a pregnancy. If you enter the study and then think you might be pregnant or suspect you have caused a pregnancy you will tell your doctor right away. The study doctor will wish to follow the outcome of your or your partner's pregnancy and condition of any newborn which may be reported to the study funding source. You also understand that there might be risks to a fetus if you become pregnant after the study is done. You should not donate to a sperm bank while in this study. These risks are unknown. If you do want to become pregnant when the study is done, you will talk about it with your

doctor. If you do become pregnant, you will be followed until the birth of the child and the child will be followed until one month of life.

ARE THERE BENEFITS TO TAKING PART IN THE RESEARCH STUDY?

If you agree to take part in this research study, there may not be a direct medical benefit to you. The investigators hope the information gained from this study may increase knowledge about the usefulness of CT angiography for hemorrhagic stroke as well as the safety and effectiveness of the study medication recombinant activated factor VII. This combined information may contribute to making the study medication available to patients with intracerebral hemorrhage.

WHAT OTHER CHOICES FOR CARE ARE THERE?

Instead of being in this research study, you have these options: the usual standard medical care or in certain cases, surgery can be done to remove the blood from your brain.

As there are no proven treatments for intracerebral hemorrhage, there may be other stroke research projects that you might qualify to be in that are being conducted at your hospital.

Ask your physician.

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE AND CONFIDENTIAL?

Every effort will be made to maintain the confidentiality of your study and hospital records relating to your treatment and follow-up care. Agents of the United States Food and Drug Administration, other National regulatory authorities, designates of the National Institute of Health, representatives of the STOP-IT Study Clinical Coordinating and Biostatistical Core Center, and the manufacturer of the study drug NovoSeven® RT / NiaStase RT® will be allowed to inspect and copy sections of your medical and research records related to this study. The data from the study may be published; however, you will not be identified by name. Your identity will remain confidential unless disclosure is required by law.

AVAILABILITY OF INFORMATION

You will receive a copy of this signed consent form.

You will be told about any new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHAT ARE YOUR COSTS TO BE IN THIS STUDY?

Funds are not available to cover the costs of any ongoing medical care. You remain responsible for the cost of non-research related care and items or services needed for reasonable and necessary care arising from study participation, in particular, for the diagnosis or treatment of complications outlined in the Risks and Discomforts section above. Some of the procedures in this study are part of the standard treatment for your condition and would be performed even if you were not in this study. The costs for these procedures will be billed to your insurance, or, if you are uninsured, will be billed to you. You will be responsible for any costs your insurance does not cover. This routine care includes but is not limited to: the initial and 24 hour follow-up CT scans, a chest x-ray, baseline electrocardiogram (EKG), and blood studies done on admission to the hospital as part of acute intracerebral hemorrhage treatment.

You will not be financially responsible or billed for the additional tests, procedures, or other costs (i.e., CT angiography, additional blood tests and EKGs), which are being done solely for the purpose of this study and are not part of your routine care. Novo Nordisk A/S, the drug manufacturer, will provide the study agent recombinant activated factor VII (NovoSeven® RT / NiaStase RT®) free of charge to participants in this study.

WILL YOU BE PAID TO PARTICIPATE IN THIS RESEARCH STUDY?

You will not be paid to participate in this study.

WHAT COMPENSATION IS AVAILABLE IN CASE OF INJURY?

In the event that you become ill or injured from participating in this research study, emergency medical care will be provided to you. *[Insert name of your participating institution]* will decide on a case by case basis whether to reimburse you for your out of pocket health care expenses.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

You may choose either to take part or not to take part in this research study. If you decide to take part, you may decide to leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to you. The investigators will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

If you have questions about the study, you will have a chance to talk to one of the study staff or your regular doctor. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers.

Nothing in this consent form waives any legal rights you may have nor does it release the investigator, the funding source, the institution, or its agents from liability for negligence.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

If you have questions, concerns or complaints about this research study or to report a research-related injury, please contact the researcher *[Insert name of participating PI]* at *[Insert contact number for participating PI]*.

Please call the *[Insert name of your IRB / EC]* at *[Insert phone number of IRB / EC]* if you:

- Think the research has hurt you.
- Have general questions about giving consent or your rights as a research participant in this research study.
- Have questions, concerns, or complaints about the research.
- Cannot reach the research team or you want to talk to someone else.

PATIENT CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Spot Sign for Predicting and Treating ICH Growth Study (STOP-IT Study)

Funding Source: NIH / NINDS

Funding Source #: 2P50NS044283-06

SIGNATURES

I have read or someone has read to me, this Informed Consent Document which describes the purpose and nature of this research. I have had time to review this information and have been encouraged to ask questions. I have received answers to my questions. If I do not participate or if I discontinue my participation, I will not lose any benefits. I will not lose any legal rights if I discontinue. My participation in this research is completely voluntary. I give my consent to participate in this study. I have received (or will receive) a copy of this form for my records and future reference.

Participant

Date

Next of Kin / Legally Authorized Representative
(State Relationship to Participant)

Date

PERSON OBTAINING CONSENT

I have read this form to the participant and/or the subject has read this form. An explanation of the research was given and questions from the subject were solicited and answered to the subject's satisfaction. In my judgment, the subject has demonstrated comprehension of the information.

Signature and Title of Person Obtaining
Consent and Identification of Role in the Study

Date

Consent if CTA IS Standard Care

PATIENT CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Spot Sign for Predicting and Treating ICH Growth Study (STOP-IT Study)

Funding Source: NIH / NINDS

Funding Source #: 2P50NS044283-06

INTRODUCTION:

If you are acting as a representative to give consent for another person to participate in this study, “you” throughout this consent form refers to that individual.

Your obligation is to try to determine what the individual would do if competent, or if the subject’s wishes cannot be determined, what you think is in the person’s best interest. If possible, an attempt should be made to obtain permission from the individual. Some persons may resist participating in a research protocol that has been approved by their representatives. Under no circumstances may individuals be forced to participate.

Before you agree to participate in this research study, it is important that you be told the purpose, procedures, benefits, risks, discomforts, and precautions of the research. You should also be told what alternative procedures are available to you if you do not participate in the research study.

Your participation in this research study is entirely voluntary. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from the study at any time without penalty. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time without unfairness to you or your medical care. We do not promise that you will receive any benefits from this study.

This informed consent document is a brief written summary of what your study doctor is telling you. Be sure to ask questions while you read this if there is anything that you do not understand.

WHY IS THIS RESEARCH BEING DONE?

The purposes of this research study are:

1. To find out if a special x-ray test called a computed tomography angiogram (CTA) can help doctors predict which patients that have suffered an intracerebral hemorrhage or breakage of a blood vessel with bleeding into the brain will experience significant growth in the size of the hemorrhage or bleed. Growth or increase in the size of the hemorrhage can cause additional injury to the brain and has been associated with a worse outcome for patients.
2. For patients considered to be at high risk for hemorrhage growth based on the results of the CTA, to compare the effects (good or bad) of the study medication called recombinant activated factor seven (NovoSeven®) with a placebo (inactive medication) on reducing intracerebral hemorrhage growth to see which is better. You may or may not receive the study drug.

CT angiography is a common imaging tool used for stroke patients. The use of CTA to predict hemorrhage growth and its potential role in the treatment of intracerebral hemorrhage is experimental. Recombinant activated factor VII (NovoSeven®, NiaStase RT®) has been approved by the Food and Drug Administration (FDA) and Health Canada [*Insert for Canadian sites*] for treatment of bleeding in some patients with a type of bleeding disorder in which blood does not clot normally called hemophilia. Recombinant activated factor VII is not FDA or Health Canada [*Insert for Canadian sites*] approved for treatment of intracerebral hemorrhage and its use for this condition is experimental.

WHY HAVE YOU BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in this research study because you are between the ages of 18 and 80 years of age and you have been diagnosed with a type of stroke called an acute intracerebral hemorrhage or hemorrhagic stroke.

HOW LONG WILL YOU BE IN THE RESEARCH STUDY?

You will be in the research study for approximately 3 months from the time of treatment for your hemorrhagic stroke. After discharge from the hospital, you will receive follow-up telephone calls at 1 month and again at three months by study staff to evaluate your condition at that time.

The researcher may decide to take you off this research study at any time. If you experience any of the side effects described in the “Risks and Discomforts” section or if you become ill during the research, you may have to drop out, even if you would like to continue. In addition, the National Institute of Health (NIH) and National Institute of Neurological Disorders and Stroke (NINDS), the study’s funding source, and the IRB / EC has the right to terminate the study or the Principal Investigator’s participation in the study at any time. Novo Nordisk A/S, the study drug manufacturer has the right to terminate their participation in the study at any time.

You may withdraw from the study at any time. If you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first so that stopping can be done safely. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful to you.

WHO IS CONDUCTING THE RESEARCH STUDY?

This study is funded by the National Institute of Health (NIH) and National Institute of Neurological Disorders and Stroke (NINDS).

The study is directed by and under the medical supervision of *[Insert name of your site PI]*, the researcher at the *[Insert name of your participating institution]*.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

About *[Insert number of subjects projected to be enrolled at your site]* people will take part in this study at *[Insert name of your participating institution]*. Approximately 184 people will take part across the United States and Canada.

WHAT IS INVOLVED IN THE RESEARCH STUDY?

If you take part in this study, you will have the following tests and procedures:

1. You will receive the same standard of care given to all hemorrhagic stroke patients.
2. An intravenous line will be started for the administration of fluids and X-ray dye.
3. An electrocardiogram (EKG), which measures the electrical activity of your heartbeat, will be obtained to assess the functioning of your heart. Access to your prior EKGs, if you have ever had one and if available, may be necessary to compare with this EKG to determine if you are eligible to participate.
4. To determine your initial condition, you will be examined by a physician who will perform a few simple tests to look for problems with your brain (for example, your ability to move your arms and legs, to talk and understand speech and to see in all directions).
5. A CT scan and CT angiography (CTA) will be obtained as standard of care for your condition. A CT scan is a special type of brain x-ray that is done to determine that you have a stroke from a breakage of a blood vessel with bleeding into your brain. The CTA is a special x-ray of the brain that will be evaluated to see if there is a “spot sign” present within the blood or hemorrhage in your brain tissue. This sign, if present, may predict a higher risk that the hemorrhage in your brain will get bigger in the next few hours. The CTA follows the regular CT scan. For this test X-ray dye will be given through an IV in your arm before the test is performed.

6. Routine blood samples will be drawn as in all stroke patients. The blood samples (about 2 tablespoons) will be taken from a vein in your arm for laboratory testing. No genetic testing will be performed on these samples.
7. If the Spot Sign is present on the CTA:
 - You will be “randomized” into one of two study groups described below. Randomization means that you are put into a group completely by chance. It is like flipping a coin. Neither you nor the researcher conducting this study will choose what group you will be in. You have an equal chance of being placed in either group. However, in the event of an emergency, your study doctor will be able to find out what treatment you are receiving.
 - You will receive either an active study medication called recombinant activated factor VII, or you will receive a placebo or an inactive study medication through the IV in your arm.
 - Additional blood samples (approximately 2 tablespoons total) will also be drawn at baseline, day 1, 2, 3 following treatment and at discharge as part of the study as a safety precaution to monitor your heart and kidney function.
 - EKG’s will also be performed as part of the study on day 1, 2 and 3 to continue to assess the functioning of your heart.
 - You will have a CT scan (a special x-ray of the brain) between 21 and 27 hours after you receive study drug as a safety check to evaluate the size of your hemorrhage.
 - If you were to have any deterioration in your condition during the first 24 hours, or at any other time, a CT scan will be obtained immediately.
 - You will be visited throughout your stay in the hospital by a stroke team physician or study nurse to evaluate your current condition.
 - After discharge from the hospital, you will have follow-up phone calls at one and three months after your hemorrhagic stroke. During these calls, you will be asked questions about your quality of life at that time.
8. If the Spot Sign is not present on the CTA:
 - You will not be randomized to receive any study medication; however you will continue to be part of the study.
 - You will continue to receive the standard of care given to all hemorrhagic stroke patients. Part of this care will include a CT scan at between 21 and 27 hours after your CTA as a safety check to evaluate the size of your hemorrhage.
 - Blood samples (approximately 1 tablespoon total) will be drawn as part of the study on day 1, 3 and discharge to monitor kidney function and a sample at baseline to monitor your heart function.
 - You will be visited throughout your stay in the hospital by a stroke team physician or study nurse to evaluate your current condition.
 - After discharge from the hospital, you will have follow-up phone calls at one and three months after your hemorrhagic stroke. During these calls, you will be asked questions about your quality of life at that time.

The following procedures/test articles are considered to be experimental: The use of the CT angiography “spot sign” to identify intracerebral hemorrhage (ICH) patients at high risk of hematoma growth and as a criterion to select patients for randomization to treatment with recombinant activated factor VII or placebo is experimental. Recombinant activated factor VII (NovoSeven®) has been approved by the Food and Drug Administration (FDA) and Health Canada [\[Insert for Canadian sites\]](#) for treatment of bleeding in some patients with a bleeding disorder called hemophilia. Recombinant activated factor VII is not FDA or Health Canada [\[Insert for Canadian sites\]](#) approved for treatment of intracerebral hemorrhage and its use for this condition is experimental.

WHAT ARE THE RISKS AND DISCOMFORTS OF THE RESEARCH STUDY?

You have been told that the study described above may involve the following risks and/or discomforts and safeguards and or precautions to avoid them.

Participation in this study may involve some risk. Like all medications recombinant activated factor VII (rFVIIa) may have side effects if you are randomized to that group. Because rFVIIa helps prevent bleeding, there is a potential risk of life-threatening blood clots developing in arteries which could lead to a heart attack or stroke. Life-threatening blood clots could also develop in veins of the legs or lungs which could cause a serious clot in the lungs called a pulmonary embolism. Based upon this study's inclusion / exclusion criteria and prior studies of rFVIIa for intracerebral hemorrhage, it is anticipated that the risk of heart attack or stroke may be 5% higher in patients receiving the rFVIIa compared to patients receiving the placebo or inactive medication. Prior studies have not shown a difference in the risk of having a blood clot in the legs or lungs between patients receiving rFVIIa or placebo.

As with any drug, there is some chance of allergic reaction. There have been very rare reports (less than 1 event per 10,000 standard doses) of allergic reactions to recombinant activated factor VII including rash, fever, nausea, headache, and vomiting.

Mild allergic reactions to x-ray dye that will be administered through your IV for the CTA may occur in up to 2 to 4% (2 to 4 out of 100) of patients having CT angiography. Severe reactions to x-ray dye occur in 1 person in 1000. You will be monitored for all possible allergic responses during the procedure. There is also a risk of kidney problems or kidney failure after receiving x-ray dye. As with any patient having this procedure, your kidney function and your individual risk factors will be evaluated before and after the CT angiogram. On rare occasions (2 to 6 people out of 1000), X-ray dye may leak out of the vein into the surrounding arm tissue.

The CT scans of your brain done at baseline and at 21 to 27 hours are generally part of standard intracerebral hemorrhage (ICH) patient care and involve exposure to only a small amount of radiation. The CTA that will be done at baseline as part of standard ICH patient care will also involve exposure to a small amount of radiation. There is a small chance that your skin or hair may be damaged. This has yet to happen as a result of studies for stroke treatments.

Collecting blood samples requires venipuncture (drawing blood from a vein in the forearm or hand). The risk of simple venipuncture commonly includes: discomfort and/or bruising at the site of the puncture, and less commonly, an infection at the site of the puncture, the formation of a small blood clot or swelling of the vein and surrounding tissue and bleeding from the puncture site.

Your skin may be slightly irritated from the sticky electrodes placed on your skin in order to perform the electrocardiogram (EKG).

There also may be risks and discomforts which are not yet known.

WHAT ARE THE REPRODUCTION RISKS?

If you are a woman able to have children, you must not be pregnant or nursing when you enter the study. You also must not become pregnant or cause a pregnancy during the study. This study could seriously harm your fetus if you are pregnant, become pregnant or suspect you caused a pregnancy. If you enter the study and then think you might be pregnant or suspect you have caused a pregnancy you will tell your doctor right away. The study doctor will wish to follow the outcome of your or your partner's pregnancy and condition of any newborn which may be reported to the study funding source. You also understand that there might be risks to a fetus if you become pregnant after the study is done. You should not donate to a sperm bank while in this study. These risks are unknown. If you do want to become pregnant when the study is done, you will talk about it with your

doctor. If you do become pregnant, you will be followed until the birth of the child and the child will be followed until one month of life.

ARE THERE BENEFITS TO TAKING PART IN THE RESEARCH STUDY?

If you agree to take part in this research study, there may not be a direct medical benefit to you. The investigators hope the information gained from this study may increase knowledge about the usefulness of CT angiography for hemorrhagic stroke as well as the safety and effectiveness of the study medication recombinant activated factor VII. This combined information may contribute to making the study medication available to patients with intracerebral hemorrhage.

WHAT OTHER CHOICES FOR CARE ARE THERE?

Instead of being in this research study, you have these options: the usual standard medical care or in certain cases, surgery can be done to remove the blood from your brain.

As there are no proven treatments for intracerebral hemorrhage, there may be other stroke research projects that you might qualify to be in that are being conducted at your hospital.

Ask your physician.

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE AND CONFIDENTIAL?

Every effort will be made to maintain the confidentiality of your study and hospital records relating to your treatment and follow-up care. Agents of the United States Food and Drug Administration, other National regulatory authorities, designates of the National Institute of Health, representatives of the STOP-IT Study Clinical Coordinating and Biostatistical Core Center, and the manufacturer of the study drug NovoSeven® RT / NiaStase RT® will be allowed to inspect and copy sections of your medical and research records related to this study. The data from the study may be published; however, you will not be identified by name. Your identity will remain confidential unless disclosure is required by law.

AVAILABILITY OF INFORMATION

You will receive a copy of this signed consent form.

You will be told about any new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHAT ARE YOUR COSTS TO BE IN THIS STUDY?

Funds are not available to cover the costs of any ongoing medical care. You remain responsible for the cost of non-research related care and items or services needed for reasonable and necessary care arising from study participation, in particular, for the diagnosis or treatment of complications outlined in the Risks and Discomforts section above. Some of the procedures in this study are part of the standard treatment for your condition and would be performed even if you were not in this study. The costs for these procedures will be billed to your insurance, or, if you are uninsured, will be billed to you. You will be responsible for any costs your insurance does not cover. This routine care includes but is not limited to: the initial and 24 hour follow-up CT scans, CT angiography, a chest x-ray, baseline electrocardiogram (EKG), and blood studies done on admission to the hospital as part of acute intracerebral hemorrhage treatment.

You will not be financially responsible or billed for the additional tests, procedures, or other costs (i.e., additional blood tests and EKGs), which are being done solely for the purpose of this study and are not part of your routine care. Novo Nordisk A/S, the drug manufacturer, will provide the study agent recombinant activated factor VII (NovoSeven® RT / NiaStase RT®) free of charge to participants in this study.

WILL YOU BE PAID TO PARTICIPATE IN THIS RESEARCH STUDY?

You will not be paid to participate in this study.

WHAT COMPENSATION IS AVAILABLE IN CASE OF INJURY?

In the event that you become ill or injured from participating in this research study, emergency medical care will be provided to you. *[Insert name of your participating institution]* will decide on a case by case basis whether to reimburse you for your out of pocket health care expenses.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

You may choose either to take part or not to take part in this research study. If you decide to take part, you may decide to leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to you. The investigators will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

If you have questions about the study, you will have a chance to talk to one of the study staff or your regular doctor. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers.

Nothing in this consent form waives any legal rights you may have nor does it release the investigator, the funding source, the institution, or its agents from liability for negligence.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

If you have questions, concerns or complaints about this research study or to report a research-related injury, please contact the researcher *[Insert name of participating PI]* at *[Insert contact number for participating PI]*.

Please call the *[Insert name of your IRB / EC]* at *[Insert phone number of IRB / EC]* if you:

- Think the research has hurt you.
- Have general questions about giving consent or your rights as a research participant in this research study.
- Have questions, concerns, or complaints about the research.
- Cannot reach the research team or you want to talk to someone else.

PATIENT CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Spot Sign for Predicting and Treating ICH Growth Study (STOP-IT Study)

Funding Source: NIH / NINDS

Funding Source #: 2P50NS044283-06

SIGNATURES

I have read or someone has read to me, this Informed Consent Document which describes the purpose and nature of this research. I have had time to review this information and have been encouraged to ask questions. I have received answers to my questions. If I do not participate or if I discontinue my participation, I will not lose any benefits. I will not lose any legal rights if I discontinue. My participation in this research is completely voluntary. I give my consent to participate in this study. I have received (or will receive) a copy of this form for my records and future reference.

Participant

Date

Next of Kin / Legally Authorized Representative
(State Relationship to Participant)

Date

PERSON OBTAINING CONSENT

I have read this form to the participant and/or the subject has read this form. An explanation of the research was given and questions from the subject were solicited and answered to the subject's satisfaction. In my judgment, the subject has demonstrated comprehension of the information.

Signature and Title of Person Obtaining
Consent and Identification of Role in the Study

Date

STOP-IT STUDY

THE **SPOT** SIGN FOR PREDICTING AND TREATING ICH GROWTH TRIAL CLINICAL PROTOCOL

Phase II, randomized, multicenter, double-blind, placebo-controlled trial comparing rFVIIa to placebo for treatment of subjects with acute ICH and contrast extravasation (the spot sign) identified on CTA.

Principal Investigator:

Matthew L. Flaherty, MD, Neurology – University of Cincinnati

Co-Principal Investigator:

Edward Jauch, MD, MS, Emergency Medicine – South Carolina REACH Stroke Program

Supported By:

**National Institute of Health / National Neurological Disorders and Stroke
2P50NS044283-06**

Clinical Trial Product Provided By:

Novo Nordisk

Sponsor of IND:

Matthew L. Flaherty, MD – Number Pending

Original Proposal Submission:	17-December-2007
Revised Proposal Submission:	11-March-2008
Revised Proposal Submission:	07-July 7-2008
Revised Proposal Submission:	18-September-2008 (Post Pre-IND Mtg.)

