CONFIDENTIAL

"Spot Sign" Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT): A Randomized Controlled Trial

Principal Investigator
Dr. David Gladstone, University of Toronto

Co-Principal Investigators
Dr. Richard Aviv, University of Toronto
Dr. Andrew Demchuk, University of Calgary

Version Number: 3.0

Date: March 10, 2014

Study funded by a peer-reviewed operating grant from the Canadian Institutes of Health Research (CIHR)

Address for correspondence:
David Gladstone MD, PhD, FRCPC
Division of Neurology, Department of Medicine
University of Toronto
Sunnybrook Health Sciences Centre
2075 Bayview Avenue, Room A442
Toronto, Ontario, Canada M4N 3M5
Tel 416-480-4866; FAX 416-480-5753
Email david.gladstone@sunnybrook.ca

Approval of Final Protocol

David Gladstone, MD, PhD, FRCPC Principal Investigator	16 APR 2014 Date
Richard Aviv, MD Co-Principal Investigator	4/10/14 Date
Andrew Demchuk, MD, FRCPC Co-Principal Investigator	April 16, 2014 Date

Site Investigator Agreement Page

"Spot Sign" Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT): A Randomized Controlled Trial

I have read and understand this protocol and concur with the study design. I agree to participate as an Investigator and to follow the protocol as outlined.

_____ _____

Site Investigator Signature Date

_____

Site Investigator Name (Please Print)

Table of Contents

List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
CTA	Computed Tomography Angiography
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic Data Capture
GCS	Glasgow Coma Scale
GCP	Good Clinical Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	Intracerebral Hemorrhage
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IVH	Intraventricular Hemorrhage
LAR	Legally Authorized Representative
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
N	Number (typically refers to participants)
NIHSS	National Institutes of Health Stroke Scale
NDA	New Drug Application
OTC	Over-the-counter
PI	Principal Investigator
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
RCT	Randomized Controlled Trial
rFVIIa	Recombinant Activated Coagulation Factor VII
REB	Research Ethics Board
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
WHO	World Health Organization

Protocol Summary

Full Title	"Spot Sign" Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT): A Randomized Controlled Trial
Short Title	SPOTLIGHT
Principal Investigators	Drs. David Gladstone, Richard Aviv, Andrew Demchuk
Funding	Canadian Institutes of Health Research (CIHR)
Primary Objective	To investigate the hemostatic effects of rFVIIa in spot-sign positive ICH patients. The study will compare the effects of rFVIIa vs. placebo on attenuating ICH growth, and explore variables that modify treatment response.
Secondary Objectives	1. To obtain feasibility and safety data for this emergency rFVIIa treatment protocol in spot-sign positive ICH patients. 2. To evaluate the applicability, acceptability and effects of implementing a waiver of consent policy in an emergency stroke trial. 3. To evaluate cognition and quality of life as endpoints in an ICH trial. 4. To obtain preliminary clinical efficacy data for rFVIIa treatment in spot-sign positive patients (a pooled analysis with other trials is planned).
Study Population	Acute spontaneous (non-traumatic) supratentorial ICH diagnosed by CT scan within 6 hours of onset, with evidence of active contrast extravasation within the hematoma as defined by the presence of a spot sign on CT angiography performed immediately after the baseline CT scan.
Study Design	Phase II multicentre, two-arm, double blind, placebo controlled, randomized trial
Sample Size	N = 110 (55 patients per group)
Accrual Period	48 months recruitment + 1 year follow-up
Study Duration	May 1, 2011 | End Date: 1 October 2016
Outcomes	*Primary Efficacy Outcome:* Difference between the 2 groups in ICH growth on CT scan within 24 hours. *Secondary Outcomes:* 1. Recruitment rates 2. Scan times (door to CT angiogram) 3. Treatment times (door to needle; CT angiogram to needle) 4. Accuracy of spot sign interpretation 5. Protocol adherence 6. Waiver of consent use, acceptability, and effect on treatment times 7. Acute blood pressure control 8. Total ICH growth at 24 hours (ICH plus IVH) 9. Cognitive function and quality of life *Exploratory Outcomes:* Difference between the 2 treatment groups in the proportion of patients with poor clinical outcome (mRS 5-6, i.e. death or severe disability) and the proportion of survivors achieving good clinical outcome (mRS 0-2; i.e. independent recovery/no disability) at 90 days

	Primary Safety Endpoint: Myocardial infarction within 4 days; ischemic stroke within 4 days; pulmonary embolism within 4 days. *Secondary Safety Endpoints:* Unstable angina within 4 days; troponin rise above upper limit of normal within 4 days (without clinical symptoms or ECG evidence of acute coronary syndrome); TIA within 4 days, deep venous thrombosis within 4 days, other arterial or venous thromboembolic SAEs within 4 days; pulmonary embolism within 30 days; acute nephropathy, 90-day mortality
Study Intervention Description	Patients randomized (1:1) to receive either a single intravenous bolus of 80 ug/kg rFVIIa (intervention group) or placebo (control group)
Assessments	Baseline assessment, post-dose assessments, 24 hours, days 2,3,4,day of discharge, days 30,90, and 1 year.