TABLE OF CONTENTS

ACRONYMS	4
1.0 Introduction	5
2.0 Study Objectives	5
3.0 Background and Significance	6
3.1 Hematoma Growth in the Acute Phase of ICH.....	6
3.2 Contrast Extravasation as a Predictor of Hematoma Growth.....	6-7
3.3 Utility of CTA for Evaluating ICH	7
3.3.1 CTA can be Performed Quickly and Easily	7
3.3.2 CTA is a Diagnostic Tool that can Identify Secondary Causes of ICH.....	7
3.3.3 CTA is a Safe Procedure.....	8
4.0 Supporting Data	8
4.1 Contrast Extravasation as a Predictor of Hematoma Growth.....	8
4.2 Prior Experience with Recombinant Activated Factor VII.....	8-9
4.2.1 Efficacy of Recombinant Activated Factor VII	9
4.2.2 Safety of Recombinant Activated Factor VII.....	10
4.3 Conclusions from Studies to Date	10-11
5.0 Research Design and Methods	11
5.1 Overview	11
5.2 STOP-IT Study Design.....	11
5.2.1 Patient Flow.....	11-12
5.2.2 Inclusion Criteria.....	13
5.2.3 Exclusion Criteria	13
5.3 Dose Selection for Recombinant Activated Factor VII	14
5.4 Drug Storage and Administration	14
5.5 CT and CTA Methodology	14
5.5.1 CT and CTA Acquisition	14
5.5.2 CTA and Standard Care for Acute ICH	14
5.6 Imaging Analysis	15
5.6.1 Image Data Management.....	15
5.6.2 Volume Measurements	15-16
6.0 Measurement of Outcomes	16
6.1 Primary Outcome: Test Performance.....	16
6.2 Primary Outcome: Clinical Parameters	16
6.3 Primary Safety Outcomes	16
6.3.1 Definitions.....	16
6.3.2 Primary Safety Measures	16-17
6.4 Recruitment Procedure and Technique.....	18
6.5 Contingency Plan for Lags in Recruitment	18
6.6 Procedure for Subject Screening	18
6.7 Competing Ongoing Clinical Trials	18
6.8 Randomization and Blinding.....	18-19
6.9 Drug Distribution and Pharmacy Support.....	19
7.0 Subject Medical Management	19
8.0 Medical and Laboratory Data Collected	19
8.1 Schedule of Events	20-21
8.2 Monitoring for Adverse Events and Assessment of Safety.....	22-23
8.3 Stopping Rules for Safety Concerns.....	23
9.0 Statistical Considerations	24
9.1 Overview and Patient Entry	24
9.2 Data Forms.....	24
9.3 Manual of Operations	25

9.4	Database Development and Security	25-26
9.5	Data Management, Monitoring and Quality Assurance	26-27
9.6	Sample Size Calculation	27-30
9.7	General Analysis Plan	30
	9.7.1 Objective #1	30-31
	9.7.2 Objective #2	31
	9.7.3 Objective #3	32
9.8	Potential Collaborations and Pooled Analysis	32
10.0	Study Timeline	32-33
11.0	Handling of Missing Data	33
12.0	Trial Administrative Structure	33
	12.1 National Institute of Neurological Disorders and Stroke (NINDS)	33-34
	Data and Safety Monitoring Board (DSMB)	
	12.2 External Medical Monitor	34
	12.3 Biostatistical Core and Data Management	34
	12.4 Coordinating Clinical Center	34-35
	12.5 Imaging Center	35
	12.6 Participating Centers	35-36
	12.7 Steering Committee	36
	12.8 Drug Distribution and Pharmacy Support	36
	12.9 Novo Nordisk	36
	12.10 Investigational New Drug (IND) Application	36
	12.11 National Institute of Neurological Disorders and Stroke	36
13.0	Human Subjects	36-37
13.1	Institutional Review Board (IRB)/Ethics Committee (EC) & Informed Consent	37
13.2	HIPAA/PIPEDA	37
13.3	Specimens	37
13.4	Recruitment of Minorities and Women	38
13.5	Inclusion of Children	38
13.6	Potential Risks and Benefits	38-39
13.7	Subject Confidentiality	39
14.0	Vertebrate Animals	39
15.0	Select Agent Research	39
16.0	Disclosure of Data	39
17.0	Data Sharing Plan	39-40
18.0	References	41-43
19.0	Appendices	44-63
	Appendix I: National Institute of Health Stroke Scale (NIHSS)	
	Appendix II: Glasgow Coma Scale (GCS)	
	Appendix III: Modified Rankin Scale (mRS)	
	Appendix VI: Barthel Index (BI)	
	Appendix V: Sample Informed Consent Form (For sites where CTA <u>IS NOT</u> standard of care)	
	Appendix VI: Sample Informed Consent Form (For sites where CTA <u>IS</u> standard of care)	

Acronyms

AE	Adverse Event
BI	Barthel Index
BMI	Biomedical Informatics
BSC	Biostatistical Core
CBC	Complete Blood Count
CCC	Clinical Coordinating Center
CCHMC	Cincinnati Children's Hospital Medical Center
CIN	Contrast-induced Nephropathy
CRF	Case Report Form
CT	Computed Tomography
CTA	Computed Tomography Angiography
DMC	Data Management Center
DSA	Digital Subtraction Angiography
DSMB	Data Safety and Monitoring Board
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
ED	Emergency Department
FAST	rFVIIa in Acute Hemorrhagic Stroke Treatment
FDA	Food and Drug Administration
GCS	Glasgow Coma Scale
GERFHS	Genetic and Environmental Risk Factors for Hemorrhagic Stroke
GFR	Glomerular Filtration Rate
GPIIa/IIIb	Platelet Receptor Inhibitors
HIPAA	Health Insurance Portability and Accountability Act
HU	Hounsfield Unit
ICH	Intracerebral Hemorrhage
IDS	Investigational Drug Service
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IS	Ischemic Stroke
ITK	Insight segmentation and Registration Tool Kit
IVH	Intraventricular Hemorrhage
MI	Myocardial Infarction
MOP	Manual of Operating Procedures
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NIH	National Institute of Health
NIHSS	National Institute of Health Stroke Scale
NINDS	National Institute of Neurological Disease and Stroke
PACS	Picture Archiving and Communication System
PE	Pulmonary Embolism
PHI	Personal Health Information
PI	Principal Investigator
PIPEDA	Personal Information, Privacy and Electronics Documents Act
PTT	Partial Thromboplastin Time
RCT	Randomized Controlled Trial
rFVIIa	Recombinant Activated Factor VII
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SID	Subject Identification Number
SPORTRIAS	Specialized Program of Translational Research in Acute Stroke
SPOTLIGHT	Spot Sign Selection of ICH to Guide Hemostatic Therapy
STOP-IT	The Spot Sign for Predicting and Treating ICH Growth Study
V/Q Scan	Ventilation/Perfusion Scan
XML	Extensible Markup Language

1.0 INTRODUCTION

Intracerebral hemorrhage (ICH) is conservatively estimated to affect 67,000 persons in the United States and 5,000 persons in Canada annually and is associated with a 40-50% case-fatality rate.^{1, 2} There are no proven treatments for ICH. The demonstration that hematoma growth after ictus is common and associated with neurological decline has spurred research into early hemostatic therapy to potentially improve patient outcomes.³⁻⁵

Recombinant activated factor VII (rFVIIa) was proven to significantly reduce hematoma growth when administered within four hours of symptom onset in two placebo-controlled, blinded, randomized clinical trials.^{6, 7} While clinical outcomes were improved in a phase IIb trial, they were not improved in a phase III trial of this drug.^{6, 7} Because rFVIIa works to stop bleeding but should not otherwise affect the natural history of ICH, only patients destined to have hematoma growth will benefit from this therapy. Ideally, clinicians will be able to identify patients who will have significant hematoma growth regardless of their time of presentation and administer hemostatic therapy to this group.

CT angiography (CTA) is a widely available, fast, non-invasive tool that has shown promise for predicting hematoma growth.^{8, 9} In two recent retrospective case series patients with contrast extravasation within their hematomas (**the spot sign**) had greater risk of subsequent hematoma growth than patients without extravasation.^{8, 9}

The next step in this treatment paradigm is to confirm the ability of CTA to predict hematoma growth and to explore the role CTA may play in the administration of hemostatic therapy. Patients presenting within five hours of ICH onset will be eligible for enrollment into one of two study arms in this multicenter phase II study. Patients who have a spot sign on CTA will be randomized to treatment with either rFVIIa or placebo. Patients without a spot sign will be enrolled in a prospective observational arm and their data will be compared to spot-positive patients treated with placebo to determine the sensitivity and specificity of the CTA spot sign for hematoma growth.

2.0 STUDY OBJECTIVES

- Determine the sensitivity and specificity of the CTA spot sign for hematoma growth.
 - Working hypothesis: For patients scanned within five hours of stroke onset, the spot sign will have a high sensitivity and specificity for hematoma growth.
- Determine the feasibility of using CTA to identify ICH patients at high risk of hematoma growth and to select patients for randomization to treatment with rFVIIa or placebo.
 - Working Hypothesis #1: Site investigators will determine the presence or absence of a spot sign in the acute setting with a high degree of accuracy as compared to blinded over-read by a study neuroradiologist.
 - Working Hypothesis #2: Use of CTA to identify candidates for randomization to rFVIIa versus placebo can be done in a time-efficient manner
- Randomize ICH patients who present within five hours of symptom onset and have a spot sign to treatment with rFVIIa versus placebo, in order to (a) determine if rFVIIa is effective at reducing hematoma growth among patients with a spot sign and (b) provide preliminary efficacy data for this treatment paradigm.
 - Working Hypothesis: Spot-positive patients treated with rFVIIa will have less hematoma growth than spot-positive patients treated with placebo.

3.0 BACKGROUND AND SIGNIFICANCE

Intracerebral hemorrhage is a devastating form of stroke.² While ICH was formerly an area of therapeutic nihilism, recent investigations into the surgical and medical management of ICH prove that large-scale clinical trials for this condition are feasible and provide hope that new treatments may improve patient outcomes.^{6, 10} Predictors of outcome after ICH include patient age, Glasgow Coma Scale (GCS) score at presentation, hemorrhage location, anticoagulant use, initial hematoma size, the presence of intraventricular hemorrhage (IVH) and hydrocephalus, and hematoma growth.^{2, 4, 11} Because the majority of deaths from ICH occur within several days of ictus, interventions for improving outcomes must occur early in a patient's clinical course.¹² Among the potentially modifiable determinants of ICH outcome, hematoma growth is a particularly attractive target for intervention. Hematoma growth occurs in the early phase of ICH and is clinically recognized by neurological deterioration, sometimes leading to death.^{3, 4} If hematoma growth can be prevented neurological outcomes may be improved. However, while hematoma growth frequently complicates ICH, until recently little progress was made in identifying markers that can reliably predict this process.

3.1 Hematoma Growth in the Acute Phase of ICH

Hematoma growth in the first few hours after ICH onset is associated with early neurological deterioration and increased mortality.^{3, 4, 13} A recent analysis of ICH outcome found that for each 10% increase in ICH growth the hazard ratio for death was increased by 5% and patients were 16% more likely to have an increase of one point in their modified Rankin Scale (mRS) score at follow-up.⁴ Hematoma growth usually implies active bleeding into the hemorrhage bed. Earlier assumptions that bleeding was self-limited and that neurological decline was invariably due to secondary mass effect and cerebral edema have proven incorrect.⁴ It is estimated that significant early hematoma growth (generally defined as > 33% volume increase) occurs in 18% to 38% of ICH patients scanned within three hours of onset.^{3, 4, 14, 15} Between three and six hours from onset 8-16% of patients show significant hematoma enlargement, implying that this is a time-dependent process.¹⁴⁻¹⁶ Potential predictors of hematoma growth include thalamic location of hemorrhage, larger initial hemorrhage, prior history of stroke, liver disease, hyperglycemia, hypertension, seizures, thrombocytopenia, alcohol use, depressed level of consciousness, irregular hematoma shape, reduced fibrinogen levels and diabetes mellitus.^{6, 17, 18} The dynamic nature of ICH enlargement during the first several hours poses a challenge and an opportunity for intervention; acute hematoma enlargement could be used as a surrogate outcome in clinical trials and to monitor therapy. No reliable radiological variable that predicts hematoma growth has yet been *prospectively* identified.

Table 1. Literature review of the frequency of hematoma growth.

Interval from onset to CT	Brott (1997) ³ (n=103) Prospective	Davis (2006) ⁴ (n=115) Prospective	Fujii (1994) ^{15, 16} (n=627) Retrospective	Fujitsu(1990) ¹⁹ (n=107) Retrospective	Kazui (1996) ¹⁴ (n=204) Retrospective
0 – 3.0 hrs	38% (39/103)	28% (32/115)	18% (78/422)	NA	36% (27/74)
3.1 – 6.0 hrs	NA	NA	8% (8/97)	NA	16% (7/45)
0 – 6.0 hrs	NA	NA	17% (86/519)	21% (23/107)	29% (34/119)
6.1 – 24.0 hrs	NA	NA	2% (2/108)	NA	10% (7/67)

NA = not available.

3.2 Contrast Extravasation as a Predictor of Hematoma Growth

Vascular imaging has revolutionized stroke medicine in the last decade. Patients with ICH often have vascular imaging to exclude a vascular abnormality (arteriovenous malformation, arteriovenous fistula, aneurysm) as a cause of the hemorrhage. Since hematoma growth largely occurs in the hyperacute phase of ICH, vascular imaging may be beneficial in identifying surrogates for active,

ongoing bleeding. One important surrogate for identifying ongoing bleeding is contrast extravasation seen on CTA, MRI, or DSA.

Previous case reports and retrospective studies suggest that contrast extravasation as seen on CT angiography, MRI and DSA in patients with hypertensive ICH correlates with hematoma growth and indicates ongoing bleeding.²⁰⁻²⁴ In the first retrospective case series, Murai showed that contrast extravasation on MRI is an indicator of continued hemorrhage in patients with acute ICH.²⁵ In this study, 108 patients with acute hypertensive ICH underwent imaging with enhanced CT, gadolinium-enhanced MR, and conventional cerebral angiography within six hours of hemorrhage onset. A repeat CT scan was obtained within 48 hours to evaluate enlargement of the hematoma. Evidence of contrast extravasation was seen in 39 patients on MRI and cerebral angiography showed extravasation in 17 patients. There was a significant correlation between extravasation on cerebral angiography and MRI and also with hematoma growth on follow-up CT scan. Yamaguchi found that 42% of patients with primary ICH had contrast extravasation during cerebral angiography performed within five hours of symptom onset.²⁶ Becker and colleagues were the first to show that extravasation of radiographic contrast on CTA was an independent predictor of hospital fatality in a large retrospective study.²⁴ Out of 113 patients studied, contrast extravasation was seen in 46% and the presence of contrast extravasation was associated with increased mortality (63.5%) compared to patients without extravasation (16.4%). The overall mortality rate from ICH was 38% consistent with other studies. Limitations of this study were its retrospective nature, small sample size, no clear protocol or indications for CTA in ICH, and lack of functional outcomes. This study concluded that extravasation of radiographic contrast on CTA is a surrogate for ongoing bleeding.

3.3 Utility of CTA for Evaluating ICH

3.3.1 CTA can be Performed Quickly and Easily

CTA can be performed quickly and easily in any hospital with a CT scanner. CTA images require the injection of iodinated contrast media and can be obtained immediately following the routine non-enhanced CT head scan. The scan time is approximately two minutes. No post-processing of images is required to identify the spot sign. The presence or absence of the spot sign can be determined immediately, often before the patient is taken off the CT scan table. Therefore, use of the CTA spot sign is ideally suited for rapid decision-making and should not introduce significant delay to treatment.

3.3.2 CTA is a Diagnostic Tool that Can Identify Secondary Causes of ICH

CTA is a non-invasive test that provides valuable information about the vascular anatomy of the brain. In many circumstances it has replaced traditional (invasive) catheter-based cerebral angiography as the method of choice for screening for a variety of vascular anomalies. In addition to potentially identifying patients at risk of hematoma expansion via the spot sign, CTA can provide valuable diagnostic information regarding potential secondary causes of hemorrhage, such as intracranial aneurysms and arteriovenous malformations. Little published data exists on the role of CTA in the context of ICH. Studies of catheter angiography for the detection of secondary causes of ICH are limited by selection bias, however indications for catheter angiography in the setting of ICH have traditionally included subarachnoid hemorrhage, abnormal calcifications, obvious vascular abnormalities, and blood in unusual locations, such as the Sylvian fissure.²⁷ The risk of a secondary cause of ICH is highest in young patients with lobar hemorrhage and patients without hypertension. The performance of CTA as compared to traditional catheter angiography for the detection of vascular anomalies associated with ICH has recently been assessed in a study which found the sensitivity, specificity and accuracy of CTA were 89%, 92% and 91% respectively (personal communication, Dr. Richard Aviv, manuscript under review). Subjects with a known or suspected vascular anomaly as a cause of their ICH will be excluded from the STOP-IT study.

3.3.3 CTA is a Safe Procedure

The major concerns for CTA are iodinated contrast media use in the acute setting where renal function or contrast allergy history may be unknown. Contrast-induced nephropathy (CIN) is often defined as a > 25% increase in serum creatinine occurring within several days of contrast administration, without an alternative explanation.²⁸ Chronic renal impairment is the main risk factor for the development of CIN.²⁸ Patients with a normal glomerular filtration rate (GFR) are at extremely low risk of CIN. If the GFR is 30-60 ml/min there is a low to moderate risk of CIN.²⁸ Recent guidelines recommended that where possible patients should be screened for risk factors associated with acute or chronic renal impairment. The guidelines acknowledge that this may not be possible in the acute setting.^{28, 29} In such situations where delay may negatively impact patient outcome, the absence of risk factors effectively eliminates the probability of a given patient having renal impairment.²⁹ A recent study of CTA in patients with acute stroke (ischemic or hemorrhagic) demonstrated a very low incidence of contrast-induced nephropathy (3%) and no patients required dialysis.³⁰ If a risk factor does exist then empiric precautions such as rehydration and choice of contrast agent and osmolarity is suggested. Contrast extravasation into a limb due to failure of intravenous access occurs on rare occasions (0.25-0.6% of contrast-enhanced radiological studies).³¹ Contrast extravasation may result in local tissue damage.³² The radiation dose delivered by a CTA is slightly more than a non-contrast CT study when centered on the intracranial vessels (1.9 mSV vs. 1.7 mSV).³³

4.0 SUPPORTING DATA

4.1 Contrast Extravasation as a Predictor of Hematoma Growth

Two recent studies have spurred further interest in the use of CTA for prediction of ICH growth. In a retrospective study reported by Goldstein, CTAs were reviewed for 104 patients with ICH.⁹ A significant number of patients received their CTA > 24 hour after onset. Contrast was present within the hematoma in 56% of patients, and this finding was the single most powerful predictor of subsequent hematoma expansion. Contrast extravasation was present in 92% of patients who developed hematoma expansion, compared with 51% of those who did not (p=0.006). The sensitivity and specificity of extravasation for predicting hematoma expansion were 93% and 50%, yielding a low positive predictive value (24%) but a striking negative predictive value (98%). The study confirmed a trend towards earlier time to presentation in patients both with contrast extravasation and hematoma expansion. It also confirmed Becker's finding an increased rate of in-hospital mortality in subjects with extravasation (p=0.04). Multivariable analysis demonstrated an independent effect of contrast extravasation on hematoma expansion (OR 18, 95% CI 2.1-162, p=0.009).

A retrospective study coauthored by Drs. Aviv and Gladstone analyzed CTAs from 39 ICH patients scanned within three hours of onset.⁸ Contrast leakage within the hematoma (the spot sign) was identified in 33% of patients and had a sensitivity of 91% and a specificity of 89% for hematoma growth of > 30% or 6 cc. The positive and negative predictive values for growth in this study were 77% and 96%. Hematoma growth was more common in patients with a spot sign than those without (p<0.001). In multiple regression analysis the spot sign (p<0.001) and anticoagulant use (p=0.02) were associated with hematoma enlargement.

4.2 Prior Experience with Recombinant Activated Factor VII

Coagulation factor VII is a naturally occurring initiator of hemostasis; normally, only 1% of factor VII circulates in its active form. Recombinant activated factor VII (rFVIIa, NovoSeven®; Novo Nordisk, Bagsvaerd, Denmark) was developed for the treatment of spontaneous and surgical bleeding in patients with hemophilia A or B and inhibitors to factors VIII or IX, respectively.³⁴ rFVIIa binds to the surface of activated platelets where it generates activated Factor X allowing partial restoration of platelet surface thrombin generation.³⁵ Through its action of enhancing local hemostasis after binding to exposed tissue factors, rFVIIa has been shown to be an effective initiator of hemostasis in patients with normal coagulation systems.³⁴⁻³⁶ Moreover, its efficacy has been reported in promoting

hemostasis in central nervous system bleeding in patients with hemophilia.³⁷ The relatively low frequency of systemic activation of coagulation associated with rFVIIa use, together with its rapid action at the site of bleeding and short half-life of 2.5 hours, suggest that rFVIIa may be an ideal agent for use during the earliest stages of ICH.³⁸

4.2.1 Efficacy of Recombinant Activated Factor VII

The effectiveness of rFVIIa for acute ICH has been tested in one dose-escalation trial, one phase IIb trial, and one phase III trial.^{6, 7, 39} Conclusions regarding efficacy of rFVIIa for ICH can be drawn from the phase IIb and phase III trials of this drug. In the phase IIb trial 399 patients (61% male, mean age 66 years) were randomized to treatment within four hours of symptom onset with placebo (n=96) or 40 µg/kg (n=108), 80 µg/kg (n=92), or 160 µg/kg (n=103) of rFVIIa.⁶ Mean ICH volume at baseline was 24 cc, mean interval from symptom onset to baseline CT scan was 114 ± 35 minutes, and mean onset-to-needle time was 167 ± 32 minutes. The mean percentage increase in ICH volume was 29% following placebo treatment, compared with 16%, 14% and 11% in the rFVIIa 40, 80 and 160 µg/kg groups, respectively (p=0.01 for the comparison of the three rFVIIa groups with the placebo group). Mean absolute growth in ICH volume was reduced by 3.3 cc, 4.5 cc and 5.8 cc with the 40, 80, and 160 µg/kg doses of rFVIIa, respectively (p=0.01, rFVIIa combined versus placebo). Notably, the reductions in ICH growth presented are mean values. While 74% of placebo patients had some hematoma growth, only 28% had hematoma growth of > 33%.⁴ Thus, the mean reduction in hematoma growth is lowered considerably by patients who had < 33% hematoma enlargement. If patients destined to have significant hematoma growth can be reliably identified and other patients excluded from treatment, the difference in hematoma growth between placebo and treatment groups is expected to be significantly magnified, and it follows biologically that differences in clinical outcomes should also be magnified. The effect of time to treatment on hematoma growth in the phase IIb trial illustrates this point. Because hematoma growth is most likely within three hours of treatment, the treatment effect is magnified within this window. In the subset of patients who were treated within three hours (n=269), the mean percentage increase in ICH volume was 34% in the placebo group compared with 13% in the rFVIIa groups (p=0.004). The absolute increase in ICH volume in this subset was 10.7 cc for placebo patients and 4.4 cc for rFVIIa patients (p=0.009). There was essentially no difference in mean percent ICH growth between rFVIIa and placebo among patients treated after three hours of onset. The randomized trials of rFVIIa show that treating all ICH patients presenting 3-6 hours after stroke onset with hemostatic therapy is unlikely to produce clinical benefit. In order to treat ICH patients beyond three hours, it is essential that we identify those at highest risk of growth.

The phase III trial of rFVIIa randomized patients to treatment within four hours of symptom onset to placebo (n= 268), rFVIIa 20 µg/kg (n= 276), or rFVIIa 80 µg/kg (n=297).⁷ The biologic effect of rFVIIa on hematoma growth was verified. Patients in the placebo group had a 26% mean increase in hematoma volume compared to 18% in the 20 µg/kg group and 11% in the 80 µg/kg group (p<0.001 for the comparison of placebo and rFVIIa 80 µg/kg). Patients in the rFVIIa 80 µg/kg group had a mean change in ICH volume of 3.8 cc less than placebo patients (p=0.009).⁷ The clinical trial endpoints were discordant in the phase IIb and phase III trials of rFVIIa. In the phase IIb trial, at three months 29% of the placebo treated patients were dead compared to 18% of rFVIIa treated patients, a relative mortality reduction of 38% (p=0.02). Three month scores on the mRS, Barthel Index, and NIHSS all favored rFVIIa treatment. However, in the phase III trial no statistical differences were seen in mortality or functional outcomes as measured by the mRS or Barthel Index at three months. It is not clear why the clinical outcomes of these trials differed but there were important imbalances in baseline patient characteristics.⁷ Placebo subjects in the phase IIb trial were also more likely to have a three-month mRS of 5-6 than placebo subjects in the phase III trial (45% vs. 24%).⁷

4.2.2 Safety of Recombinant Activated Factor VII

The safety profile of rFVIIa for the treatment of acute ICH has been reasonably established by the studies described above. To date, over 800 patients with acute ICH have received rFVIIa in the setting of a blinded, randomized clinical trial. The only safety concern identified for rFVIIa to date is its prothrombotic potential. Because rFVIIa activates the coagulation system, there is concern it may cause an excess of venous (deep venous thrombosis, pulmonary embolism) or arterial (myocardial infarction, ischemic stroke) serious adverse events (SAEs). In the phase IIb trial there was no difference in the overall rate of thromboembolic SAEs between groups (7% in the rFVIIa groups vs. 2% in the placebo group, $p=0.12$) but there was an excess of arterial SAEs in the rFVIIa groups (5% vs. 0%, $p=0.01$).⁶ These SAEs included seven myocardial ischemic events and nine cases of cerebral infarction that occurred within four days of dosing. In the phase III trial there was no difference in the rates of venous thromboembolic SAEs but patients in the 80 $\mu\text{g}/\text{kg}$ rFVIIa had a 4% excess of arterial thromboembolic SAEs compared to placebo ($p=0.04$).⁷ Most of the cardiac events were small troponin elevations and non-ST elevation myocardial infarctions with good clinical recovery.^{6, 7} Rates of ST-elevation myocardial infarction in the phase III trial were 1.5% in the placebo group, 0.4% in the 20 $\mu\text{g}/\text{kg}$ group, and 2.0% in the 80 $\mu\text{g}/\text{kg}$ group. CT evidence of acute ischemic stroke was seen in 2.2% of placebo patients, 3.3% of 20 $\mu\text{g}/\text{kg}$ patients, and 4.7% of 80 $\mu\text{g}/\text{kg}$ patients.⁷ Event rates are summarized in Table 2.

Table 2. Rates of thromboembolic serious adverse events in rFVIIa trials

Trial	Dose	Patients (n)	Arterial thromboembolic serious adverse events (%)	Venous thromboembolic serious adverse events (%)
Phase IIb ⁶	Placebo	96	0 (0)	2 (2)
	rFVIIa 40 $\mu\text{g}/\text{kg}$	108	6 (6)	1 (1)
	rFVIIa 80 $\mu\text{g}/\text{kg}$	92	2 (2)	2 (2)
	rFVIIa 160 $\mu\text{g}/\text{kg}$	103	8 (8)	2 (2)
	All rFVIIa doses	303	16 (5)	5 (2)
Phase III ⁷	Placebo	268*	11 (4)	11 (4)
	rFVIIa 20 $\mu\text{g}/\text{kg}$	276*	14 (5)	10 (4)
	rFVIIa 80 $\mu\text{g}/\text{kg}$	297*	25 (8)	7 (2)
	Both rFVIIa doses	573*	39 (7)	17 (3)

*Intention-to-treat population. The safety population (patients exposed to a study agent) included 263 patients in the placebo group, 265 patients in the 20 $\mu\text{g}/\text{kg}$ group, and 293 patients in the 80 $\mu\text{g}/\text{kg}$ group.

4.3 Conclusions from Studies to Date

Hematoma growth is an important determinant of outcome after ICH. Hematoma growth is time dependent, occurring in up to 38% of patients imaged within three hours of ictus but in progressively fewer patients presenting at later time periods. Recombinant activated factor VII effectively reduces ongoing bleeding in patients with acute ICH. However, benefit from this therapy in large trials may be diluted by patients who will not have hematoma growth. To date, rFVIIa has only been tested within four hours of ICH onset because the percentage of patients with ICH growth beyond this window is expected to be too small to show improved outcomes among all patients. Clinical results in trials of rFVIIa treating patient in less than four hours have been mixed.

Ideally, a diagnostic and prognostic test exists which reliably identifies ICH patients who will have significant subsequent hematoma growth. Such a test would allow treatments to be tailored to individual patients. Patients presenting early after ICH onset who are not at risk for hematoma expansion would not be subjected to the potential risk and cost of hemostatic therapy. Conversely, patients presenting later who are destined to have hematoma growth would not be excluded from an effective treatment by time of onset. Furthermore, such a test would substantially increase the chance that a clinical trial of hemostatic therapy would show positive results by excluding patients who will not benefit from treatment and need not be exposed to potential thromboembolic risk.

Recombinant activated factor VII is biologically effective. It remains to be demonstrated which patients will derive clinical benefit from its use. The STOP-IT study is the next step in identifying these patients and determining whether CT angiography can be used to guide their treatment. The combined use of CTA to predict hematoma growth and rFVIIa to stop hematoma growth is a biologically and clinically elegant and plausible means to improve patient outcome after ICH.

5.0 Research Design and Methods

5.1 Overview

STOP-IT will enroll patients with acute ICH less than five hours from symptom onset. Patients will be included in one of two study arms. The first arm will be a multicenter, randomized, double-blind, placebo-controlled trial comparing rFVIIa to placebo for treatment of patients with acute ICH and a spot sign on CTA. The second arm will be a multicenter, prospective observational study of hematoma growth among patients without a spot sign on CTA. Comparisons will be made between 1) patients with a spot sign randomized to placebo and patients without a spot sign, in order to determine the value of the spot sign for predicting hematoma growth and 2) patients who have a spot sign and are randomized to rFVIIa or placebo in order to determine the effect of study drug upon hematoma growth.

This phase II study will determine whether the spot sign is a reliable predictor of hematoma growth, if site investigators (neurologists and emergency department physicians) can reliably identify the spot site, whether CTA is a practical tool for making treatment decisions in the acute period, and whether subjects with a spot sign treated with rFVIIa have less hematoma growth than subjects with a spot sign who are treated with placebo. Preliminary data on clinical efficacy will be collected to help determine whether a phase III trial which uses the spot sign to select subjects for hemostatic therapy is warranted. For the STOP-IT study 11 clinical sites will recruit an estimated 184 subjects.

5.2 STOP-IT Study Design

5.2.1 Patient Flow

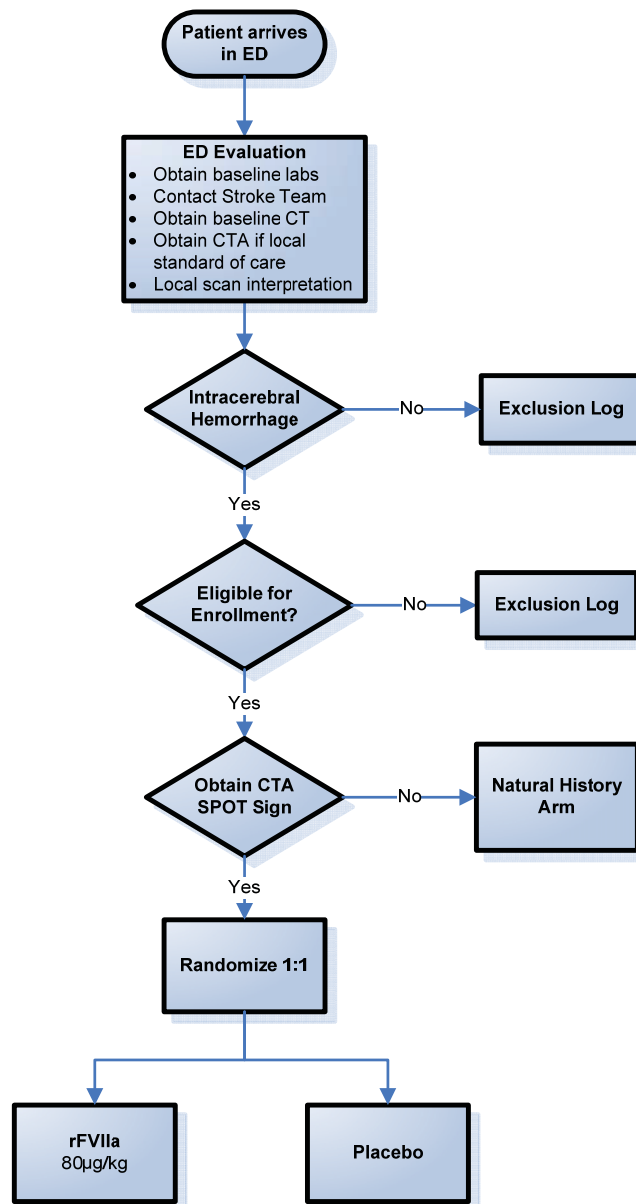
Patients presenting with ICH to participating study centers will be screened for eligibility. Only patients who meet study inclusion criteria, do not meet study exclusion criteria, and have a non-contrast head CT head within five hours of symptom onset will be approached for study participation. After the patient and/or their legally authorized representative has provided informed consent, if not already performed as standard of care (see section 5.5.2) the CTA will be performed. Patients transferred from an outside hospital will also have their non-contrast head CT repeated at the participating study center. The CTA will be reviewed by the local study investigator to determine the presence or absence of the CTA spot sign. Patient flow will be determined by the local investigator's interpretation of the CTA. One goal of the STOP-IT study is to determine whether local investigators can identify the spot sign with a high degree of accuracy. This will be crucial in generalizing the results of any study based upon the spot sign to widespread clinical use. Patients with a spot sign will be randomized to treatment with rFVIIa 80 µg/kg IV bolus or placebo. Patients without a spot sign will receive standard medical care (Figure 1).

For a patient to be enrolled, all of the following must be performed:

1. Time of stroke onset verified.
2. Non-enhanced head CT obtained within five hours of symptom onset. Results determined by investigator to be consistent with primary ICH (i.e. no radiographic features of hemorrhagic cerebral infarction, aneurysmal subarachnoid hemorrhage, traumatic contusion, vascular malformation, tumor, or venous sinus thrombosis).
3. Plans for early (<24 hours) neurosurgical hematoma evacuation excluded. This may require emergent neurosurgical consultation, especially for cerebellar hemorrhages or hemorrhages producing significant mass effect.
4. ECG showing no acute ischemic changes and no clinical history to suggest acute myocardial ischemia (e.g., ST elevation in two contiguous leads, new LBBB, or ST depression).

5. Normal baseline troponin
6. Medical history including current medications obtained to exclude warfarin use, history of recent thromboembolic event, history of coagulopathy (documentation of normal INR and PTT will be required before enrollment only if the patient has used warfarin or heparin, has a history suggesting coagulopathy, or if accurate medication inventory is not available), or other conditions detailed in study exclusion criteria.
7. Pregnancy ruled out by stat urine pregnancy test in women of childbearing potential.
8. Baseline clinical assessment performed (including vital signs, NIHSS score, mRS and GCS score).
9. For patients with a spot-sign, study drug (rFVIIa or placebo) should be administered as quickly as possible and must be administered within 90 minutes of the baseline non-contrast head CT. Patients transferred from outlying hospitals will have their non-contrast head CT repeated at the participating study site. This must be done within five hours of symptoms onset and will be considered the qualifying CT for both study analyses and study drug administration time limits.

Figure 1. STOP-IT Study Patient Flow



5.2.2 Inclusion Criteria

1. Acute, spontaneous ICH (including bleeding in cerebellum) diagnosed by non-enhanced CT scan within five hours of symptom onset. Time of onset is defined as the last time the patient was witnessed to be a baseline (i.e., subjects who have stroke symptoms upon awakening will be considered to have their onset at beginning of sleep)
2. Age \geq 18 years (candidates must have had their 18th birthday)
3. For spot positive patients, dosing of study drug within 90 minutes of enrolling CT scan

5.2.3 Exclusion Criteria

1. Time of symptom onset of ICH is unknown or more than five hours prior to baseline CT scan
2. ICH secondary to known or suspected trauma, aneurysm, vascular malformation, hemorrhagic conversion of ischemic stroke, venous sinus thrombosis, thrombolytic treatment of any condition (e.g., myocardial infarction, cerebral infarction, etc.), CNS tumor, or CNS infection
3. Brainstem location of hemorrhage (patients with cerebellar hemorrhage may be enrolled)
4. Serum creatinine $>$ 1.4 mg/dl (123 μ mol/L)*
5. Known allergy to iodinated contrast media
6. Intravenous or intra-arterial administration of iodinated contrast media within the previous 24 hours of baseline CT scan
7. Known hereditary (e.g., hemophilia) or acquired hemorrhagic diathesis, coagulation factor deficiency, or anticoagulant therapy with INR $>$ 1.2
8. Known or suspected thrombocytopenia (unless current platelet count documented above 50,000 / μ l)
9. Unfractionated heparin use with abnormal PTT
10. Low-molecular weight heparin use within the previous 24 hours
11. GPIIb/IIIa antagonist use in the previous two weeks
12. Glasgow Coma Scale $<$ 8 at time of proposed enrollment
13. Pre-admission modified Rankin Scale score $>$ 2
14. Baseline ICH volume of $<$ 0.5 cc (Hematoma volume will be estimated by local investigators from the baseline CT using the abc / 2 method⁴⁰)
15. Baseline ICH volume of $>$ 90 cc
16. Planned surgical evacuation of ICH within 24 hours of symptom onset (Placement of intraventricular catheter is not a contraindication to study enrollment)
17. Recent (within 90 days) myocardial infarction, coronary artery bypass surgery, unstable angina, transient ischemic attack, ischemic stroke, cerebral bypass surgery, carotid endarterectomy, deep venous thrombosis, pulmonary embolism, or coronary or cerebrovascular angioplasty or stenting
18. Baseline electrocardiogram shows evidence of acute cardiac ischemia (ST elevation in two contiguous leads, new LBBB, or ST depression)
19. Clinical history suggestive of acute cardiac ischemia (e.g. chest pain)
20. Abnormal baseline troponin
21. Females of childbearing potential who are known to be pregnant and / or lactating or who have positive pregnancy tests on admission
22. Advanced or terminal illness or any other condition the investigator feels would pose a significant hazard to the patient if rFVIIa were administered.
23. 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 the time of STOP-IT enrollment
24. Planned withdrawal of care or comfort care measures
25. Patient known or suspected of not being able to comply with trial protocol (e.g., due to alcoholism, drug dependency or psychological disorder)
26. Informed consent cannot be obtained from the patient or legally authorized representative

*For participating sites that do not perform CTA as part of standard of care for evaluation of ICH and will be screening and obtaining informed consent before the CTA. Other sites will follow their standard procedures regarding renal insufficiency

5.3 Dose Selection for Recombinant Activated Factor VII

The dose of rFVIIa chosen for this study is 80 µg/kg. This dose was based upon extensive preclinical testing, testing for non-stroke medical indications, dose-escalation studies in ICH, and a phase III clinical trial in ICH.^{6, 7, 39, 41} The safety profile of rFVIIa use for acute ICH was previously discussed above in section 4.4.2.

5.4 Drug Storage and Administration

The Investigator or designated trial staff must ensure the availability of proper storage conditions and record and evaluate the temperature. The trial product are to be stored under refrigeration at 2-8° C (the original formula) or the new product version can be kept at room temperature (up to 25° C) for up to 2 years. The study drug is stable until expiration date stated on each subject box. The investigator or designated trial staff must record the temperature of the trial product storage facility. A temperature log should be kept for the trial product facility.

Once eligibility is confirmed by the Investigator, subjects will be randomized 1:1 to receive rFVIIa (80 µg/kg) or placebo. Study drug or placebo will be reconstituted by the site pharmacist and administered as a single intravenous bolus dose over 2-5 minutes no later than 90 minutes after the enrolling CT scan and no later than 6.5 hours from symptom onset. All physicians, nurses, participating subjects, and pharmacy staff are blinded to the content of the study medication. No trial products may be dispensed to any person not enrolled in the trial.

5.5 CT and CTA Methodology

5.5.1 CT and CTA Acquisition

Non-enhanced CT scans are performed at baseline, 24 hours (+/- 3 hours from baseline CT scan) and for change in subject condition (safety CTs). These scans are considered part of standard clinical care for patients with ICH. CTA is performed once at baseline to determine the presence or absence of the CTA spot sign.

5.5.2 CTA and Standard Care for Acute ICH

The use of CTA for the evaluation of acute stroke is not standardized in North America. There is evidence that CTA provides useful diagnostic information for patients with ICH and that it is safe for patients with acute stroke (see section 3.3). However, CTA has not been proven to improve patient outcomes compared to other diagnostic paradigms (such as delayed imaging or imaging with MRI or digital subtraction angiography). Medical standards of care are often not explicitly defined and the legal interpretation of these standards may vary by community, state, and nation.⁴² Standard imaging for patients with ICH differs at different centers in North America. Some centers routinely perform CTA at the time of the initial head CT for all patients without definite contraindications to contrast administration such as known renal failure or contrast allergy. Other sites do not use CTA as part of their standard diagnostic evaluation. **The design of the STOP-IT study must therefore take this practice variation into consideration.** Sites that have routinely performed CTA as part of their initial, standard evaluation for ICH patients will continue this practice. At these sites, patient consent for participation in the STOP-IT study will occur after the CTA. For sites that do not currently perform CTA as standard initial care for patients with ICH, patient consent for the STOP-IT study must occur before performance of the CTA. All CTAs will be available to local radiologists and clinicians as they may provide additional diagnostic utility beyond the spots sign for detection of occult aneurysms, vascular malformations, etc. All patients will have serial creatinine measurements following the CTA to monitor for the development of contrast-induced nephropathy.

5.6 Imaging Analysis

The local investigator will use the baseline CT as part of the screening process for eligibility. Baseline hematoma volume for study screening will be calculated by the abc/2 method.⁴⁰ De-identified baseline and 24-hour CTs will be provided to the University of Calgary via the CCC for subsequent interpretation by a blinded clinician. Hematoma volumes for study endpoints will be calculated by volumetric analysis. Scans will also be analyzed for the location of hemorrhage, the presence and volume of IVH, the presence or absence of hydrocephalus, edema volume, and mass effect.

The CTA spot sign will be defined as one or more foci of contrast enhancement seen within the hematoma on CTA source images. Based upon our prior experience with the spot sign, the following criteria will be used to identify the spot sign:

2. The shape may be spot-like, serpiginous, and/or linear.
3. The location must be within the margin of a parenchymal hematoma.
4. The size must be >1.5 mm diameter in at least one dimension.
5. The density (in Hounsfield units) should be double that of the background hematoma (site investigators are not required to document the density).
6. There should be no connection to a vessel outside the hematoma margin.

Local investigators will interpret the CTA for the presence or absence of the spot sign in the acute setting. Digital copies of the CTAs will be provided to the Clinical Coordinating Center (CCC) for subsequent interpretation by a blinded neuroradiologist. All CTAs will also be subsequently reviewed for the presence or absence of the spot sign by a blinded study neurologist and a blinded study emergency medicine physician. Measures of inter-rater reliability will be determined among the evaluators, with the neuroradiologist's reading considered the gold-standard. Before study initiation training sessions will be held for study investigators reviewing the abc/2 method of ICH volume calculation and use of CTA source images to identify the spot sign.

5.6.1 CT Image Data Management

All imaging data will be sent to the Clinical Coordinating Center at the University of Cincinnati for standardized archiving and data blinding if needed. De-identified CT image data will then be transferred via a secure file transfer protocol (SFTP) to a research PACS system at the University of Calgary Neuro Imaging Centre and subsequently analyzed, under the direction of Dr. Andrew Demchuk, on a personal workstation using Quantomo software that was developed at the University of Calgary. User-selected parameters used to segment the volumes (i.e., seed-points, HU intensity thresholds, etc.) will be saved in Extensible Markup Language (XML) files to allow retrospective analysis (i.e., reproduce and validate the results from the operators). This cost-effective approach will also allow us to perform future retrospective studies using the same data from the current study. In addition to user-selected parameters, the masked segmented volume and the mean and standard deviation of the volumes will also be saved in the XML files. Statistical analysis will be performed off-line using the data collected in the XML files. De-identified CTA image data will be transferred via a secure transfer protocol to Sunnybrook Health Sciences Centre in Toronto, Canada, where Dr. Richard Aviv, study neuroradiologist, will review scans as the "gold standard" for the presence or absence of the spot sign.

5.6.2 Volume Measurements

Segmented volumes will be obtained with Quantomo software using a user-assisted neighborhood-connected region-growing threshold-segmentation method implemented in the Insight Segmentation and Registration Toolkit (ITK; National Library of Medicine, Bethesda, MD) in conjunction with freehand drawing tools for the ICH, IVH and edema volumes. The operator will be required to place seed-points within the volume of interest and adjust lower and upper intensity HU thresholds until the entire volume is correctly selected. In cases where the ICH volume cannot be differentiated from IVH volume, the operator will use freehand drawing tools in order to remove the IVH volume using

their best estimate. In this situation, the IVH will be determined using the original over-segmented volume that includes the combined ICH and IVH volumes, V_{total} , as $IVH = V_{total} - ICH$. This limitation is unavoidable as IVH has the same intensity as ICH and the two volumes often border each another. The volume (ml), mean (HU), standard deviation (HU) and the affected part(s) of the brain will be measured from the segmented volume.