Abstract

Background – Intracerebral hemorrhage (ICH) is a devastating type of stroke (case fatality 40%). Patients frequently deteriorate within hours of hospital arrival due to continued bleeding in the brain resulting in hematoma expansion. For every 10% increase in ICH size, the risk of death increases by 5% and patients are 16% more likely to worsen by 1 point on the Rankin disability scale. There currently are no emergency treatments proven to improve patient outcomes. The most promising investigational treatment to date is hemostatic therapy with recombinant activated factor VII (rFVIIa), which significantly reduced ICH expansion (≈50% reduction) in 2 RCTs. Despite its ability to reduce bleeding, rFVIIa did not improve clinical outcomes in an unselected (heterogeneous) population of a phase III trial (*NEJM* 2008). We believe efficacy was diluted by inclusion of patients without active ICH expansion (rFVIIa will not help if bleeding has already stopped). Previous trials did not select patients for treatment based on any markers of active bleeding. Therefore, we propose a *focused trial* targeting only the "active bleeders" as the most logical next step. Based on our previous work, we now have a way for clinicians in the emergency department to predict which patients are at greatest risk of worsening due to ICH expansion. We described a radiographic sign ("spot sign") on CT angiography, a non-invasive X-ray of the intracranial blood vessels (*Stroke* 2007). This sign, present in 1/3 of acute ICH patients, refers to contrast extravasation within a hematoma and appears as foci of bright contrast enhancement, easily identified by visual inspection of CT angiography source images. This sign readily distinguishes 2 types of ICH patients: "spot sign positive" patients represent the active bleeders (extravasating contrast) who are destined to deteriorate and should theoretically benefit most from hemostatic therapy, whereas "spot sign negative" patients have stopped bleeding and are not expected to respond to treatment. Encouraging pilot data from our multicentre prospective PREDICT study (*Stroke* 2008) confirm the feasibility of performing hyperacute CT angiography and validate the prognostic value of the spot sign (mean ICH growth 34 ml with a spot sign vs. 6 ml without a spot sign). Image-guided stroke therapy is becoming the way of the future and now is the time to test the spot sign for guiding treatment in a trial.

Objectives – The primary objective is to test the ability of rFVIIa treatment to reduce ICH growth in ICH patients who have a spot sign (the highest risk ICH subgroup). Secondary objectives are to collect key feasibility data and additional safety data necessary to guide the design of a future phase III trial. We will assess applicability of a waiver of consent policy designed to minimize door-to-needle times, adherence to a standardized blood pressure protocol, and cognition, quality of life, and MRI outcomes. The tertiary objective is to explore preliminary clinical efficacy.

Methods – This phase II double blind RCT will enroll 110 patients from approximately 15 leading Canadian stroke centres. Acute ICH patients who can be treated within 6 hours of onset will undergo CT angiography using standard CT scanners (scan time 2 minutes). Those with a spot sign will be randomly assigned in a 1:1 ratio to a single injection of rFVIIa 80 µg/kg or placebo; patients without a spot sign will not be treated. Because ICH growth is highly time-sensitive and informed consent cannot always be immediately obtained, a waiver of consent protocol has been developed for this study and is justified on ethical grounds. The primary endpoint is ICH expansion within 24 hours. Secondary endpoints are scan-to-needle times, safety outcomes (thromboembolic SAEs), neurological impairment (NIHSS), cognition (MoCA), and global recovery measure (Stroke Impact Scale). Preliminary clinical endpoints (day 90 modified Rankin scale) will be explored through a planned pooled analysis with an independent (NIH-funded) U.S. study that will run in parallel with this trial.

Significance – The ultimate goal of this research is to reduce death and disability from ICH. SPOTLIGHT capitalizes on Canadian strengths in stroke imaging research and fosters international collaboration. rFVIIa deserves further investigation and this proposal for image-guided patient selection is the most rational way forward. By combining CT angiography to predict ICH growth, and rFVIIa to stop ICH growth, this trial offers a plausible means to improve patient outcomes. SPOTLIGHT will advance knowledge about ICH and is an essential step toward developing an efficacious emergency treatment protocol for this life-threatening condition.