Based on initial experimentation, we anticipate more difficulties in segmenting edema volumes as edema has more subtle HU intensity differences relative to normal tissue. Thus, edema segmentation will likely require more operator effort (i.e., seed-points, freehand tools, etc.) Although initial testing has shown that the current user-assisted technique will be sufficient for this study, we wish to reduce the amount of time operators spend to perform the user-assisted volume segmentations. Thus, we are currently investigating more sophisticated segmentation methods based on level-sets (i.e., shape) in order to further automate the segmentation process

6.0 MEASUREMENT OF OUTCOMES

Measuring outcomes for acute stroke trials should be clinically relevant, valid, reproducible, and easy to perform. There is no single accepted clinical endpoint for acute stroke trials since no single endpoint encompasses all of the domains that stroke affects including functional disability, neurological deficit, volume of brain infarction or hemorrhage, and quality of life. It is for this reason that all stroke trials include multiple clinical endpoints.

6.1 Primary Outcome: Test Performance

A primary outcome of the STOP-IT study will be the sensitivity and specificity of the spot sign for predicting hematoma growth. Secondary outcomes will be the positive and negative predictive value of the spot sign and the accuracy of site investigators for correct identification of the spot sign as compared to a blinded study neuroradiologist.

6.2 Primary Outcome: Clinical Parameters

The primary para-clinical outcome of the STOP-IT study will be the rate of hematoma growth among spot-positive subjects at 24 hours, comparing subjects treated with rFVIIa to those treated with placebo. Hematoma growth will be defined as a > 33% or > 6 cc increase in volume.

Secondary outcomes measures will be clinical outcomes among patients treated with rFVIIa vs. those treated with placebo. Analysis will be performed for mortality at 90 days and good (mRS 0-4) versus poor (mRS 5-6) functional outcome.

6.3 Primary Safety Outcomes

6.3.1 Definitions

Adverse events (AE) are defined as any undesirable event involving a study patient, whether or not it is felt to be related to the study drug. This includes events occurring after the patient and/or legally authorized representative has signed the informed consent but before study drug administration through the follow-up period as defined in the study. A serious adverse event (SAE) is a medical event defined as (but not limited to) any experience that is: fatal, life-threatening, permanently disabling, requires or prolongs inpatient hospitalization, overdose, laboratory values or abnormal trends judged to be clinically serious, or a congenital anomaly or birth defect. A non-serious adverse event (AE) is any adverse event which does not fulfill the above definition of a serious adverse event.

6.3.2 Primary Safety Measures

The primary safety measures 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 ischemia 2) acute cerebral ischemia and 3) acute pulmonary embolism.

Clinical definitions of significant thromboembolic adverse events:

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. ECG 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 ischemia:

New focal neurological deficits consistent with cerebral ischemia and without alternative explanation lasting > 24 hours. For patients with suspected new cerebral ischemia which is not detected on CT scan, MRI is recommended if clinically feasible. This definition is also satisfied by deficits lasting < 24 hours but associated with signs of new cerebral ischemia on CT or MRI.
3. Acute pulmonary embolus (PE)

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

Other adverse events potentially related to study drug that must be reported as SAEs but will be analyzed separately from the primary safety measures above 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 (e.g., chest pain, dyspnea) or ECG evidence (ST depression) of reduced myocardial flow without a significant elevation in troponin.
3. Deep venous thrombosis.

For a discussion of stopping rules related to arterial thromboembolic SAEs please see section 8.3.

Localization of ischemia:

- The location of each type of ECG change will be classified as follows:
 - Inferior distribution II, III, aVF
 - Anterior distribution V3, V4
 - Septal distribution V1, V2
 - Lateral distribution I, aVL, V5, V6
 - Posterior distribution (relevant only for tall R waves, upright T) V1, V2
 - Right ventricular V4R

Adverse Event Attribution Categories:

Unrelated	The AE is clearly NOT related to the study drug
Unlikely	The AE is doubtfully related to the study drug
Possible	The AE may be related to the study drug
Probable	The AE is likely related to the study drug
Definite	The AE is clearly related to the study drug

6.4 Recruitment Procedure and Technique

The primary means for recruitment of patients is to ensure rapid identification of potential study candidates at the respective hospitals and to minimize the time for evaluation and treatment with study medication. All of the participating hospitals in the study have an active acute stroke intervention team, and in particular, a strong representation of emergency medicine within those stroke teams. Each of these emergency departments is already equipped to treat stroke as a medical emergency. The systems approach that was used in the FAST trial of rFVIIa will be used in the emergency departments at each of the participating hospitals to identify potential sources of delay and to suggest potential solutions.

6.5 Contingency Plan for Lags in Recruitment

Based upon recruitment in the FAST trial of rFVIIa, we expect that we will be able to reach our goal of 184 patients at the study centers. We will recruit 2-4 more participating centers should recruitment lag behind our expectations.

6.6 Procedure for Subject Screening

For the purpose of documenting the emergency department and hospital population from which the patients in this trial are drawn, each clinical center will maintain a study screening log. All patients with spontaneous intracerebral hemorrhage who are admitted to the participating hospitals within five hours of onset during the accrual phase of the study, whether eligible or not, will be recorded in the study screening log. A reason for exclusion for each patient not entered into the trial will be recorded. Each participating performance site will enter the information on its Stroke Log in the STOP-IT Study web site on a monthly basis. This information will be used when planning the recruitment of patients for the potential, future Phase III trial. The number of patients enrolled per center as well as the number of screened patients along with a tabulation of reasons for exclusion will be included in the monthly accrual report to the steering committee.

6.7 Competing Ongoing Clinical Trials

At this time there are few competing clinical trials for patients with intracerebral hemorrhage. Should other trials compete with STOP-IT in the future, a planned stratification of enrollment must be put into place in those hospitals actively enrolling patients in multiple studies, thereby preventing preferential enrollment into any one trial. Centers that have more than one ongoing ICH trial within the five hour time window must submit their assignment system of patient allocation into the various trials to the Clinical Coordinating Center.

6.8 Randomization and Blinding

In order to reduce bias, the treatment arm of this study will be conducted as a double-blind, placebo-controlled trial. The randomization will be performed with equal allocation between treatment arms. Neither the treating physicians nor the patients will know to which treatment arm the patient is randomized. In order to avoid a situation of bias with respect to important covariates a system of adaptive randomization will be used. In general, the process of adaptive randomization determines the allocation of the participant into one of the groups based on the composition of the groups at the time of randomization. The process described below will provide a tighter balance of time from symptom onset to CT and baseline hematoma volume in the two groups than using stratified randomization. The implementation of this process involves the examination of the marginal totals for each level of each covariate. Given the time and hematoma volume for the patient to be randomized, the imbalance will be calculated if the person is assigned to the rFVIIa arm and also for assignment to the placebo arm. The assignment that results in the smaller imbalance will be chosen. Although this is not strictly a pure randomization scheme, the data are treated as if they were assigned randomly. The variables considered in the adaptive randomization scheme will be time from symptom onset to baseline CT scan (dichotomized as 0 to 3 hours vs. > 3 hours to 5 hours) and baseline hemorrhage volume (trichotomized as < 30 cc, 30 to 60 cc, and > 60 to 90 cc).

Periodically, study biostatisticians will review the distributions of the two variables and decide if an adjustment to the categorization is warranted.

Assignment to a treatment group will be done centrally. The local study investigator enrolling a patient will access a web-based program to determine the randomization number. If for some reason the web system cannot be accessed there will be a back-up phone system to provide a randomization number. Pharmacies at study sites will have a list of randomization numbers and when given the assigned number for the study subject will know which trial product to mix.

To achieve appropriate blinding, the study drug will be supplied in a blinded fashion - as a freeze-dried powder in vials containing either rFVIIa or placebo. It will be reconstituted in sterile water before being administered intravenously over a period of two to five minutes. The volumes of the doses will be comparable to allow blinding to remain intact.

It is not anticipated that it will be necessary to unblind the study for an individual patient. Any adverse event related to rFVIIa will be treated according to routine standards of care. However, blinding may be broken if deemed necessary by the treating physician. If the study site needs to break the randomization code, the Clinical Coordinating Center should be notified within 24 hours after the randomization code has been broken. When a code is broken, the time, date, and reason must be recorded on the source documents and the CRF.

6.9 Drug Distribution and Pharmacy Support

The Department of Pharmacy Services at The University Hospital (TUH) at the University of Cincinnati has 20 years experience in industry and NIH funded pharmaceutical research. The TUH Pharmacy-Coordinated Investigational Drug Service (IDS) has successfully facilitated, dispensed and provided accountability and control of medications used in multiple acute stroke drug studies including the NIH funded rt-PA dose escalation trial, the randomized NINDS rt-PA Stroke Study, and the EMS, IMS I, IMS II, IMS III and CLEAR Trials. The IDS, under the direction of Caron Sue, PharmD, PhD, is staffed by both investigational drug pharmacists and pharmacy technicians.

The University of Calgary will act as the drug distribution center for Canada and main contact for Health Canada. As a member of the Canadian Stroke Consortium, the University of Calgary has already acted as the drug distribution center for Canada in the IMS I, II, and III trials.

7.0 SUBJECT MEDICAL MANAGEMENT

Management of ICH after study entry will be determined by local clinicians who will be encouraged to follow published guidelines where applicable.²⁷ It is anticipated that almost all patients will be admitted to an intensive care unit for at least 24 hours. Planned hematoma evacuation within 24 hours of stroke onset is a study exclusion criterion. However, it is recognized that some patients will experience clinical deterioration and may require emergent surgical treatment at the discretion of their treating clinicians prior to the 24-hour CT scan. In these cases a repeat head CT should be performed before surgical intervention. This scan will be used as the follow-up CT to assess hematoma growth.

8.0 MEDICAL AND LABORATORY DATA COLLECTED

Data collected will differ slightly based upon whether subjects are enrolled in the observational arm (spot negative) or the treatment arm (spot positive). Subjects in the treatment arm of the study will have additional troponin levels and electrocardiograms performed for safety monitoring.

8.1 Schedule of Events

Table 3a. Summary of Data Collection: Treatment Arm – All Spot-Positive Subjects

Event	Baseline	1 hour post dose (± 10 min)	Day 1 24 hours (± 3 hrs) after baseline CT	Day 2 48 hours (± 6 hrs) after baseline CT	Day 3 72 hours (± 6 hrs) after baseline CT	Discharge (± 2 Days)	Day 30* (± 7 Days)	Day 90* (± 7 Days)
Informed consent	X							
Medical history	X							
Physical exam	X							
Vital signs	X	X	X	X	X	X		
Demographic information	X							
Creatinine	X		X		X	X		
Pregnancy test‡	X							
INR + PTT	X							
Complete blood count (CBC)	X							
GCS Score	X	X	X			X		
NIHSS score	X	X	X			X		
Barthel Index (BI)						X	X	X
mRS score	X					X	X	X
CT scan of head	X		X					
CT angiography of head	X							
Electrocardiogram	X		X	X	X			
Serum troponin	X		X	X	X			
Adverse event assessment	X	X	X	X	X	X	X	X

- NIHSS = National Institutes of Health Stroke Scale, INR = international normalized ratio, PTT = partial thromboplastin time, GCS = Glasgow Coma Scale, mRS = modified Rankin Scale
- *30-day and 90-day follow-ups will be via telephone
- ‡Women of childbearing potential

Table 3b. Summary of Data Collection: Observation Arm - All Spot-Negative Subjects

Event	Baseline	Day 1 24 hours (± 3 hrs) after baseline CT	Day 2 48 hours (± 6 hrs) after baseline CT	Day 3 72 hours (± 6 hrs) after baseline CT	Discharge (± 2 Days)	Day 30* (± 7 Days)	Day 90* (± 7 Days)
Informed consent	X						
Medical history	X						
Physical exam	X						
Vital signs	X	X	X	X	X		
Demographic information	X						
Creatinine	X	X		X	X		
Pregnancy test‡	X						
INR + PTT	X						
Complete blood count (CBC)	X						
GCS Score	X	X			X		
NIHSS score	X	X			X		
Barthel Index (BI)					X	X	X
mRS score	X				X	X	X
CT scan of head	X	X					
CT angiography of head	X						
Electrocardiogram	X						
Serum troponin	X						
Adverse event assessment	X	X	X	X	X	X	X

- NIHSS = National Institutes of Health Stroke Scale, INR = international normalized ratio, PTT = partial thromboplastin time, GCS = Glasgow Coma Scale, mRS = modified Rankin Scale
- *30-day and 90-day follow ups will be via telephone
- ‡Women of childbearing potential

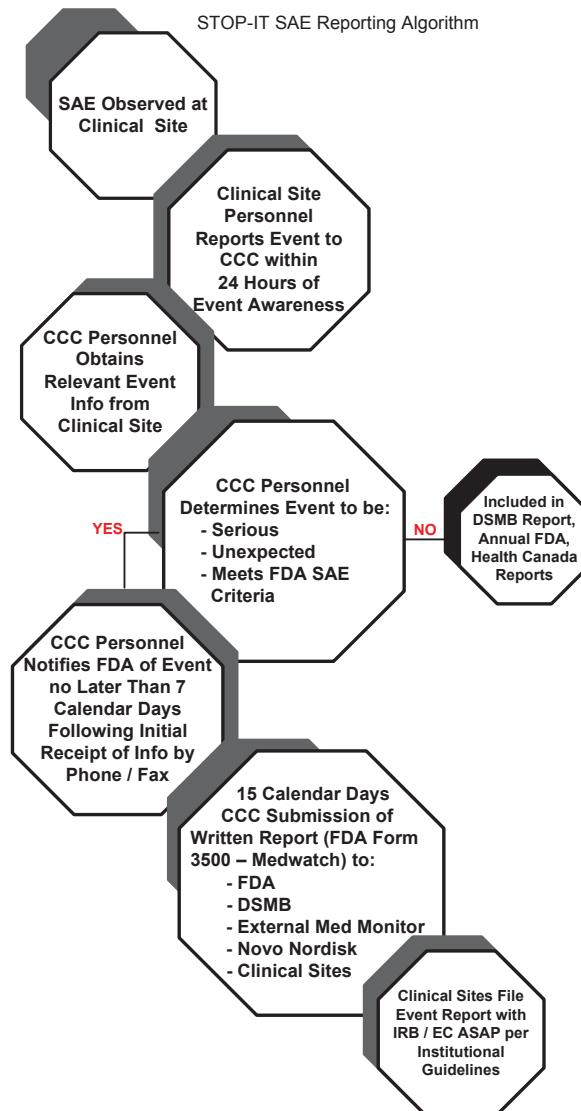
8.2 Monitoring for Adverse Events and Assessment of Safety

Figure 2

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs); both anticipated and unanticipated that are considered related to study drug, CTA, and the disease itself. Clinical performance sites are instructed to report all fatal events, unanticipated problems and other serious adverse events in the Biostatistical Core Database System within 24 hours of their becoming aware of the event. Upon notification Dr. Jauch or Dr. Flaherty and the project manager will investigate the event. If the event is determined to be unexpected (not previously observed) and related to trial participation (study drug) and meets FDA criteria as a serious event the Clinical Coordinating Center will notify the FDA as soon as possible but no later than 7 calendar days after initial receipt of the information by

telephone or fax transmission. A written report describing the results of the event analysis will be submitted to the FDA, DSMB, External Medical Monitor, and Novo Nordisk as soon as possible, but no later than 15 calendar days after the determination is made (Refer to MOP for complete safety assessment and AE/SAE reporting procedures). The coordinating center safety staff will then inform all the study investigators of these events (as described above) within 15 days of receipt of the event report. In turn, each investigator is responsible for promptly informing his/her IRB / EC of these events per their institutional guidelines. All reported SAE events determined *not* to be related to trial participation, or are not unexpected will be included in the annual FDA report (see Figure 2). The Biostatistical Core will also provide the Steering Committee and the DSMB with safety monitoring statistics.

Additionally, an external Medical Monitor (Dr. Julio Chalela of the Medical University of South Carolina) will independently review all serious clinical thromboembolic adverse events and submit his opinion as to the relationship of the event to study drug administration to the study PIs and trial



biostatistician. The primary determination of whether or not a thromboembolic event is symptomatic will be made by the treating investigator at the enrolling site but the designation will be independently reviewed by Drs. Flaherty, Jauch, and Chalela.

8.3 Stopping Rules for Safety Concerns

The only serious safety concern identified in prior studies of rFVIIa for intracerebral hemorrhage is an excess risk of arterial thromboembolic serious adverse events (SAEs) with rFVIIa treatment compared to placebo. These SAEs were primarily non-ST elevation myocardial infarctions and ischemic strokes, but also included individual cases of renal artery thrombosis, intracardiac thrombus, and retinal artery occlusion.^{6,7} In the STOP-IT Study we anticipate randomizing 42 subjects to rFVIIa treatment. This number is considerably smaller than the previous phase IIb and phase III trials of rFVIIa for intracerebral hemorrhage and so it is unlikely the STOP-IT Study will reveal additional, statistically robust information on arterial thromboembolic SAE risk. However, a stopping rule for excess arterial thromboembolic SAEs in the active treatment arm of the study will be followed.

For this investigation, the stopping rules are based upon the 8% rate of arterial thromboembolic SAEs observed in subjects treated with 80 µg/kg of rFVIIa in the phase III trial.⁷ Patients treated with placebo in that trial had a 4% risk of arterial thromboembolic SAEs. Thus we will consider the expected rate of arterial SAEs for patients treated with rFVIIa in the STOP-IT Study to be 8%. If the rate is significantly greater than 8%, the treatment arm of the STOP-IT Study will be put on voluntary hold pending DSMB review. For the purposes of these stopping rules, myocardial injury without acute coronary syndrome (“enzyme leak”) and unstable angina without evidence of infarction (see section 6.2.3) will NOT be counted toward the number of arterial thromboembolic SAEs needed to place the treatment arm on hold.

Using the binomial observed event rate, the associated lower 90% confidence interval was calculated for the observed event, as we were only interested in looking at that part of the distribution. The decision is based on when the assumed true event rate, 8%, falls below the lower 90% confidence interval for the observed rate which is dependent upon the number of subjects accrued. **All arterial thromboembolic SAEs will be monitored on a continuous basis, in real time, by an unblinded study biostatistician.**

In summary, the treatment arm of the study is placed on voluntary hold if there are:

- 2 arterial SAEs within the first 5 subjects treated with rFVIIa
- 3 arterial SAEs within the first 10 subjects treated with rFVIIa
- 4 arterial SAEs within the first 15 subjects treated with rFVIIa
- 4 arterial SAEs within the first 20 subjects treated with rFVIIa
- 5 arterial SAEs within the first 25 subjects treated with rFVIIa
- 6 arterial SAEs within the first 30 subjects treated with rFVIIa
- 6 arterial SAEs within the first 35 subjects treated with rFVIIa

This means that the treatment arm of the study will be placed on voluntary hold pending DSMB review if there are two arterial thromboembolic SAEs within the first five subjects treated with rFVIIa, three arterial thromboembolic SAEs within the first ten subjects treated with rFVIIa, etc. Clinical sites that perform CTA as part of routine standard of care can continue to enroll spot-negative subjects into the observational arm.

9.0. STATISTICAL CONSIDERATIONS

9.1 Overview and Patient Entry

The Biostatistical Core (BSC) and the Clinical Coordinating Center (CCC) at the University of Cincinnati SPOTRIAS Center will be responsible for the data management activities. All drafts of the protocol will be dated and cataloged on the study website and in the study library so that material development is documented. If a new version of the protocol is developed, a list of changes since the last version will also be available on the website. Case report forms and a manual of operating procedures (MOP) will be developed for and maintained during the course of the trial. The manual will detail the specific steps that must be taken from the initial presentation of a potentially eligible patient to the completion of the study. The manual will also address each data form item on a question-by-question basis. An orderly discussion of each question contained on the data forms will be incorporated into the case report form as well as the manual. The BSC will prepare for this manual content describing, in detail, standard operating procedures of the BSC such as the organizational structure of the BSC, the data management system, computer edit specifications, data flow, and quality control procedures. The directors of the BSC and the personnel of the Clinical Coordinating Center will be involved in the decision making process concerning any changes in the trial.

All patients enrolled in the study will be registered and entered into the study database by identification number only. Only the personnel at the clinic site where the patient is receiving care will have personal identifiers. No names or birth dates or other information that can identify a patient will be entered on the website and sent to the BSC. Each clinical site will either access the assigned web site or call the dedicated phone line to receive a randomization designation by means of a unique study randomization number when an eligible patient is identified. This number will be passed along to the site pharmacist who will have the randomization list to interpret and prepare the appropriate study product. The web site will automatically update the randomization number according to a pre-defined scheme. The phone will also be monitored 24 hours a day and seven days a week and updated as appropriate. The site will then either enter information at the web site or fax, within 24 hours, a completed eligibility form after enrolling the patient. If a form is sent, it will be reviewed and the information compiled into the accrual database. The clinical site will receive a confirmation that the patient is entered into the accrual database. If a patient is found not to meet the inclusion criteria, the BSC will immediately notify the clinical site of this decision and the reason why. The patient will continue to be monitored and information gathered on them.

A table will be created that is the master list of all patients entered into the trial. From this table a monthly recruitment report will be generated and sent to the Steering Committee and all key personnel. Each clinical site will maintain a Stroke Patient Inclusion/Exclusion Log on the web site. Full reports will be generated for the Data Safety and Monitoring Committee and for the trials Steering Committee, as required. These reports will include details of enrollment, demographic and medical description of patients enrolled, efficacy and safety outcomes, and adverse events.

9.2 Data Forms

The data forms used in the STOP-IT Study will be easy to read and unambiguous. Each clinical site will use a unique identification convention for their study subjects; this number will also be recorded on the form. This will ensure proper compliance with HIPAA / PIPEDA regulations. Data entry screens on the web will follow the flow that has been created on the forms. Although we will use web-based entry, the CRFs will be available on the web site for a clinical site to use as a worksheet, if desired. Instructions on completing the data forms will be addressed in detail in the Manual of Operations.

9.3 Manual of Operations

The Manual of Operations will be a document containing detailed instructions on the recruitment process, study procedures, and data collection. The document is used primarily by the clinical sites for day-to-day operations. The manual will be maintained on the web site.

The manual will detail the specific steps that must be taken from the initial presentation of a potentially eligible patient to the completion of the study. The steps will be arranged in chronological order with appropriate references to subsequent sections. This manual will cover many of the same topics as the protocol but in greater detail.

The operations of the BSC will be described in this manual. Topics such as the organizational structure of the Clinical Coordinating Center, BSC, complete safety assessment and AE/SAE reporting procedures, the data management system, computer edit specifications, data flow, and quality of control procedures will be included. Revisions to the Manual of Operations will be made as necessary. All versions of the manual of operations will be dated and archived in the study library.

9.4 Database Development and Security

The Biostatistical Core and the Clinical Coordinating Center will be located at the University of Cincinnati and Cincinnati Children's Hospital Medical Center (CCHMC). The Biostatistical Core and Clinical Coordinating Center will ensure the completeness and accuracy of the collected data while maintaining subject confidentiality, as well as providing the operational infrastructure to facilitate cooperation and communication among the clinical sites, FDA, NIH personnel, and BSC personnel. Each site will be expected to designate a contact person (research coordinator) who will communicate with the BSC concerning data management issues and will be responsible for the collection of data and entry of data into the web-based system. Necessary qualifications of this person include knowledge of the day-to-day site-specific data collection activities and email capabilities. This person will also be responsible for communicating with BSC personnel with regards to data queries.

The approach to data management will be a web-based data entry system using Microsoft (MS) Infopath 2007. Microsoft Infopath 2007 allows users to create electronic forms or questionnaires of varying complexity. These forms can contain workflow logic, data validation, and conditional formatting or controls based on user responses. With MS Infopath, the forms will be created from the pre-existing Word documents. When coupled with Microsoft Sharepoint, these forms will be placed on the Internet (or corporate Intranet) and subsequently be accessed by the appropriate personnel at the study sites using proper authorization. MS Infopath allows the creation of "browser-compatible" forms that are published in Extensible Markup Language (XML), which makes them viewable in any modern web browser. Furthermore, all data entered are stored in a Microsoft SQL Server database and can then be exported into SAS for analysis.

The Division of Biomedical Informatics (BMI) at Cincinnati Children's Hospital Medical Center has significant experience with Infopath/Sharepoint based web-enabled forms and data capture and is committed to supporting the work proposed here. BMI will provide expertise in the use of Infopath and Sharepoint, including (and in particular) for the addition of custom code to implement the randomization algorithm that assigns patients to trial arms. BMI will collaborate closely with Drs. Bean and Khoury to update the randomization assignments if deemed necessary. Furthermore, BMI staff will provide training for local and remote users of the web forms.

BMI will support and host the web server as well as the database on a server that resides in the CCHMC corporate network behind the corporate firewall. HIPAA compliance will be ensured by assigning unique usernames and secure passwords to each authorized user. Furthermore, all data will be incrementally backed up nightly, with full backups occurring weekly. Access to the web-based data entry forms for external (non-CCHMC) study participants will be granted (in coordination with

the CCHMC corporate Department of Information Services) through the CCHMC Extranet portal. Remote users will first authenticate through the CCHMC firewall and then be granted access to a web page, which in turn will let them authenticate themselves as study coordinators/personnel. Finally, access to the data obtained as part of proposed study will be given only to the BSC personnel, who will monitor enrollment and provide analyses.

Security measures will be established to prevent the ability of any unauthorized personnel to access the data for any patient enrolled into the trial and access to any information collected for the subjects in the other two studies. Confidentiality of data maintained by the BSC is of the utmost priority. Standard Operating Procedures provide for confidentiality of all information. The designated person at each site, the research coordinator will be given security clearance in order to enter data via the website onto a CCHMC server. Data can only be entered under a login with the system attributing all entry and changes to that person. The password to the system will be changed at established intervals. When the database is exited it will be locked. The data will then be transferred to another server by the data manager at CCHMC. At that time the data will undergo further consistency and completeness checks from which the data queries will be generated. Access to the file will be under the control of the director of the Biostatistical Core (BSC) at the CCHMC SPROTRIAS Center. The Data backup on this server is performed daily with a complete backup once every week. A monthly back up is stored in an off campus facility. A virus package is used to detect viruses. All computers are updated monthly and are continuously monitored.

9.5 Data Management, Monitoring and Quality Assurance

To ensure the highest possible quality of data collected, the BSC will establish standard operating procedures. The essential features in having high quality data for analyses are excellent documentation, control over data flow, communication, and training. A major responsibility of the BSC is to ensure the completeness and accuracy of the data collected in all of the projects.

The BSC will work closely with the project manager and clinical coordinator of the CCC to perform the monitoring functions. Data sheets, equivalent to case report forms, generated by the BSC will be compared to the appropriate source documents to check for accuracy and completeness. If corrections are to be made, a form designed for this purpose will be completed and brought back to the BSC.

Site visits will be conducted to inspect study data, subjects' medical records, and CRFs in accordance with current U.S. Good Clinical Practice guidelines and the respective local and national government regulations and guidelines. Authorized Agents of the United States Food and Drug Administration, the University of Cincinnati, the National Institute of Neurological Diseases and Stroke, Novo Nordisk (manufacturer of the study drug recombinant activated factor VII), and respective national or local health and IRB / EC authorities will be allowed to inspect the medical and research records related to this study.

Prior to starting the study, the STOP-IT project manager will visit each site to verify that the site can conduct the trial by the operating procedures outlined in the Manual of Operations. An evaluation checklist will be designed and completed at the time of the site visit. At this time the project manager will instruct the site personnel on procedures specific to this trial. The BSC, in collaboration with the project manager, will develop a PowerPoint presentation to review the steps with each site.

During the trial, the BSC will monitor the activities of each site in order to identify any problems. Areas to be reviewed include rate of subject recruitment, rate of ineligible subject recruitment, entering data in a timely manner, rate of missing or incomplete data, ability of locating the documents pertaining to each individual in the trial, and rate of aberrant data.

The research coordinator at each site is responsible for all the data collected in the study and oversight of the data entry. The process of standardization will be achieved through the Manual of

Operating Procedures, the site visit prior to the start of the study, and the ongoing communications between the coordinator and BSC and CCC staff.

A designated data entry person at the site will enter the data into the database. Pop up menus will be provided for valid values for variables. Skip patterns will be built into the data entry system. Fields will have range and/or validity checks built into the system. If disagreement is found, a Data Discrepancy Report will be generated, and posted on the web for the site to access. This report will note the discrepancy and will require documentation of the resolution of the problem, as well as correction of the error. Data edits will be performed to identify missing, out of range, and inconsistent/erroneous data in the database and reports generated to allow correction of these problems.

The procedure at the BSC will be:

1. The data manager of the BSC will review the file from the center; this will reside on a secured server at CCHMC.
2. The data items will undergo edit checks, more stringent than the gross range checks that will be ongoing during data entry. Consistency checks, both within and across forms, will be made at this time.
3. A query will automatically go back to the research coordinator at the originating site for any out-of-range or inconsistent data. The queries will be maintained at the website.

Upon resolution, via an electronic response, the data will be combined into the master database, maintained in SAS format ready for analysis. Data that are determined to be correct, but still fail edit checks, will be flagged rather than be removed from the data files. Repeated flagging of data points indicates the need to modify data collection and/or edit specifications.

The BSC will do computer runs to check the data for patterns of errors not detected by simple range checks. These runs allow the BSC to determine if one question is causing problems across the sites or if one site is having continuing problems. The Steering Committee will have the responsibility for deciding if changes need to be made to the case report forms.

9.6 Sample Size Calculation

The statistical center for the STOP-IT study will be at Cincinnati Children's Hospital Medical Center (study statisticians Judy Bean, PhD and Jane Khoury, PhD). For all analyses the definition of hematoma growth will be an increase in hematoma volume from baseline CT to 24-hour CT of >33% or >6 cc. Secondary analyses will involve any amount of hematoma growth, using growth in absolute terms and as a percentage of hematoma volume. Because of the time necessary for potential study drug dosing after baseline head CT for spot-positive subjects, the maximal time from symptom onset to baseline head CT was set at five hours (rather than the six hour limit reported in several retrospective series of ICH growth). To ensure similarity in spot-negative and spot-positive subjects, this time limit will be applied to both groups. Data on hematoma growth in the 3-5 hour window is not available; therefore data was extrapolated based upon the 3-6 hour window from previous studies.

The first objective of the STOP-IT study is to prospectively determine the sensitivity and specificity of the spot sign for prediction of hematoma growth. Thus, sample size calculations were based upon this analysis rather than calculations regarding preliminary efficacy of rFVIIa vs. placebo as described below for objective #3.

Several estimates regarding the characteristics of the ICH patient population and the performance of the spot sign were required to determine our sample size (see Table 4 below). We attempted to harmonize the best available data for each item but acknowledge that information is sometimes limited. We were able to estimate the percentage of ICH patients arriving in the 0-3 hour and 3-5

hour strata using population-based data from the Genetic and Environmental Risk Factors for Hemorrhagic Stroke (GERFHS) Study.⁴³ As part of the GERFHS study we attempted to ascertain all patients with ICH presenting to an emergency department or hospital in the Greater Cincinnati area between 1998 and 2003. Within this population, using inclusion and exclusion criteria approximating the STOP-IT study criteria, among patients presenting within five hours of ICH onset, approximately 66% presented in the 0-3 hour window while approximately 34% presented in the 3-6 hour window (authors' unpublished data).

Table 4. Variables considered in sample-size calculations (extrapolations from the literature).

Time window hours	Subjects arriving (%)	ICH growth, all patients* (%)	Spot sign prevalence (%)	Spot sign sensitivity	Spot sign specificity
0-3	66	33	34	0.91	0.94
3-5	34	13	34	0.77	0.72
0-5	100	26	34	0.88	0.85

*Overall ICH growth rates among all patients within the specified time windows, without regard to spot sign status.

Based upon a prior prospective study in Greater Cincinnati, 30-40% of ICH patients presenting within three hours will have subsequent hematoma growth by our criteria. There are no prospective data on the rate of hematoma growth in the 3-5 hour window. Retrospective studies indicate the range may be 8-16% (see Table 1). For the purposes of STOP-IT we estimate the overall ICH growth rate (0-5 hour window) to be 26%. For patients in the 0-3 hour strata the growth rate is assumed to be 33%. For patients in the 3-5 hour strata the growth rate is assumed to be 13%. Estimates of the prevalence of the spot sign among ICH patients were obtained from the studies of Becker, Wada, and Goldstein.^{8, 9, 24} For patients presenting within three hours, Wada found that 33% had a spot sign. The prevalence of the spot sign in the 3-5 hour window is more speculative, especially since definitions of the spot sign and contrast extravasation differed between studies. We conservatively estimated that 34% of patients in the 3-5 hour window will have a spot sign. Prior retrospective studies suggest the CTA spot sign has a sensitivity of approximately 90% for ICH growth. The specificity appears high within the first three hours but likely declines somewhat thereafter.^{8, 9, 24}

Taking into consideration the percentage of patients arriving in each time window, the prevalence of the spot sign, our estimated ICH growth rates, and the available literature, we estimate the spot sign will have 91% sensitivity and 94% specificity within the first three hours. Between 3-5 hours we predict 77% sensitivity and 72% specificity. For the overall 0-5 window we therefore predict a sensitivity of 88% and a specificity of 85%.

Using these values we can construct a 2 x 2 table (see Table 5) based upon 100 hypothetical subjects enrolled in the STOP-IT study. For each 100 subject enrolled in the 0-5 hour window, 34 will have a spot sign and 66 will not have a spot sign. ICH growth will occur in 26/100 patients and will not occur in 74/100 patients. Among spot-positive subjects (who are not treated with a hemostatic agent), 23 of 34 (68%) will have hematoma growth.

Table 5. Expected ICH growth characteristics for every 100 subjects enrolled in the STOP-IT study between 0-5 hours of stroke onset.

	ICH growth occurs	ICH growth does not occur	
Spot-sign positive	23	11	34
Spot-sign negative	3	63	66
	26	74	100

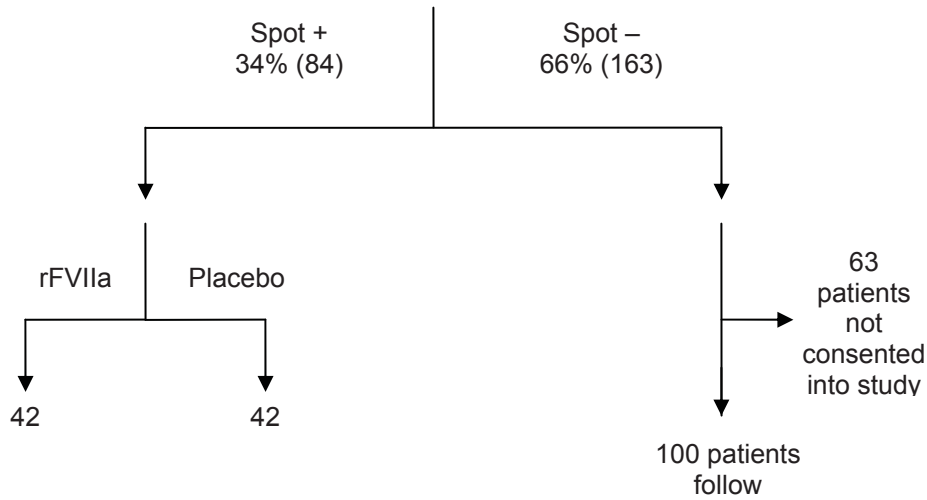
The sample sizes required for a 95% confidence interval of a given width for sensitivity and a 95% confidence interval of a given width for specificity were computed using the approach of Fenn.⁴⁴ This paper describes how to incorporate the prevalence of disease (or in our case ICH growth rates) into computations of the total sample size for sensitivity or specificity. The larger of the two sample sizes calculated is the one required.

The sample of subjects to be used for estimation of sensitivity and specificity of the spot sign is drawn from those who are spot-positive and randomized to the placebo group as well as those who are spot-negative. The method of sample size estimation was the following: the number of true positives plus the number of false negatives is equal to the squared value from the standard normal table times the variance of the sensitivity divided by the width of the confidence interval squared. The variance of sensitivity is the sensitivity times one minus the sensitivity. To obtain the total number required the number calculated from the equation is divided by the growth rate. For the combined group (0-5 hours) the sample size of patients required for a 95% confidence interval of 0.14 are 80 for a sensitivity of 0.88. For the specificity, the variance of the specificity is used and then the number of true negatives plus the number of false negatives is divided by one minus the growth rate. For a specificity of .85 and allowing the width of the confidence interval to be .14, the sample size is 58. Therefore, the sample size of subjects required is 80 (the larger of the two numbers), composed of 40 spot-positive subjects randomized to placebo and 40 spot-negative subjects. Because spot-positive subjects will be randomized 1:1 to rFVIIa or placebo, a total of 80 spot-positive subjects will be required.

Given that 34% of patients have a spot sign, the number to screen is $80/.34 = 235$. We believe that our selection criteria should minimize drop-outs during the first 24 hours, however we will increase our total sample size by 5% to account for this possibility. Based upon these numbers, we will need to screen 247 eligible patients with CTA within 0-5 hours of ICH onset in order to verify the sensitivity and specificity of the spot sign with a 95% confidence interval of 0.14. Patients with a spot sign will be randomized to rFVIIa 80 µg/kg (42 patients) or placebo (42 patients). The remaining patients will not have a spot sign. **Forty-two spot-negative subjects will be needed to determine the sensitivity and specificity of the spot sign for hematoma growth (forty subjects completing the 24-hour CT plus two drop-outs). Once we reach this number, sites that perform CTA as standard care (and therefore perform CTA before patient consent) will stop enrolling subjects without a spot sign.** Sites that have not performed CTA as standard care and require consent before the CTA will continue to enroll both spot-negative and spot-positive subjects (see section 5.5.2 for the discussion of CTA as standard practice). Because many of our sites will consent patients before the CTA and therefore enroll twice as many spot-negative subjects as spot-positive subjects, we conservatively estimate that 100 spot-negative patients will ultimately be enrolled, although it is possible the number will be less. See the figure 3 below for patient flow.

Figure 3

247 patients eligible and screened



The effect of rFVIIa on hematoma growth among spot-positive patients will be determined by comparing subjects randomized to rFVIIa vs. placebo. A one-sided alpha is appropriate in this circumstance as all research to date indicates rFVIIa stops bleeding and there is no reason to believe it will increase hematoma size. We anticipate the rate of hematoma growth in the spot-positive placebo arm will be 68%. Given 40 subjects in each treatment arm (42 enrolled minus two drop-outs), using a one-sided alpha of 0.05 we will have 82% power to detect a 30% absolute reduction in the number of subjects with growth in the rFVIIa arm or 71% power to detect a 26% absolute reduction in the number of subjects with growth in the rFVIIa arm. Table 6 summarized our power calculations for hematoma growth.

Table 6. Power calculations for hematoma growth in spot-positive subjects, rFVIIa vs. placebo, n=40* in each group, one-sided alpha.

Percentage in rFVIIa group with growth	38%	42%
Percentage in placebo group with growth	68%	68%
Power	82%	71%

*Original n of 42 in each group minus 5% drop-outs

9.7 General Analysis Plan

The primary statistical package used will be SAS, version 9.1. Prior to any analysis, means, ranges, standard deviations and descriptive measures will be computed for each continuous variable as well as frequencies for categorical variables. Plots and statistics will be used to determine if a continuous variable is not normally distributed; when necessary an appropriate transformation will be performed and analyses will be done with transformed values.

9.7.1 Objective #1: Determine the sensitivity and specificity of the CTA spot sign for hematoma growth.

The first step in analysis will be to calculate estimates of the sensitivity and specificity of the CTA spot sign for hematoma growth (defined as > 33% increase in volume or 6 cc from baseline to 24 hour CT scan). The estimates will utilize the data from those patients who had a spot sign and were randomized to placebo and patients without a spot sign. The next step will be to calculate the 95% confidence intervals. The method developed by Agresti and Coull will be used.⁴⁵ Additionally, positive and negative predictive values and a likelihood ratio for hematoma growth based upon the presence of the spot sign will be calculated, along with 95% confidence intervals.

Next, categorization of subgroups of the patients will be examined. It is conceivable that variables which are important in stroke survival and outcome will be predictors of hematoma growth. Therefore, logistic regression modeling will be performed using the variables age, gender, race, baseline hematoma volume, time from onset to CTA, baseline GCS, baseline blood pressure, baseline antiplatelet drug use, and presence or absence of the spot sign. Variables will be examined for association with either the outcome of hematoma growth or spot sign prior to entry into a model due to sample size considerations and modeling will be considered exploratory. Those variables either reported in the literature to be associated with hematoma growth or statistically associated at $p < 0.25$ will be potentially entered into the multiple logistic regression model.

9.7.2 Objective #2: Determine the feasibility of using CTA to identify ICH patients at high risk of hematoma growth and select patients for randomization to treatment with rFVIIa or placebo.

In order for the spot sign to be a practical, widely applicable test that informs immediate treatment decisions, it is paramount that clinicians are able to accurately determine the presence or absence of the spot sign in an emergency setting. Site investigators will interpret the CTA locally in the acute setting to determine whether the patient is enrolled in the treatment (spot-positive) arm or observation (spot-negative) arm of the study. The scan will later be over-read in a blinded fashion by the study neuroradiologist (Dr. Aviv) who will represent the gold standard for diagnostic accuracy. In order to assess the agreement between the gold standard and the site investigators, intraclass correlation will be estimated using a mixed model design as each investigator will read a different number of scans depending upon recruitment. The mixed model will allow us to account for this potential additional correlation which may exist between scans. A secondary analysis will determine whether interrater reliability improves for sites as the study progresses and more experience is gained by local investigators in identifying the spot sign, by including time in the model.

Additionally, at a later time each scan will be blindly read for the presence or absence of the spot sign by a study neurologist (Dr. Demchuk or Flaherty) and a study emergency physician (Dr. Jauch or Goldstein). Each scan will be randomly allocated to one of the physicians in each group. A Kappa statistic will be computed for agreement between the study neurologist, the study emergency physician, and the study neuroradiologist. Both individual Kappas and a mean of the Kappas will be reported.

The time required for obtaining and interpreting CTAs as well as randomization and study drug administration for patients in the treatment arm will be determined by calculating mean intervals from baseline head CT to CTA and for baseline head CT to study drug administration. Time intervals for patients from sites which currently perform CTA as standard care (and obtain informed consent after the CTA) will be compared to times for patients at sites who obtain informed consent before the CTA. Time values will be assessed for normality. Because these values are often badly skewed, it is anticipated a non-parametric test will be used for comparisons.

9.7.3 Objective #3: Randomize ICH patients who present within five hours of onset and have a spot sign to treatment with rFVIIa versus placebo, in order to a) determine if rFVIIa is effective at reducing hematoma growth among patients with a spot sign and b) provide preliminary efficacy data for this treatment paradigm.

The primary approach will be a Chi-square analysis of spot-positive patients comparing the rate of growth (increase in hematoma size of >33% or 6cc from baseline) between the group treated with rFVIIa and the placebo group. There should be 42 subjects entered into each arm of the study, with an anticipated drop-out of 5%, to give a sample size of 40 evaluable subjects in each arm of the study, with enough power to detect a 30% absolute difference in growth rate. The adaptive randomization scheme will allow a balance of time from symptom onset and initial hematoma size between the two arms of the study. However analysis will involve assessment of differences between the study groups of these variables and other potential factors that may effect hematoma growth. Bivariate analysis will be done in a systematic way to compare demographic and potential risk factors for hematoma growth between the groups. Variables that are associated with growth at $p < 0.25$ or thought clinically important will be included in a multiple logistic regression model to assess the independent effect of rFVIIa on hematoma growth. Another approach, which may be more powerful will be to use a multiple linear regression model with percent growth as the dependent variable. The advantage to this would be a potential increase in power, however the dependent variable would have to be transformed as percentage growth would violate the assumption of normality. Appropriate transformations will be tried and the residuals will be assessed to ensure validity of interpretation.

The STOP-IT Study is not powered to detect differences in clinical outcomes among subjects in the treatment arm. However, in a secondary analysis clinical outcomes among spot-positive patients treated with rFVIIa and those treated with placebo will be compared using multiple logistic regression analysis as described for hematoma growth, with consideration of covariates. Analysis will be performed for mortality at 90 days and also good (mRS 0-4) versus poor (mRS 5-6) functional outcome. An exploratory analysis will consider differences in outcome for the two groups when defining good outcome as mRS 0-3 and also over the entire range of the mRS using a cumulative logit model with adjustments for important baseline variables such as age, baseline hemorrhage volume, baseline GCS, the presence of IVH, and ICH location. Hematoma growth, mortality, and functional outcome will also be compared for patients with a spot sign randomized to placebo and patients without a spot sign.

9.8 Potential Collaborations and Pooled Analyses

Two participating STOP-IT sites are Canadian (University of Calgary and Sunnybrook Medical Centre). Canadian investigators are pursuing separate funding through Canadian public sources for a parallel trial called the “**Spot Sign Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT) Study**” which will be conducted at other Canadian centers. It is anticipated that this study will have a similar protocol to the NINDS-funded STOP-IT Study. Data from SPOTLIGHT will be pooled with data from STOP-IT as a pre-specified part of all primary and secondary analyses. Additional patient recruitment via this mechanism would allow greater power to show differences in hematoma growth and clinical outcomes between subjects randomized to rFVIIa vs. placebo.

10.0 STUDY TIMELINE

The University of Cincinnati and other enrolling sites in the STOP-IT study have extensive experience in research involving subjects with acute ICH and have a proven track record of patient enrollment in ICH studies. In addition to treating patients who arrive directly to the study institutions, most of our sites serve as tertiary referral centers for ICH and receive patients in transfer from other hospitals. Each enrolling site in the STOP-IT study participated in the FAST trial of rFVIIa for intracerebral hemorrhage.⁷ The recruitment goals we have set for STOP-IT are presented in Tables 7 and 8.