1. BACKGROUND AND RATIONALE

The Problem of Intracerebral Hemorrhage

This study addresses the management of intracerebral hemorrhage (ICH), the most deadly and disabling type of stroke. ICH is caused by sudden bleeding into the brain from a ruptured blood vessel, most often related to hypertension and amyloid angiopathy. It accounts for about 10-30% of all strokes worldwide, often afflicting young people. Many ICH patients arrive at hospital early with initially modest deficits that then rapidly worsen, minute by minute, due to ongoing bleeding in the brain[1,2] (Figure 1). Such ICH expansion during the first few hours is an independent predictor of neurological deterioration and mortality: for each 10% increase in ICH size, the risk of death increases by 5% and patients are 16% more likely to have an increase of 1 disability level on the 7-point modified Rankin scale.[3] Significant ICH growth (>33% volume increase from baseline) occurs in 18-38% of patients scanned within 3 hours of symptom onset[1,4,5,6] and 8-16% scanned within 3-6 hours, indicating this phenomenon is time-dependent.[5,6,7] The clinical consequences are dire: Canadian data on spontaneous ICH in the Registry of the Canadian Stroke Network (n=1546) reveals a 39% in-hospital mortality.[8] In other studies, the 30-day mortality is 30-50%, half of deaths occur within 48 hours, and most survivors are left with serious long-term disability.[4,9] Unfortunately, there are currently no proven hyperacute medical treatments for this life-threatening condition.

The Opportunity

Treatment aimed at preventing ICH expansion, if administered early enough and to the right patient, should translate into improved recovery and reduced disability. The most promising investigational treatment to date is hemostatic therapy with recombinant activated Factor VII (rFVIIa), which has been in clinical use for many years for other life-threatening bleeding conditions. Two landmark trials recently showed that rFVIIa can significantly reduce bleeding in the brain (about 50% reduction in ICH growth vs. placebo).[10,11] However, clinical efficacy was not demonstrated when studied in a heterogeneous (unselected) group of ICH patients in a phase III trial.[10,11] Now, with the discovery of a new imaging sign that is present in about 1/3 of acute ICH patients (termed the "**spot sign**"),[12] ICH trials can now be designed with a much more rational treatment approach. Using the spot sign, it has become possible for the first time for clinicians in the emergency department to rapidly and accurately predict the patients who are at highest risk for imminent deterioration due to ICH expansion and might, therefore, benefit most from rFVIIa treatment.

The spot sign is defined as tiny bright foci of enhancement within a parenchymal hematoma, detected by visual inspection of CT angiography source images[13] (Figure 2 and 3).

With a 2-minute non-invasive CT angiogram (CTA), 2 types of ICH patients are readily distinguished:

1. ***"Spot sign positive" patients*** are the active bleeders who are at highest risk for deterioration and should, we hypothesize, be the best candidates to respond to hemostatic therapy.
2. ***"Spot sign negative" patients*** are at low risk for ICH expansion and are not expected to benefit from hemostatic therapy.

Previous rFVIIa trials did not use CTA to assess spot sign status and, thus, failed to target only the patients with active bleeding. SPOTLIGHT will test the ability of the spot sign to guide rFVIIa treatment in a clinical trial.

Literature Review, Previous Trials, Pilot Data, and the Need for This Trial

rFVIIa Stops Bleeding in the Brain

Hemostatic therapy with rFVIIa (intravenous injection) is the first intervention proven to significantly reduce ICH growth, and has opened the exciting prospect that this devastating condition can be treated in selected patients. rFVIIa for ICH has been tested in dose-escalation, phase IIb, and phase III trials.[10,11,14] The phase IIb trial (n=399) randomized patients within 4 hours of onset to placebo or rFVIIa 40 µg/kg, 80 µg/kg or 160 µg/kg.[10] The mean percentage increase in ICH volume was 29% with placebo vs. 16%, 14% and 11% in the rFVIIa 40, 80 and 160 µg/kg groups, respectively (p=0.01). Mean absolute growth in ICH volume was reduced by 3.3 ml, 4.5 ml, and 5.8 ml with the 3 doses, respectively (p=0.01). A phase III trial (n=841) confirmed rFVIIa reduces ICH expansion in a dose-dependent fashion.[11] This trial randomized patients within 4 hours of onset to placebo, rFVIIa 20 µg/kg or 80 µg/kg. The placebo group had a 26% mean increase in ICH volume vs. 18% in the 20 µg/kg group and 11% in the 80 µg/kg group (p<0.001).[11] While 74% of placebo patients had some ICH growth, only 28% had growth >33%. Thus, the overall treatment effect is reduced considerably by patients with little or no ICH expansion. *If patients destined to have significant ICH growth can be identified right away and other patients excluded from treatment, the difference in ICH growth (and clinical outcomes) between treatment and placebo groups is expected to be magnified.*