Table 7. STOP-IT/SPOTRIAS Timeline

Year 1		Year 2	Year 3	Year 4	Year 5	
0-6 months	7-12 months	12-24 months	24-36 months	36-48 months	48-54 months	54-60 months
Study initiation	Patient enrollment				Data analysis and study close-out	
					Planning and submission of NIH R01 or industry-sponsored phase III study	

Table 8. STOP-IT/SPOTRIAS Anticipated Patient Enrollment

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
University of Cincinnati	5	7	7	6	3	28
University of California at San Diego	6	6	6	6	6	30
Other sites	31	39	24	24	8	126
Total	42	52	37	36	17	184

11.0 HANDLING OF MISSING DATAT

Based upon our trial design, it is anticipated that there will be minimal loss to follow up for the 24-hour CT scan for hematoma growth or the 90-day assessment of clinical outcome. Nevertheless, some missing data will be inevitable. For patients who require emergency surgery before 24 hours, a CT scan should be obtained before surgery if possible. The presence or absence of hematoma growth will be determined from this scan. The number, timing, and reasons for early scans will be tracked and reported. For patients without 24-hour CT scans, the baseline scan results will be carried forward (patient will be assigned no hematoma growth). If a substantial number of subjects have no follow-up scans or have early scans without subsequent 24-hour scans, an additional analysis using only the study population with 24-hour scans will be performed. Patients lost to follow-up after hospital dismissal will be assigned the worst possible outcomes (short of death) on the mRS and Barthel Index. These assumptions are consistent with the handling of missing outcome data in the NINDS rt-PA Stroke Study.⁴⁶ In addition, all analyses will be repeated excluding the cases with missing data to check for potential bias.

Missing covariate data will be imputed using the multiple imputation, regression method, or hot-decking. If imputation is needed the specific method will be decided at the time of analysis, using SOLAS®.

12.0 TRIAL ADMINISTRATIVE STRUCTURE

12.1 National Institute of Neurological Disorders and Stroke (NINDS) Data and Safety Monitoring Board (DSMB)

A NINDS appointed independent Data and Safety Monitoring Board will act in an advisory capacity to monitor participant safety, data quality and evaluate the progress of the study. The DSMB is responsible for assuring the NINDS that study participants are not exposed to unnecessary or unreasonable risks and that the study is being conducted according to high scientific and ethical standards. Specifically, the DSMB will:

- protect the safety of the study participants;
- review the research protocol, informed consent documents, amendments, and plans for data safety and monitoring;
- evaluate the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, performance of the trial sites, and other factors that may potentially affect study outcome;

- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator;
- report to NINDS on the safety and progress of the trial;
- make recommendations to the NINDS, the Principal Investigator, and, if required, to the Food and Drug Administration (FDA) concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- ensure the confidentiality of the study data and the results of monitoring; and,
- advise the NINDS and the study investigators as to whether the protocol should continue as scheduled or undergo a modification due to a finding from the monitoring process.

For a detailed description of the DSMB monitoring guidelines, go to the following website: http://www.ninds.nih.gov/funding/research/clinical_research/policies/data_safety_monitoring.htm

12.2 External Medical Safety Monitor

Dr. Julio Chalela of the Medical University of South Carolina will serve as the external Medical Safety Monitor and is responsible for ongoing monitoring of reports of SAEs submitted by clinical sites to ensure good clinical practice and to quickly identify safety concerns.

12.3 Biostatistical Core and Data Management (BSC)

The University of Cincinnati and Cincinnati Children's Hospital Medical Center will provide the data management and analysis for this study. Judy Bean, PhD, and Jane Khoury, PhD, experienced biostatisticians, will lead this center. This center will be responsible for providing the case report forms, procedure manual, clinical monitoring and source document review, data entry and programming and reports for the NINDS, the DSMB, SPOTRIAS, Novo Nordisk, and participating centers. In addition, Dr. Matthew Flaherty will apply for an the IND for the study and will be responsible for timely and appropriate reporting of adverse drug experiences to the Food and Drug Administration (FDA), the NINDS, the DSMB, and the enrolling centers.

12.4. Coordinating Clinical Center

The Clinical Coordinating Center (CCC) will provide overall clinical guidance and leadership for the execution of the STOP-IT Study. The overall Principal Investigators, Drs. Flaherty and Jauch, will be responsible for oversight of the conduct of the trial, recruitment of centers, and management of day-to-day issues.

The Clinical Coordinating Center physicians and overall project manager will be available to discuss any treatment issues that arise at a given center. Sites will be instructed to contact the Clinical Coordinating Center prior to deviating from the protocol.

The Clinical Coordinating Center will be responsible for coordinating the response to regulatory agencies by communicating with any center in the preparation and submission of all NINDS, DSMB, and FDA IND safety reports (Medwatch), and to all corporate partners and the clinical centers. The coordinating site will maintain a record of all safety correspondence with these entities.

The Clinical Coordinating Center staff will be responsible for training and verifying the training of the investigator and staff at the clinical centers. Specifically this will include standardized training for the trial's major clinical measures: the NIHSSS, modified Barthel Index, and the modified Rankin Scale. All training will require verification of participation.

The Clinical Coordinating Center will coordinate and supervise site recruitment. They will monitor site performance and make decisions regarding the dropping of poorly performing clinical centers

and the screening and addition of new clinical centers. Intermittently, CCC personnel will make site visits to re-evaluate a site or to assist a center in developing a more effective recruitment strategy. All subject enrollment confirmation notices will be faxed to the Clinical Coordination Center where it will be entered in the web database. The Coordinating Center in Cincinnati will create and maintain the trials central regulatory document file and coordinate communication regarding verification of these documents at the centers with the site monitoring staff.

The data-monitoring plan will be developed by the Clinical Coordinating Center with guidance provided by the Biostatistical Core. The contract research data monitoring staff will be supervised and managed by Clinical Coordinating staff. All monitoring trip assignments and reimbursement for monitoring services and expenses will be made by the Coordinating Center Clinical staff.

12.5 Imaging Center

Primary imaging analyses will be provided by the investigators at the University of Calgary and Sunnybrook Health Sciences Centre, Toronto. Image analysis will be led by Drs. Demchuk and Aviv in a standard manner, blinded to clinical data.

12.6 Participating Centers

The participating centers in this trial are comprised of one or more Principal Investigators (either neurology or emergency medicine), co-investigators, research coordinators, radiologists, and other necessary staff who will be responsible for enrolling the patients and collecting the data for this trial. The Principal Investigator at each participating center is responsible for the overall conduct and performance of the clinical center. A participating center may have one or more participating performance sites. All participating centers and its performance sites must demonstrate clear involvement and leadership within the emergency medicine department, as the emergency department is where initial contact with most patients is made and the early diagnostic and treatment activities occur. The clinical coordinator will be responsible for such critical matters as completing exclusion logs, tracking and or performing telephone follow-up visits, coordinating and verifying the completion and web-based entering of case report forms and regulatory documents, and arranging the shipment of CT and CTA data to the Clinical Coordinating Center. The storage and documentation of study medication will be the responsibility of either the hospital pharmacy or the clinical coordinator.

Each clinical center is expected to provide all applicable regulatory documents deemed necessary by the Clinical Coordinating Center for the initiation of a clinical research protocol at each of its clinical performance sites. All sites will be expected to comply with state and federal requirements for the initiation and ongoing performance of a clinical trial and adherence to its local IRB / EC requirements for obtaining subject consent, reporting of protocol defined SAEs and the storage and accountability of study medication. Each site is expected to screen all acute ICH patients at IRB / EC approved performance sites for inclusion into the STOP-IT Study and enter the information on its Stroke Log in the STOP-IT Study web site on a monthly basis. Sites will identify and recruit appropriate study candidates as defined by the trial's inclusion and exclusion criteria. All performance sites will observe trial defined imaging and imaging acquisition protocols as well as other protocol-defined procedures. Clinical Centers are expected to provide clinical and imaging data in a time frame consistent with those defined in the Manual of Procedures. All centers must permit inspection of site regulatory documents and monitoring of CRF source documents by trial representatives and/or representatives of local or federal regulatory agencies. Each clinical center in the STOP-IT Study will provide a site representative at all required investigator meetings and trial conference calls.

Enrollment and compliance with all protocols will be reviewed periodically by the research coordinator. If serious protocol breaks or decreased enrollment occur, the center may be dropped from the study at the discretion of Dr. Flaherty or Dr. Jauch. The clinical coordinator at each

participating center will be responsible for such critical matters as checking emergency department logs, appointment scheduling, checking the completeness of forms and arranging the shipment of imaging data to the Coordinating Center.

12.7 Steering Committee

The steering committee will be comprised of the Co-Principal Investigators for this project (Drs. Matthew Flaherty and Edward Jauch), the overall Principal Investigator for the University of Cincinnati SPOTRIAS site (Dr. Joseph Broderick), Dr. Joshua Goldstein (Harvard University), Dr. Stephan Mayer (Columbia), Drs. Richard Aviv and David Gladstone (Sunnybrook Health Sciences Centre, Toronto), and Drs. Andrew Demchuk and Michael Hill (University of Calgary). The Steering Committee will advise and assist the Clinical Coordinating Center on operational matters, monitor the performance of the clinical centers, receive requests for any proposed ancillary studies, and establish publication policies for the pilot trial. The Steering Committee will also report major problems and recommend changes in the protocol to the NINDS Project Officer and the Data and Safety Monitoring Board. Beyond providing study guidance, the Steering Committee also provides the forum for Principal Investigators to serve as study collaborators. Members of the steering committee will be responsible for overseeing publications which result from the STOP-IT Study.

12.8 Drug Distribution and Pharmacy Support

The Department of Pharmacy Services at The University Hospital (TUH) at the University of Cincinnati has 20 years experience in industry and NIH funded pharmaceutical research. The TUH Pharmacy-Coordinated Investigational Drug Service (IDS) has successfully facilitated, dispensed and provided accountability and control of medications used in multiple acute stroke drug studies including the NIH funded rt-PA dose escalation trial, the randomized NINDS rt-PA Stroke Trial, the EMS, IMS I, IMS II, and IMS III trials, and the CLEAR trial as part of the previous SPOTRIAS funding period. IDS, under the direction of Caron Sue, PharmD, Ph.D, is staffed by both an investigational drug pharmacist and pharmacy technician.

The University of Calgary will act as the drug distribution center for Canada and main contact for Health Canada. As a member of the Canadian Stroke Consortium, the University of Calgary has already acted as the drug distribution center for Canada in the IMS I, II, and III trials.

12.9 Novo Nordisk

Novo Nordisk manufactures rFVIIa and will be responsible for providing study drug and placebo to the participating centers via the University of Cincinnati drug distribution center.

12.10 Investigational New Drug (IND) Application

With the cooperation of Novo Nordisk an IND will be submitted to the US Food and Drug Administration for use of rFVIIa in this trial.

12.11 National Institute of Neurological Disorders and Stroke

The NINDS will provide funding for all aspects of this trial other than cost of study drug, via the SPOTRIAS consortium. Scott Janis, Ph.D, will be the Program Scientific Officer. Dr. Janis will have substantial scientific-programmatic involvement during the conduct of this phase II trial.

13.0 HUMAN SUBJECTS

This study will be conducted in accordance with current US Food and Drug Administration Good Clinical Practice and local ethical and legal requirements. Subjects for this trial will be recruited from all subjects with suspected acute ICH admitted to participating performance sites. All subjects with acute ICH, whether eligible or not, who are admitted to the participating site within five hours of onset during the accrual phase of the study will be recorded in a Stroke Log. Informed consent from the patient, or if the patient is aphasic or confused, the legal representative of that patient will be required prior to randomization.

It is ethical to conduct this randomized controlled trial (RCT) because clinical equipoise currently exists: there is uncertainty whether or not rFVIIa can produce a clinically meaningful benefit to patients. The drug is available but is currently not approved for the indication of ICH treatment by Health Canada or the United States FDA. Only a properly conducted RCT will provide the evidence base necessary for clinical decision making. Because rFVIIa is a prothrombotic drug, its use in the ICH population is associated with an increase in the incidence of arterial thromboembolic complications, as detailed previously. This is considered an acceptable low risk, particularly given the fact that it is being administered for a life-threatening emergency. Study patients will continue to receive routine clinical stroke care that is standard practice at each of the participating centers. This is an investigator-initiated, academic trial.

13.1 Institutional Review Board (IRB) / Ethics Committee (EC) and Informed Consent

This protocol, the informed consent document, and relevant supporting information must be submitted to local IRBs / ECs for review and approval before the study is initiated. The principal investigator at each clinical site is responsible for keeping the local IRB / EC apprised of the progress of the study and of any changes made to the study protocol, as well as any serious adverse events.

The final IRB/EC approved document will be provided to the Clinical Coordinating Center. Prior to participation/randomization in the study, the IRB/EC approved informed consent statement must be obtained from a competent subject and/or subject's legally authorized representative. The process for obtaining consent of the subject (i.e., from the subject and/or legal representative) must be in compliance with the local performance site's IRB/EC guidelines and policies for obtaining informed consent for research participation. Waiver of consent (exception of informed consent) will not be allowed in this study and a subject will not be enrolled if consent cannot be obtained from the subject themselves or their legally authorized surrogate. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

13.2 HIPAA / PIPEDA

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. Each participating U.S. clinical center is expected to comply with its individual performance site's requirements established for compliance of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) affecting the research process with respect to subject PHI. The CCC will require the authorization include that subject PHI may be disclosed to specific agencies or persons for their use with regard to the STOP-IT Study. The document will be provided to the CCC for final approval.

Under Canadian federal legislation effective early 2004, all Canadian centers will be expected to comply with the Personal Information, Privacy and Electronic Documents act (PIPEDA).

13.3 Specimens

Blood tests that are routinely obtained on patients with ICH will be recorded. Troponin levels will be obtained at baseline, 24, and 48 hours for subjects in the treatment arm. A baseline troponin will be obtained for subjects in the observational arm. Serum creatinine will be obtained for subjects in the treatment and observational arm at baseline, 24 hours, 72 hours, and day 5 or discharge (whichever is sooner). No genetic testing will be performed on obtained blood samples and no blood samples will be stored for research purposes as part of this study.

13.4 Recruitment of Minorities and Women

This study will encourage enrollment of all eligible subjects regardless of gender, race, or ethnicity. Any gender, racial or ethnic disparity in recruitment detected will be the result of differences in the pattern of referral to the participating institutions. Pregnant women are excluded from this protocol because of potential risk to the fetus.

Table 9. Targeted/planned enrollment

Ethnic Categories	Sex		
	Female	Male	Total
○ Hispanic or Latino	4	4	8
○ Not Hispanic or Latino	88	88	176
Total	92	92	184
Racial Categories			
○ American Indian/Alaska Native	0	0	0
○ Asian	2	2	4
○ Native Hawaiian or Other Pacific Islander	0	0	0
○ Black or African American	13	13	26
○ White	77	77	154
Total	92	92	184

13.5 Inclusion of Children

Only persons 18 years and older will be enrolled in the study. ICH in the neonatal period is a different disease process than ICH in adults and is not appropriate for inclusion in this study. Spontaneous ICH is otherwise extremely rare in children and is often due to vascular malformations or aneurysms.

13.6 Potential Risks and Benefits

Intracerebral hemorrhage is the most devastating form of stroke with overall 30-day mortality ranging from, 30-50%. While many patients arrive in the emergency department significantly impaired by the hemorrhage, others arrive with modest deficits which rapidly worsen due to hemorrhage expansion. No targeted intervention currently exists to mitigate the clinical effect of the hemorrhage and hemorrhage expansion. While phase II studies suggested clinical benefit from hemostatic therapy, a recently completed phase III trial left uncertainty as to optimal patient selection to minimize the potential thromboembolic side effects of hemostatic therapy while maximizing potential hemostatic benefit. Adequate protections against excessive risk of thromboembolic are in place by conservative patient selection criteria. The major risk associated with participation in this study is serious arterial thromboembolic events (e.g., acute myocardial ischemia and ischemic stroke) associated with rFVIIa administration. Treatment with rVIIa in this setting carries an approximately 5% excess risk of arterial thromboembolic events compared to placebo.^{6, 7} There appears to be no difference in the rate of venous thromboembolic events in rFVIIa-treated subjects versus placebo-treated subjects^{6, 7} (see section 4.2.2 for further discussion of the safety profile of rVIIa). Aggressive clinical and laboratory monitoring are essential components of this study to monitor for and address this risk.

An additional risk from participating in this trial is associated with the use of intravenous contrast medium for the CTA. Radiographic iodinated contrast agents are used extensively in health care. As discussed in section 5.5.2, CTA is already used as a standard method of evaluation for patients with acute ICH at some centers in North America. Allergic reactions are a real but relatively rare occurrence with modern contrast agents; mild allergic reactions occur in 2% of patients receiving intravenous contrast dye, severe reactions to contrast media occur in roughly 0.1% of patients. Contrast extravasation into a limb due to failure of the intravenous access may occur in 0.25-0.6% of

injections.³¹ Contrast extravasation may result in local tissue damage.³² Based upon clinical literature, reported deaths from the administration of iodinated contrast agents range from 6.6 per million (0.00066%) to 1 in 10,000 (0.01%).⁴⁷ An additional risk with the use of iodinated radiographic contrast medium is contrast-induced nephropathy.²⁸ A recent study of CTA in patients with acute stroke demonstrated a very low incidence of contrast-induced nephropathy (3%) and no patients required dialysis.³⁰ This risk is greatest in patients with chronic kidney disease and is proportional to the amount of agent administered.²⁸ Our patient selection includes a conservative serum creatinine level for inclusion among patients entered at sites that do not perform CTA as standard care for patients with ICH. Centers that do perform CTA as standard acute care for patients with ICH also have protocols in place to exclude patients with significant renal insufficiency.³⁰ Only a single administration of contrast medium will be associated with this study. Serial monitoring for elevations in serum creatinine will be performed to identify any increase in creatinine as a sign of contrast-induced nephropathy.

The CT scans and CT angiography used in this study involve exposure to a small amount of radiation in addition to the usual x-ray studies done in patients with intracerebral hemorrhage. The radiation dose delivered by a CTA is slightly more than a non-contrast CT study when centered on the intracranial vessels (1.9 mSV vs. 1.7 mSV)³³ There is a very small chance of skin or hair damage.

13.7 Subject Confidentiality

All information concerning subjects (e.g., imaging and laboratory data, evaluation forms, CRFs, etc.) will be identified only by the assigned Subject Identification Number (SID) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using SIDs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB/EC, the FDA, or NINDS, the study's sponsor. No personal identifying information will be used in presentation or publication of data from this study.

14.0 VERTEBRATE ANIMALS

No vertebrate animals will be used in this study.

15.0 SELECT AGENT RESEARCH

Not applicable.

16.0 DISCLOSURE OF DATA

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited. Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Data generated by this study must be available for inspection upon request by Authorized Agents of the United States Food and Drug Administration, national and local health authorities, the University of Cincinnati, the National Institute of Neurological Disorders and Stroke, Novo Nordisk (manufacturer of the study drug recombinant activate factor VII), and respective IRB/EC authorities.

17.0 Data Sharing Plan

The BSC will be responsible for constructing a file from each trial that can be used by the public. After completion and finalization of the data base and publication of study results, the data base will be made available to clinical investigators as has been done for the NINDS rt-PA Stroke Trial through the NINDS. The public use database will be stripped of any and all personal identifiers.

The public use database will consists of several data files: 1) baseline data file; 2) outcome assessments file; 3) CT and/or CTA data file; 4) concomitant medications file 5) procedures file; and

6) adverse events file. Each data file will be made available as a formatted SAS® dataset or as a MS Excel or Access data file. The data files will be distributed, along with the data dictionary. Anyone wishing access to the data may do so by completing a data request form and submitting it to the Trial Steering Committee. The data files can be distributed on CD or via email on password protected zip file. Limited information for the trial subjects will be available through the SPOTRIAS shared database.

18.0 REFERENCES

1. Kissela B, Schneider A, Kleindorfer D, Khoury J, Miller R, Alwell K, Woo D, Szaflarski J, Gebel J, Moomaw CJ, Pancioli A, Jauch E, Shukla R, Broderick J. Stroke in a biracial population: The excess burden of stroke among blacks. *Stroke*. 2004;35:426-431.
2. Flaherty ML, Haverbusch M, Sekar P, Kissela BM, Kleindorfer D, Moomaw CJ, Sauerbeck L, Broderick JP, Woo D. Long-term mortality after intracerebral hemorrhage. *Neurology*. 2006;66:1182-1186.
3. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, Spilker J, Duldner J, Khoury J. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke*. 1997;28:1-5.
4. Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, Begtrup K, Steiner T, for the Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology*. 2006;66:1175-1181.
5. Mayer SA. Ultra-early hemostatic therapy for intracerebral hemorrhage. *Stroke*. 2003;34:224-229.
6. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T, for the Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators. Recombinant activated factor vii for acute intracerebral hemorrhage. *NEJM*. 2005;352:777-785.
7. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer M, Skolnick BE, Steiner T, for the Fast Trial Investigators. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *NEJM*. 2008; 358: 2127-2137.
8. Wada R, Aviv RI, Fox AJ, Sahlas DJ, Gladstone DJ, Tomlinson G, Symons SP. CT angiography "spot sign" predicts hematoma expansion in acute intracerebral hemorrhage. *Stroke*. 2007;38:1257-1262.
9. Goldstein JN, Fazen LE, Snider R, Schwab K, Greenberg SM, Smith EE, Lev MH, Rosand J. Contrast extravasation on CT angiography predicts hematoma expansion in intracerebral hemorrhage. *Neurology*. 2007;68:889-894.
10. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope T, Karimi A, Shaw MDM, Barer DH, for the STICH investigators. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the international Surgical Trial in Intracerebral Haemorrhage (STICH): A randomised trial. *Lancet*. 2005;365:387-397.
11. Hemphill JC, 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: A simple, reliable grading scale for intracerebral hemorrhage. *Stroke*. 2001;32:891-897.
12. Broderick J, Brott T, Tomsick T, Tew J, Duldner J, Huster G. Management of intracerebral hemorrhage in a large metropolitan population. *Neurosurgery*. 1994;34:882-887.
13. Leira R, Davalos A, Silva Y, Gil-Peralta A, Tejada J, Garcia M, Castillo J, for the Stroke Project Cerebrovascular Diseases Group of the Spanish Neurological Society. Early neurologic deterioration in intracerebral hemorrhage: Predictors and associated factors. *Neurology*. 2004;63:461-467.
14. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. *Stroke*. 1996;27:1783-1787.
15. Fujii Y, Takeuchi S, Sasaki O, Minakawa T, Tanaka R. Multivariate analysis of predictors of hematoma enlargement in spontaneous intracerebral hemorrhage. *Stroke*. 1998;29:1160-1166.
16. Fujii Y, Tanaka R. Predictors of hematoma growth? Response. *Stroke*. 1998;29:2442-2443 (letter).
17. Kazui S, Minematsu K, Yamamoto H, Sawada T, Yamaguchi T. Predisposing factors to enlargement of spontaneous intracerebral hematoma. *Stroke*. 1997;28:2370-2375

18. Fujii Y, Takeuchi S, Sasaki O, Minakawa T, Tanaka R. Multivariate analysis of predictors of hematoma enlargement in spontaneous intracerebral hemorrhage. *Stroke*. 1998;29:1160-1166
19. Fujitsu K, Muramoto M, Ikeda Y, Kim I, Kuwabara T. Indications for surgical treatment of putaminal hemorrhage. *J Neurosurg*. 1990;73:518-525.
20. Yamaki T, Yoshino E, Higuchi T. Extravasation of contrast medium during both computed tomography and cerebral angiography. *Surg Neurol*. 1983;19:247-250.
21. Yamamoto T, Muraki M, Oishi H, Uemura K. Contrast-enhanced MRI of hypertensive intracerebral hemorrhage in the hyperacute stage--extravasation of contrast medium as detector of growing hematoma. *Nippon Rinsho*. 1993;51 (Suppl):48-54.
22. Wolpert SM, Schatzki SC. Extravasation of contrast material in the intracerebral basal ganglia. *Radiology*. 1972;102:83-85.
23. Huckman MS, Weinberg PE, Kim KS, Davis DO. Angiographic and clinico-pathologic correlates in basal ganglionic hemorrhage. *Radiology*. 1970;95:79-92.
24. Becker KJ, Baxter AB, Bybee HM, Tirschwell DL, Abouelsaad T, Cohen WA. Extravasation of radiographic contrast is an independent predictor of death in primary intracerebral hemorrhage. *Stroke*. 1999;30:2025-2032.
25. Murai Y, Ikeda Y, Teramoto A, Tsuji Y. Magnetic resonance imaging-documented extravasation as an indicator of acute hypertensive intracerebral hemorrhage. *J Neurosurg*. 1998;88:650-655.
26. Yamaguchi K, Uemura K, Takahashi H, Kowada M, Kutsuzawa T. Extravasation of contrast media in hypertensive cerebral hemorrhage. *Rinsho Hoshasen*. 1972;17:257-263.
27. Broderick J, Connolly S, Feldmann E, Hanley D, Kase C, Krieger D, Mayberg M, Morgenstern L, Ogilvy CS, Vespa P, Zuccarello M. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update. *Stroke*. 2007;38:2001-2023.
28. Benko A, Fraser-Hill M, Magner P, Capusten B, Barrett B, Myers A, Owen RJ. Consensus guidelines for the prevention of contrast induced nephropathy. *Canadian Association of Radiologists Journal*. 2007;58:79-87.
29. Rudnick MR, Goldfarb S, Wexler L, Ludbrook PA, Murphy MJ, Halpern EF, Hill JA, Winniford M, Cohen MB, VanFossen DB. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: A randomized trial. The Iohexol Cooperative Study. *Kidney Int*. 1995;254-261.
30. Krol AL, Dzialowski I, Roy J, Puetz V, Subramaniam S, Coutts SB, Demchuk AM. Incidence of radiocontrast nephropathy in patients undergoing acute stroke computed tomography angiography. *Stroke*. 2007;38:2364-2366.
31. Cochrane ST, Bomyea K, Sayre JW. Trends in adverse events after IV administration of contrast media. *AJR*. 2001;176:1385-1388.
32. Bellin M-F, Jakobsen JA, Tomassin I, Thomsen HS, Morcos SK, and members of the Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR). Contrast medium extravasation injury: Guidelines for prevention and management. *Eur Radiol*. 2002;12:2807-2812.
33. Cohnen M, Wittsack H-J, Assadi S, Muskalla K, Ringelstein A, Poll LW, Saleh A, Modder U. Radiation exposure of patients in comprehensive computed tomography of the head in acute stroke. *AJNR Am J Neuroradiol*. 2006;27:1741-1745
34. Hedner U. Recombinant activated factor VII as a universal haemostatic agent. *Blood Coagul Fibrinolysis*. 1998;9 Suppl 1:S147-152.
35. Hedner U, Ingerslev J. Clinical use of recombinant FVIIa (rFVIIa). *Transfus Sci*. 1998;19:163-176.
36. Friederich PW, Henny CP, Messelink EJ, Geerdink MG, Keller T, Kurth K-H, Buller HR, Levi M. Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: A double-blind placebo-controlled randomised trial. *Lancet*. 2003;361:201-205.
37. Rice KM, Savidge GF. Novoseven (recombinant factor VIIa) in central nervous system bleeds. *Haemostasis*. 1996;26 Suppl 1:131-134.

38. Fewel ME, Park P. The emerging role of recombinant-activated factor VII in neurocritical care. *Neurocrit Care*. 2004;1:19-30.
39. Mayer SA, Brun NC, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T, for the Europe/AustralAsia NovoSeven Trial Investigators. Safety and feasibility of recombinant factor VIIa for acute intracerebral hemorrhage. *Stroke*. 2005;36:74-79.
40. Kothari RU, Brott TG, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M. The abcs of measuring intracerebral hemorrhage volume. *Stroke*. 1996;27:1304-1305.
41. Roberts HR, Monroe DM, White GC. The use of recombinant factor VIIa in the treatment of bleeding disorders. *Blood*. 2004;104:3858-3864.
42. Lewis MH, Gohagan JK, Merenstein DJ. The locality rule and the physician's dilemma. *JAMA*. 2007;297:2633-2637.
43. Flaherty ML, Woo D, Haverbusch M, Moomaw CJ, Sekar P, Sauerbeck L, Kissela B, Kleindorfer D, Broderick JP. Potential applicability of recombinant factor VIIa for intracerebral hemorrhage. *Stroke*. 2005;36:2660-2664.
44. Fenn-Buderer NM. Statistical methodology: I. Incorporating the prevalence of disease into the sample size calculation for sensitivity and specificity. *Acad Emerg Med*. 1996;3:895-900.
45. Agresti A, Coull B. Approximate is preferred over "exact" for interval estimation of binomial proportions. *Am Stat*. 1998;52:119-126.
46. National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group. Effect of intravenous recombinant tissue plasminogen activator on ischemic stroke lesion size measure by computed tomography. *Stroke*. 2000;31:2912-2919.
47. GE Healthcare Inc. Visipaque (iodixanol) injection package insert. 2006.

STOP-IT | | | | Subject # | | - | | - | | | | Consent Date | | | | | | | | | | | | | | | | (Page 1 of 3)
 NIHSS Worksheet

NIH STROKE SCALE
 WORKSHEET

<input type="checkbox"/> BASELINE	<input type="checkbox"/> 1 Hour (+/- 10 Minutes) – Required For Treatment Arm Subjects Only	
<input type="checkbox"/> 24 Hour + 3 Hours (Blinded)	<input type="checkbox"/> Discharge + 2 Days (Blinded) <input type="checkbox"/> Other	
Was stroke scale rating done? 1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	Date ___/___/___ Time ___:___	
DD / MMM / YYYY 24 hr. clock		
Is patient intubated and paralyzed? 1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No (IF YES, score as unexaminable using all 9s)		
<small>Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).</small>		
IF ANY ITEM IS LEFT UNTESTED, A DETAILED EXPLANATION MUST BE CLEARLY WRITTEN ON THE FORM. ALL UNTESTED ITEMS WILL BE REVIEWED BY THE MEDICAL MONITOR, AND DISCUSSED WITH THE EXAMINER BY TELEPHONE.		
Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation. <i>* Use coma scoring detailed on instruction page for patients scoring a “3” on this item</i>	0 = Alert; keenly responsive 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond 2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped) *3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, areflexic	___
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not “help” the patient with verbal or non-verbal cues.	0 = Answers both questions correctly 1 = Answers one question correctly 2 = Answers neither question correctly	___
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to them (pantomime) and score the result (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly	___
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored but calorimetric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI) score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness or other disorder of visual acuity or fields should be tested with reflexive movements and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = Normal 1 = Partial gaze palsy. This score is given when gaze is abnormal in one or both eyes, but where forced deviation or total gaze paresis are not present 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver	___
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat as appropriate. Patient must be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia is found. If patient is blind from any cause score 3. Double simultaneous stimulation is performed at this point. If there is extinction patient receives a 1 and the results are used to answer question 11.	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia (blind including cortical blindness)	___

STOP-IT
NIHSS Worksheet

Subject # [] - [] - [] - [] - [] Consent Date [] - [] - [] (Page 2 of 3)

NIH STROKE SCALE WORKSHEET *continued*

<input type="checkbox"/>	BASELINE	<input type="checkbox"/>	1 Hour (+/- 10 Minutes) – Required For Treatment Arm Subjects Only
<input type="checkbox"/>	24 Hour ± 3 Hours (Blinded)	<input type="checkbox"/>	Discharge ± 2 Days (Blinded)
		<input type="checkbox"/>	Other
Instructions		Scale Definition	Score
<p>4. Facial Palsy: Ask, or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barrier obscures the face, these should be removed to the extent possible.</p>		<p>0 = Normal symmetrical movement 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling) 2 = Partial paralysis (total or near total paralysis of lower face) 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)</p>	_____
<p>5 & 6. Motor Arm and Leg: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder or hip may the score be "9" and the examiner must clearly write the explanation for scoring as a "9".</p> <p style="text-align: center;">* SCORE BOTH SIDES</p>		<p>0 = No drift, limb holds 90 (or 45) degrees for full 10 seconds 1 = Drift, limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support 2 = Some effort against gravity, limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity, limb falls 4 = No movement 9 = Amputation, joint fusion explain: _____</p> <p style="text-align: right;">5a. Left Arm 5b. Right Arm</p>	<p>_____</p> <p>_____</p>
		<p>0 = No drift, leg holds 30 degrees position for full 5 seconds. 1 = Drift, leg falls by the end of the 5 second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity, leg falls to bed immediately. 4 = No movement 9 = Amputation, joint fusion explain: _____</p> <p style="text-align: right;">6a. Left Leg 6b. Right Leg</p>	<p>_____</p> <p>_____</p>
<p>7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, insure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion may the item be scored "9", and the examiner must clearly write the explanation for not scoring. In case of blindness test by touching nose from extended arm position.</p>		<p>0 = Absent 1 = Present in one limb 2 = Present in two limbs</p> <p>If present, is ataxia in:</p> <p>Right arm 1=Yes 2=No 9=amputation or joint fusion explain _____ Left arm 1=Yes 2=No 9=amputation or joint fusion explain _____ Right leg 1=Yes 2=No 9=amputation or joint fusion explain _____ Left leg 1=Yes 2=No 9=amputation or joint fusion explain _____</p>	<p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p>

STOP-IT
NIHSS Worksheet

Subject # _____ - _____ - _____ Consent Date _____ - _____ - _____
(Page 3 of 3)

NIH STROKE SCALE WORKSHEET *continued*

<input type="checkbox"/> BASELINE	<input type="checkbox"/> 1 Hour (+/- 10 Minutes) – Required For Treatment Arm Subjects Only	
<input type="checkbox"/> 24 Hour ± 3 Hours (Blinded)	<input type="checkbox"/> Discharge ± 2 Days (Blinded)	<input type="checkbox"/> Other
Instructions	Scale Definition	Score
<p>8. Sensory: Sensation or grimace to pin prick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas [arms (not hands), legs, trunk, face] as needed to accurately check for hemisensory loss. A score of 2, "severe or total," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will therefore probably score 1 or 0. The patient with brain stem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic score 2. Patients in coma (item 1a=3) are arbitrarily given a 2 on this item.</p>	<p>0 = Normal; no sensory loss. 1 = Mild to moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick but patient is aware he/she is being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.</p>	_____
<p>9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. The patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences. Comprehension is judged from responses here as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in coma (question 1a=3) will arbitrarily score 3 on this item. The examiner must choose a score in the patient with stupor or limited cooperation but a score of 3 should be used only if the patient is mute and follows no one step commands.</p>	<p>0 = No aphasia, normal 1 = Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided material difficult or impossible. For example in conversation about provided materials examiner can identify picture or naming card from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.</p>	_____
<p>10. Dysarthria: If patient is thought to be normal an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barrier to producing speech, may the item be scored "0", and the examiner must clearly write an explanation for not scoring. Do not tell the patient why he/she is being tested.</p>	<p>0 = Normal 1 = Mild to moderate; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. 0 = Intubated or other physical barrier, explain</p>	_____
<p>11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.</p>	<p>0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space.</p>	_____
<p>FOR THIS EVALUATION, WAS THE PATIENT SEDATED?</p>		<p>1 <input type="checkbox"/> YES 2 <input type="checkbox"/> NO</p>
<p>If yes, did the sedation effect the score?</p>		<p>1 <input type="checkbox"/> YES 2 <input type="checkbox"/> NO</p>

Signature (Site Investigator): _____

Date _____
DD / MMM / YYYY (ie - 01 / JAN / 1901)

Print Name (Last, First): _____

Appendix II

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Appendix II: Glasgow Coma Scale

GLASGOW COMA SCALE	
Points:	Best Eye Response
4	• Eyes opening spontaneously
3	• Eyes opening to speech
2	• Eyes opening in response to pain
1	• No eye opening
	Best Verbal Response
5	• Oriented (Patient responds coherently and appropriately to questions)
4	• Confused (Patient responds to questions coherently but there is some disorientation)
3	• Inappropriate words (Random articulated speech, but no conversational exchange)
2	• Incomprehensible sounds (Moaning but no words)
1	• No verbal response
	Best Motor Response
6	• Obeys commands
5	• Localized to pain (Purposeful movements towards painful stimuli)
4	• Flexion / withdrawal to pain
3	• Abnormal flexion to pain (Decorticate response)
2	• Abnormal extension to pain (Decerebrate response)
1	• No motor response
	GCS Score
_____	Total from above (15 – 3)

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Appendix III: Modified Rankin Scale

MODIFIED RANKIN SCALE (mRS)	
Total Score (0–6):	
0 = No symptoms at all	
1 = No significant disability despite symptoms; able to carry out all usual duties and activities	
2 = Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance	
3 = Moderate disability; requiring some help, but able to walk without assistance	_____
4 = Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance	
5 = Severe disability; bedridden, incontinent and requiring constant nursing care and attention	
6 = Dead	

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Appendix IV: Barthel Index

Feeding	0 = Unable 5 = Needs help cutting, spreading butter, or requires modified diet 10 = Independent
Transfer (bed to chair and back)	0 = Unable, no sitting balance 5 = Major help (one or two people; physical), can sit 10 = Minor help (verbal or physical) 15 = Independent
Grooming	0 = Needs help with personal care 5 = Independent face/hair/teeth/shaving (implements provided)
Toilet Use	0 = Dependent 5 = Needs some help, but can do something alone 10 = Independent (on and off, dressing, wiping)
Bathing	0 = Dependent 5 = Independent (or in shower)
Mobility (on level surface)	0 = Immobile or < 50 yards 5 = Wheelchair independent, including corners, > 50 yards 10 = Walks with help of one person (verbal or physical) > 50 yards 15 = Independent (but may use aid, e.g., cane) > 50 yards
Stairs	0 = Unable 5 = Needs help (verbal, physical, carrying aid) 10 = Independent
Dressing	0 = Dependent 5 = Needs help but can do about half unaided 10 = Independent (including buttons, zips, laces, etc.)
Bowels	0 = Incontinent (or needs to be given enemas) 5 = Occasional accident 10 = Continent
Bladder	0 = Incontinent, or catheterized and unable to manage alone 5 = Occasional accident 10 = Independent

Consent if CTA IS NOT Standard of Care
PATIENT CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Spot Sign for Predicting and Treating ICH Growth Study (STOP-IT Study)

Sponsor: NIH / NINDS

Sponsor #: 2P50NS044283-06

INTRODUCTION:

If you are acting as a representative to give consent for another person to participate in this study, “you” throughout this consent form refers to that individual.

Your obligation is to try to determine what the individual would do if competent, or if the subject’s wishes cannot be determined, what you think is in the person’s best interest. If possible, an attempt should be made to obtain permission from the individual. Some persons may resist participating in a research protocol that has been approved by their representatives. Under no circumstances may individuals be forced to participate.

Before you agree to participate in this research study, it is important that you be told the purpose, procedures, benefits, risks, discomforts, and precautions of the research. You should also be told what alternative procedures are available to you if you do not participate in the research study.

Your participation in this research study is entirely voluntary. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from the study at any time without penalty. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time without unfairness to you or your medical care. We do not promise that you will receive any benefits from this study.

This informed consent document is a brief written summary of what your study doctor is telling you. Be sure to ask questions while you read this if there is anything that you do not understand.

WHY IS THIS RESEARCH BEING DONE?

The purposes of this research study are:

1. To find out if a special x-ray test called a computed tomography angiogram (CTA) can help doctors predict which patients that have suffered an intracerebral hemorrhage or breakage of a blood vessel with bleeding into the brain will experience significant growth in the size of the hemorrhage or bleed. Growth or increase in the size of the hemorrhage can cause additional injury to the brain and has been associated with a worse outcome for patients.
2. For patients considered to be at high risk for hemorrhage growth based on the results of the CTA, to compare the effects (good or bad) of the study medication called recombinant activated factor seven (NovoSeven®) with a placebo (inactive medication) on reducing intracerebral hemorrhage growth to see which is better. You may or may not receive the study drug.

CT angiography is a common imaging tool used for stroke patients. The use of CTA to predict hemorrhage growth and its potential role in the treatment of intracerebral hemorrhage is investigational. Recombinant activated factor VII (NovoSeven®) has been approved by the Food and Drug Administration (FDA) for treatment of bleeding in some patients with a type of bleeding disorder in which blood does not clot normally called hemophilia. Recombinant activated factor VII is not FDA approved for treatment of intracerebral hemorrhage and its use for this condition is investigational.

WHY HAVE YOU BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in this research study because you are 18 years of age or older and you have been diagnosed with a type of stroke called an acute intracerebral hemorrhage or hemorrhagic stroke.

HOW LONG WILL YOU BE IN THE RESEARCH STUDY?

You will be in the research study for approximately 3 months from the time of treatment for your hemorrhagic stroke. After discharge from the hospital, you will receive follow-up telephone calls at 1 month and again at three months by study staff to evaluate your condition at that time.

The researcher may decide to take you off this research study at any time. If you experience any of the side effects described in the “Risks and Discomforts” section or if you become ill during the research, you may have to drop out, even if you would like to continue. In addition, the National Institute of Health (NIH) and National Institute of Neurological Disorders and Stroke (NINDS), the study’s sponsor, and the IRB / EC has the right to terminate the study or the Principal Investigator’s participation in the study at any time. Novo Nordisk A/S, the study drug manufacturer has the right to terminate their participation in the study at any time.

You may withdraw from the study at any time. If you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first so that stopping can be done safely. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful to you.

WHO IS CONDUCTING THE RESEARCH STUDY?

This study is sponsored by the National Institute of Health (NIH) and National Institute of Neurological Disorders and Stroke (NINDS).

The study is directed by and under the medical supervision of *[Insert name of your site PI]*, the researcher at the *[Insert name of your participating institution]*.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

About *[Insert number of subjects projected to be enrolled at your site]* people will take part in this study at *[Insert name of your participating institution]*. Approximately 184 people will take part across the United States and Canada.

WHAT IS INVOLVED IN THE RESEARCH STUDY?

If you take part in this study, you will have the following tests and procedures:

1. You will receive the same standard of care given to all hemorrhagic stroke patients.
2. An intravenous line will be started for the administration of fluids and X-ray dye.
3. An electrocardiogram (EKG), which measures the electrical activity of your heartbeat, will be obtained to assess the functioning of your heart.
4. To determine your initial condition, you will be examined by a physician who will perform a few simple tests to look for problems with your brain (for example, your ability to move your arms and legs, to talk and understand speech and to see in all directions). A CT scan, a special type of brain x-ray, will be done to determine that you have a stroke from a breakage of a blood vessel with bleeding into your brain.
5. Routine blood samples will be drawn as in all stroke patients. The blood samples (about 2 tablespoons) will be taken from a vein in your arm for laboratory testing. No genetic testing will be performed on these samples.
6. You will also receive a CT angiography (CTA), as part of the study, which is a special x-ray of the brain that will check to see if there is a “spot sign” present within the blood or hemorrhage in your brain tissue. This sign, if present, may predict a higher risk that the hemorrhage in your brain will get bigger in the next few hours. The CTA follows the regular CT scan (or you will be

returned to the scanner if the CT scan has already been performed). For this test X-ray dye will be given through an IV in your arm before the test can be performed.

7. If the Spot Sign is present on the CTA:

- You will be “randomized” into one of two study groups described below. Randomization means that you are put into a group completely by chance. It is like flipping a coin. Neither you nor the researcher conducting this study will choose what group you will be in. You have an equal chance of being placed in either group. However, in the event of an emergency, your study doctor will be able to find out what treatment you are receiving.
- You will receive either an active study medication called recombinant activated factor VII, or you will receive a placebo or an inactive study medication through the IV in your arm.
- Additional blood samples (approximately 2 tablespoons total) will also be drawn at baseline, day 1, 2, 3 following treatment and at discharge as part of the study as a safety precaution to monitor your heart and kidney function.
- EKG’s will also be performed as part of the study on day 1, 2 and 3 to continue to assess the functioning of your heart.
- You will have a CT scan (a special x-ray of the brain) between 21 and 27 hours after you receive study drug as a safety check to evaluate the size of your hemorrhage.
- If you were to have any deterioration in your condition during the first 24 hours, or at any other time, a CT scan will be obtained immediately.
- You will be visited throughout your stay in the hospital by a stroke team physician or study nurse to evaluate your current condition.
- After discharge from the hospital, you will have follow-up phone calls at one and three months after your hemorrhagic stroke. During these calls, you will be asked questions about your quality of life at that time.

8. If the Spot Sign is not present on the CTA:

- You will not be randomized to receive any study medication; however you will continue to be part of the study.
- You will continue to receive the standard of care given to all hemorrhagic stroke patients. Part of this care will include a CT scan at between 21 and 27 hours after your CTA as a safety check to evaluate the size of your hemorrhage.
- Blood samples (approximately 1 tablespoon total) will be drawn as part of the study on day 1, 3 and discharge to monitor kidney function and a sample at baseline to monitor your heart function.
- You will be visited throughout your stay in the hospital by a stroke team physician or study nurse to evaluate your current condition.
- After discharge from the hospital, you will have follow-up phone calls at one and three months after your hemorrhagic stroke. During these calls, you will be asked questions about your quality of life at that time.

The following procedures/test articles are considered to be investigational: The use of the CT angiography “spot sign” to identify intracerebral hemorrhage (ICH) patients at high risk of hematoma growth and as a criterion to select patients for randomization to treatment with recombinant activated factor VII or placebo is investigational. Recombinant activated factor VII (NovoSeven®) has been approved by the Food and Drug Administration (FDA) for treatment of bleeding in some patients with a bleeding disorder called hemophilia. Recombinant activated factor VII is not FDA approved for treatment of intracerebral hemorrhage and its use for this condition is investigational

WHAT ARE THE RISKS AND DISCOMFORTS OF THE RESEARCH STUDY?

You have been told that the study described above may involve the following risks and/or discomforts and safeguards and or precautions to avoid them.

Participation in this study may involve some risk. Like all medications recombinant activated factor VII (rFVIIa) may have side effects if you are randomized to that group. Because rFVIIa helps prevent bleeding, there is a potential risk of life-threatening blood clots developing in arteries which could lead to a heart attack or stroke. Life-threatening blood clots could also develop in veins of the legs or lungs which could cause a serious clot in the lungs called a pulmonary embolism. In prior studies of rFVIIa for intracerebral hemorrhage, the risk of heart attack or stroke was about 5% higher in patients receiving the rFVIIa compared to patients receiving the placebo or inactive medication. The risk of having a blood clot in the legs or lungs did not differ between patients receiving rFVIIa or placebo.

As with any drug, there is some chance of allergic reaction. There have been very rare reports (less than 1 event per 10,000 standard doses) of allergic reactions to recombinant activated factor VII including rash, fever, nausea, headache, and vomiting.

Mild allergic reactions to x-ray dye that will be administered through your IV for the CTA may occur in up to 2 to 4% (2 to 4 out of 100) of patients having CT angiography. Severe reactions to x-ray dye occur in 1 person in 1000. You will be monitored for all possible allergic responses during the procedure. There is also a risk of kidney problems or kidney failure after receiving x-ray dye. As with any patient having this procedure, your kidney function and your individual risk factors will be evaluated before and after the CT angiogram. On rare occasions (2 to 6 people out of 1000), X-ray dye may leak out of the vein into the surrounding arm tissue.

The CT scans of your brain done at baseline and at 21 to 27 hours are generally part of standard intracerebral hemorrhage patient care and involve exposure to only a small amount of radiation. The CTA that will be done at baseline as part of the study will also involve exposure to a small amount of radiation. There is a small chance that your skin or hair may be damaged. This has yet to happen as a result of studies for stroke treatments.

Collecting blood samples requires venipuncture (drawing blood from a vein in the forearm or hand). The risk of simple venipuncture commonly includes: discomfort and/or bruising at the site of the puncture, and less commonly, an infection at the site of the puncture, the formation of a small blood clot or swelling of the vein and surrounding tissue and bleeding from the puncture site.

Your skin may be slightly irritated from the sticky electrodes placed on your skin in order to perform the electrocardiogram (EKG).

There also may be risks and discomforts which are not yet known.

WHAT ARE THE REPRODUCTION RISKS?

If you are a woman able to have children, you must not be pregnant or nursing when you enter the study. You also must not become pregnant or cause a pregnancy during the study. This study could seriously harm your fetus if you are pregnant, become pregnant or suspect you caused a pregnancy. If you enter the study and then think you might be pregnant or suspect you have caused a pregnancy you will tell your doctor right away. The study doctor will wish to follow the outcome of your or your partner's pregnancy and condition of any newborn which may be reported to the study sponsor. You also understand that there might be risks to a fetus if you become pregnant after the study is done. You should not donate to a sperm bank while in this study. These risks are unknown. If you do want to become pregnant when the study is done, you will talk about it with your doctor. If

you do become pregnant, you will be followed until the birth of the child and the child will be followed until one month of life.

ARE THERE BENEFITS TO TAKING PART IN THE RESEARCH STUDY?

If you agree to take part in this research study, there may not be a direct medical benefit to you. The investigators hope the information gained from this study may increase knowledge about the usefulness of CT angiography for hemorrhagic stroke as well as the safety and effectiveness of the study medication recombinant activated factor VII. This combined information may contribute to making the study medication available to patients with intracerebral hemorrhage.

WHAT OTHER CHOICES FOR CARE ARE THERE?

Instead of being in this research study, you have these options: the usual standard medical care or in certain cases, surgery can be done to remove the blood from your brain.

As there are no proven treatments for intracerebral hemorrhage, there may be other stroke research projects that you might qualify to be in that are being conducted at your hospital.

Ask your physician.

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE AND CONFIDENTIAL?

Every effort will be made to maintain the confidentiality of your study and hospital records relating to your treatment and follow-up care. Agents of the United States Food and Drug Administration, other National regulatory authorities, designates of the National Institute of Health, representatives of the STOP-IT Study Clinical Coordinating and Biostatistical Core Center, and the manufacturer of the study drug NovoSeven® will be allowed to inspect and copy sections of your medical and research records related to this study. The data from the study may be published; however, you will not be identified by name. Your identity will remain confidential unless disclosure is required by law.

AVAILABILITY OF INFORMATION

You will receive a copy of this signed consent form.

You will be told about any new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHAT ARE YOUR COSTS TO BE IN THIS STUDY?

Funds are not available to cover the costs of any ongoing medical care. You remain responsible for the cost of non-research related care and items or services needed for reasonable and necessary care arising from study participation, in particular, for the diagnosis or treatment of complications outlined in the Risks and Discomforts section above. Some of the procedures in this study are part of the standard treatment for your condition and would be performed even if you were not in this study. The costs for these procedures will be billed to your insurance, or, if you are uninsured, will be billed to you. You will be responsible for any costs your insurance does not cover. This routine care includes but is not limited to: the initial and 24 hour follow-up CT scans, a chest x-ray, baseline electrocardiogram (EKG), and blood studies done on admission to the hospital as part of acute intracerebral hemorrhage treatment.

You will not be financially responsible or billed for the additional tests, procedures, or other costs (i.e., CT angiography, additional blood tests and EKGs), which are being done solely for the purpose of this study and are not part of your routine care. Novo Nordisk A/S, the drug manufacturer, will provide the study agent recombinant activated factor VII (NovoSeven®) free of charge to participants in this study.

WILL YOU BE PAID TO PARTICIPATE IN THIS RESEARCH STUDY?

You will not be paid to participate in this study.

WHAT COMPENSATION IS AVAILABLE IN CASE OF INJURY?

In the event that you become ill or injured from participating in this research study, emergency medical care will be provided to you. *[Insert name of your participating institution]* will decide on a case by case basis whether to reimburse you for your out of pocket health care expenses.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

You may choose either to take part or not to take part in this research study. If you decide to take part, you may decide to leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to you. The investigators will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

If you have questions about the study, you will have a chance to talk to one of the study staff or your regular doctor. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers.

Nothing in this consent form waives any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

If you have questions, concerns or complaints about this research study or to report a research-related injury, please contact the researcher *[Insert name of participating PI]* at *[Insert contact number for participating PI]*.

Please call the *[Insert name of your IRB / EC]* at *[Insert phone number of IRB / EC]* if you:

- Think the research has hurt you.
- Have general questions about giving consent or your rights as a research participant in this research study.
- Have questions, concerns, or complaints about the research.
- Cannot reach the research team or you want to talk to someone else.

PATIENT CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Spot Sign for Predicting and Treating ICH Growth Study (STOP-IT Study)

Sponsor: NIH / NINDS

Sponsor #: 2P50NS044283-06

SIGNATURES

I have read or someone has read to me, this Informed Consent Document which describes the purpose and nature of this research. I have had time to review this information and have been encouraged to ask questions. I have received answers to my questions. If I do not participate or if I discontinue my participation, I will not lose any benefits. I will not lose any legal rights if I discontinue. My participation in this research is completely voluntary. I give my consent to participate in this study. I have received (or will receive) a copy of this form for my records and future reference.

Participant

Date

Next of Kin / Legally Authorized Representative
(State Relationship to Participant)

Date

PERSON OBTAINING CONSENT

I have read this form to the participant and/or the subject has read this form. An explanation of the research was given and questions from the subject were solicited and answered to the subject's satisfaction. In my judgment, the subject has demonstrated comprehension of the information.

Signature and Title of Person Obtaining
Consent and Identification of Role in the Study

Date

Consent if CTA IS Standard Care

PATIENT CONSENT TO PARTICIPATE IN A RESEARCH STUDY

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INTRODUCTION:

If you are acting as a representative to give consent for another person to participate in this study, “you” throughout this consent form refers to that individual.

Your obligation is to try to determine what the individual would do if competent, or if the subject’s wishes cannot be determined, what you think is in the person’s best interest. If possible, an attempt should be made to obtain permission from the individual. Some persons may resist participating in a research protocol that has been approved by their representatives. Under no circumstances may individuals be forced to participate.

Before you agree to participate in this research study, it is important that you be told the purpose, procedures, benefits, risks, discomforts, and precautions of the research. You should also be told what alternative procedures are available to you if you do not participate in the research study.

Your participation in this research study is entirely voluntary. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from the study at any time without penalty. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time without unfairness to you or your medical care. We do not promise that you will receive any benefits from this study.

This informed consent document is a brief written summary of what your study doctor is telling you. Be sure to ask questions while you read this if there is anything that you do not understand.

WHY IS THIS RESEARCH BEING DONE?

The purposes of this research study are:

3. To find out if a special x-ray test called a computed tomography angiogram (CTA) can help doctors predict which patients that have suffered an intracerebral hemorrhage or breakage of a blood vessel with bleeding into the brain will experience significant growth in the size of the hemorrhage or bleed. Growth or increase in the size of the hemorrhage can cause additional injury to the brain and has been associated with a worse outcome for patients.
4. For patients considered to be at high risk for hemorrhage growth based on the results of the CTA, to compare the effects (good or bad) of the study medication called recombinant activated factor seven (NovoSeven®) with a placebo (inactive medication) on reducing intracerebral hemorrhage growth to see which is better. You may or may not receive the study drug.

CT angiography is a common imaging tool used for stroke patients. The use of CTA to predict hemorrhage growth and its potential role in the treatment of intracerebral hemorrhage is investigational. Recombinant activated factor VII (NovoSeven®) has been approved by the Food and Drug Administration (FDA) for treatment of bleeding in some patients with a type of bleeding disorder in which blood does not clot normally called hemophilia. Recombinant activated factor VII is not FDA approved for treatment of intracerebral hemorrhage and its use for this condition is investigational.

WHY HAVE YOU BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in this research study because you are 18 years of age or older and you have been diagnosed with a type of stroke called an acute intracerebral hemorrhage or hemorrhagic stroke.

HOW LONG WILL YOU BE IN THE RESEARCH STUDY?

You will be in the research study for approximately 3 months from the time of treatment for your hemorrhagic stroke. After discharge from the hospital, you will receive follow-up telephone calls at 1 month and again at three months by study staff to evaluate your condition at that time.

The researcher may decide to take you off this research study at any time. If you experience any of the side effects described in the “Risks and Discomforts” section or if you become ill during the research, you may have to drop out, even if you would like to continue. In addition, the National Institute of Health (NIH) and National Institute of Neurological Disorders and Stroke (NINDS), the study’s sponsor, and the IRB / EC has the right to terminate the study or the Principal Investigator’s participation in the study at any time. Novo Nordisk A/S, the study drug manufacturer has the right to terminate their participation in the study at any time.

You may withdraw from the study at any time. If you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first so that stopping can be done safely. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful to you.

WHO IS CONDUCTING THE RESEARCH STUDY?

This study is sponsored by the National Institute of Health (NIH) and National Institute of Neurological Disorders and Stroke (NINDS).

The study is directed by and under the medical supervision of *[Insert name of your site PI]*, the researcher at the *[Insert name of your participating institution]*.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

About *[Insert number of subjects projected to be enrolled at your site]* people will take part in this study at *[Insert name of your participating institution]*. Approximately 184 people will take part across the United States and Canada.

WHAT IS INVOLVED IN THE RESEARCH STUDY?

If you take part in this study, you will have the following tests and procedures:

1. You will receive the same standard of care given to all hemorrhagic stroke patients.
2. An intravenous line will be started for the administration of fluids and X-ray dye.
3. An electrocardiogram (EKG), which measures the electrical activity of your heartbeat, will be obtained to assess the functioning of your heart.
4. To determine your initial condition, you will be examined by a physician who will perform a few simple tests to look for problems with your brain (for example, your ability to move your arms and legs, to talk and understand speech and to see in all directions).
5. A CT scan and CT angiography (CTA) will be obtained as standard of care for your condition. A CT scan is a special type of brain x-ray that is done to determine that you have a stroke from a breakage of a blood vessel with bleeding into your brain. The CTA is a special x-ray of the brain that will be evaluated to see if there is a “spot sign” present within the blood or hemorrhage in your brain tissue. This sign, if present, may predict a higher risk that the hemorrhage in your brain will get bigger in the next few hours. The CTA follows the regular CT scan. For this test X-ray dye will be given through an IV in your arm before the test is performed.

6. Routine blood samples will be drawn as in all stroke patients. The blood samples (about 2 tablespoons) will be taken from a vein in your arm for laboratory testing. No genetic testing will be performed on these samples.
7. If the Spot Sign is present on the CTA:
 - You will be “randomized” into one of two study groups described below. Randomization means that you are put into a group completely by chance. It is like flipping a coin. Neither you nor the researcher conducting this study will choose what group you will be in. You have an equal chance of being placed in either group. However, in the event of an emergency, your study doctor will be able to find out what treatment you are receiving.
 - You will receive either an active study medication called recombinant activated factor VII, or you will receive a placebo or an inactive study medication through the IV in your arm.
 - Additional blood samples (approximately 2 tablespoons total) will also be drawn at baseline, day 1, 2, 3 following treatment and at discharge as part of the study as a safety precaution to monitor your heart and kidney function.
 - EKG’s will also be performed as part of the study on day 1, 2 and 3 to continue to assess the functioning of your heart.
 - You will have a CT scan (a special x-ray of the brain) between 21 and 27 hours after you receive study drug as a safety check to evaluate the size of your hemorrhage.
 - If you were to have any deterioration in your condition during the first 24 hours, or at any other time, a CT scan will be obtained immediately.
 - You will be visited throughout your stay in the hospital by a stroke team physician or study nurse to evaluate your current condition.
 - After discharge from the hospital, you will have follow-up phone calls at one and three months after your hemorrhagic stroke. During these calls, you will be asked questions about your quality of life at that time.
8. If the Spot Sign is not present on the CTA:
 - You will not be randomized to receive any study medication; however you will continue to be part of the study.
 - You will continue to receive the standard of care given to all hemorrhagic stroke patients. Part of this care will include a CT scan at between 21 and 27 hours after your CTA as a safety check to evaluate the size of your hemorrhage.
 - Blood samples (approximately 1 tablespoon total) will be drawn as part of the study on day 1, 3 and discharge to monitor kidney function and a sample at baseline to monitor your heart function.
 - You will be visited throughout your stay in the hospital by a stroke team physician or study nurse to evaluate your current condition.
 - After discharge from the hospital, you will have follow-up phone calls at one and three months after your hemorrhagic stroke. During these calls, you will be asked questions about your quality of life at that time.

The following procedures/test articles are considered to be investigational: The use of the CT angiography “spot sign” to identify intracerebral hemorrhage (ICH) patients at high risk of hematoma growth and as a criterion to select patients for randomization to treatment with recombinant activated factor VII or placebo is investigational. Recombinant activated factor VII (NovoSeven®) has been approved by the Food and Drug Administration (FDA) for treatment of bleeding in some patients with a bleeding disorder called hemophilia. Recombinant activated factor VII is not FDA approved for treatment of intracerebral hemorrhage and its use for this condition is investigational

WHAT ARE THE RISKS AND DISCOMFORTS OF THE RESEARCH STUDY?

You have been told that the study described above may involve the following risks and/or discomforts and safeguards and or precautions to avoid them.

Participation in this study may involve some risk. Like all medications recombinant activated factor VII (rFVIIa) may have side effects if you are randomized to that group. Because rFVIIa helps prevent bleeding, there is a potential risk of life-threatening blood clots developing in arteries which could lead to a heart attack or stroke. Life-threatening blood clots could also develop in veins of the legs or lungs which could cause a serious clot in the lungs called a pulmonary embolism. In prior studies of rFVIIa for intracerebral hemorrhage, the risk of heart attack or stroke was about 5% higher in patients receiving the rFVIIa compared to patients receiving the placebo or inactive medication. The risk of having a blood clot in the legs or lungs did not differ between patients receiving rFVIIa or placebo.

As with any drug, there is some chance of allergic reaction. There have been very rare reports (less than 1 event per 10,000 standard doses) of allergic reactions to recombinant activated factor VII including rash, fever, nausea, headache, and vomiting.

Mild allergic reactions to x-ray dye that will be administered through your IV for the CTA may occur in up to 2 to 4% (2 to 4 out of 100) of patients having CT angiography. Severe reactions to x-ray dye occur in 1 person in 1000. You will be monitored for all possible allergic responses during the procedure. There is also a risk of kidney problems or kidney failure after receiving x-ray dye. As with any patient having this procedure, your kidney function and your individual risk factors will be evaluated before and after the CT angiogram. On rare occasions (2 to 6 people out of 1000), X-ray dye may leak out of the vein into the surrounding arm tissue.

The CT scans of your brain done at baseline and at 21 to 27 hours are generally part of standard intracerebral hemorrhage (ICH) patient care and involve exposure to only a small amount of radiation. The CTA that will be done at baseline as part of standard ICH patient care will also involve exposure to a small amount of radiation. There is a small chance that your skin or hair may be damaged. This has yet to happen as a result of studies for stroke treatments.

Collecting blood samples requires venipuncture (drawing blood from a vein in the forearm or hand). The risk of simple venipuncture commonly includes: discomfort and/or bruising at the site of the puncture, and less commonly, an infection at the site of the puncture, the formation of a small blood clot or swelling of the vein and surrounding tissue and bleeding from the puncture site.

Your skin may be slightly irritated from the sticky electrodes placed on your skin in order to perform the electrocardiogram (EKG).

There also may be risks and discomforts which are not yet known.

WHAT ARE THE REPRODUCTION RISKS?

If you are a woman able to have children, you must not be pregnant or nursing when you enter the study. You also must not become pregnant or cause a pregnancy during the study. This study could seriously harm your fetus if you are pregnant, become pregnant or suspect you caused a pregnancy. If you enter the study and then think you might be pregnant or suspect you have caused a pregnancy you will tell your doctor right away. The study doctor will wish to follow the outcome of your or your partner's pregnancy and condition of any newborn which may be reported to the study sponsor. You also understand that there might be risks to a fetus if you become pregnant after the study is done. You should not donate to a sperm bank while in this study. These risks are unknown. If you do want to become pregnant when the study is done, you will talk about it with your doctor. If

you do become pregnant, you will be followed until the birth of the child and the child will be followed until one month of life.

ARE THERE BENEFITS TO TAKING PART IN THE RESEARCH STUDY?

If you agree to take part in this research study, there may not be a direct medical benefit to you. The investigators hope the information gained from this study may increase knowledge about the usefulness of CT angiography for hemorrhagic stroke as well as the safety and effectiveness of the study medication recombinant activated factor VII. This combined information may contribute to making the study medication available to patients with intracerebral hemorrhage.

WHAT OTHER CHOICES FOR CARE ARE THERE?

Instead of being in this research study, you have these options: the usual standard medical care or in certain cases, surgery can be done to remove the blood from your brain.

As there are no proven treatments for intracerebral hemorrhage, there may be other stroke research projects that you might qualify to be in that are being conducted at your hospital.

Ask your physician.

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE AND CONFIDENTIAL?

Every effort will be made to maintain the confidentiality of your study and hospital records relating to your treatment and follow-up care. Agents of the United States Food and Drug Administration, other National regulatory authorities, designates of the National Institute of Health, representatives of the STOP-IT Study Clinical Coordinating and Biostatistical Core Center, and the manufacturer of the study drug NovoSeven® will be allowed to inspect and copy sections of your medical and research records related to this study. The data from the study may be published; however, you will not be identified by name. Your identity will remain confidential unless disclosure is required by law.

AVAILABILITY OF INFORMATION

You will receive a copy of this signed consent form.

You will be told about any new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHAT ARE YOUR COSTS TO BE IN THIS STUDY?

Funds are not available to cover the costs of any ongoing medical care. You remain responsible for the cost of non-research related care and items or services needed for reasonable and necessary care arising from study participation, in particular, for the diagnosis or treatment of complications outlined in the Risks and Discomforts section above. Some of the procedures in this study are part of the standard treatment for your condition and would be performed even if you were not in this study. The costs for these procedures will be billed to your insurance, or, if you are uninsured, will be billed to you. You will be responsible for any costs your insurance does not cover. This routine care includes but is not limited to: the initial and 24 hour follow-up CT scans, CT angiography, a chest x-ray, baseline electrocardiogram (EKG), and blood studies done on admission to the hospital as part of acute intracerebral hemorrhage treatment.

You will not be financially responsible or billed for the additional tests, procedures, or other costs (i.e., additional blood tests and EKGs), which are being done solely for the purpose of this study and are not part of your routine care. Novo Nordisk A/S, the drug manufacturer, will provide the study agent recombinant activated factor VII (NovoSeven®) free of charge to participants in this study.

WILL YOU BE PAID TO PARTICIPATE IN THIS RESEARCH STUDY?

You will not be paid to participate in this study.

WHAT COMPENSATION IS AVAILABLE IN CASE OF INJURY?

In the event that you become ill or injured from participating in this research study, emergency medical care will be provided to you. *[Insert name of your participating institution]* will decide on a case by case basis whether to reimburse you for your out of pocket health care expenses.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

You may choose either to take part or not to take part in this research study. If you decide to take part, you may decide to leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to you. The investigators will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

If you have questions about the study, you will have a chance to talk to one of the study staff or your regular doctor. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers.

Nothing in this consent form waives any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

If you have questions, concerns or complaints about this research study or to report a research-related injury, please contact the researcher *[Insert name of participating PI]* at *[Insert contact number for participating PI]*.

Please call the *[Insert name of your IRB / EC]* at *[Insert phone number of IRB / EC]* if you:

- Think the research has hurt you.
- Have general questions about giving consent or your rights as a research participant in this research study.
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Participant

Date

Next of Kin / Legally Authorized Representative
(State Relationship to Participant)

Date

PERSON OBTAINING CONSENT

I have read this form to the participant and/or the subject has read this form. An explanation of the research was given and questions from the subject were solicited and answered to the subject's satisfaction. In my judgment, the subject has demonstrated comprehension of the information.

Signature and Title of Person Obtaining
Consent and Identification of Role in the Study

Date