Treatment with rFVIIa is Time-Sensitive

The treatment effect of rFVIIa is maximal within the first 3 hours. Among patients in the phase IIb trial treated within 3 hours (n=269), the mean percentage increase in ICH volume was 34% (placebo) vs. 13% (rFVIIa) (p=0.004). The absolute increase in ICH volume was 10.7 ml (placebo) vs. 4.4 ml (rFVIIa) (p=0.009). The phase III trial provided further evidence that earlier treatment is associated with greater reduction in ICH growth: 5.6 ml less growth for patients treated within 2 hours vs. 4.5 ml less for those treated within 3 hours and 3.8 ml less for those treated up to 4 hours. [11] There was a significant reduction in death or severe disability at day 15 with rFVIIa vs. placebo (33% vs. 47%, p=0.03) in the subgroup treated under 2 hours (S. Mayer, personal communication). Thus, like ischemic stroke, the concept of *"time is brain"* applies to ICH treatment.

Improved Patient Selection in RCTs is Necessary to Achieve Clinical Efficacy

Despite the significant reductions in ICH growth with rFVIIa, clinical efficacy remains to be proven. In the phase IIb trial, 90-day mortality was 29% (placebo) vs. 18% (rFVIIa), a relative mortality reduction of 38% (p=0.02). Clinical outcomes at 90 days all favoured rFVIIa treatment. However, in the phase III trial there were no significant differences in 90-day mortality or functional outcomes in the overall (heterogeneous) population. Baseline imbalances in intraventricular hemorrhage may have contributed, but we believe that clinical efficacy in that trial was most likely diluted by the inclusion of patients who were never at risk for ICH expansion (rFVIIa will not help if bleeding has already stopped). None of the previous trials selected patients based on any markers of active bleeding. Thus, a focused trial targeting only the "active bleeders" is now the next logical step in the investigation of this promising therapy.

Image-Guided Patient Selection is the Way Forward: The Spot Sign Story

Contrast extravasation (leakage of radiographic contrast dye) within an intracerebral hematoma can be visualized by CTA, MR angiography or catheter angiography, and correlates with an actively bleeding vessel and ICH growth.[15-22] Initial work on the spot sign in Toronto and Calgary has stimulated major international interest in the value of CTA for predicting ICH growth. Dr. Aviv's group at Sunnybrook in Toronto described the spot sign in 2007,[12] and along with Dr. Demchuk's group published a radiographic definition of the sign, characterized different morphological patterns[13] (Figure 4), and distinguished the spot sign from its radiographic mimics (e.g. calcification, tumour).[23] In the Toronto Sunnybrook study, CT angiograms were analyzed from ICH patients scanned within 3 hours of onset.[12]

A spot sign was identified in 33% and predicted ICH growth >30% or 6 ml with 91% sensitivity and 89% specificity. The positive and negative predictive values for growth were 77% and 96%. ICH expansion was more common in patients with a spot sign than those without ($p<0.001$), and the spot sign independently predicted ICH enlargement ($p<0.001$). The outcome of death or severe disability occurred in 50% of those with a spot sign vs. 35% in those without. Inter-observer agreement was high (k=0.92-0.94). Becker et al. found contrast extravasation on CTA to be an independent predictor of in-hospital mortality: extravasation was present in 46% of 113 patients and was associated with higher mortality (64%) vs. patients without extravasation (16%). [19] Goldstein et al. (2007) reported CT angiograms from 104 patients that corroborated our spot sign findings. [24] Contrast was present within the ICH in 56% and this finding was the single most powerful predictor of ICH expansion. Sensitivity and specificity of extravasation for predicting ICH growth was 93% and 50%, with a 98% negative predictive value. There was a trend toward earlier time to patient presentation in those with extravasation and ICH expansion, and increased mortality in those with extravasation (p=0.04). Multivariable analysis confirmed an independent effect of extravasation on ICH growth (OR 18, 95% CI 2.1-162, p=0.009). Kim et al. (2007) added further evidence that contrast extravasation independently predicts ICH growth and mortality: 30-day mortality was 53% in those with extravasation vs. 19.5% without. [25,26]

A large Harvard study (n=367) provided very strong validation of the spot sign. [27] The PPV for significant ICH growth was highest for spot signs with the certain characteristics: ≥3 spots (PPV 96%), axial dimension ≥5mm (PPV 91%), and attenuation ≥180 HU (PPV 84%). The authors developed a 4-point "spot sign score" based on the number of spots, maximal axial dimension and attenuation, and this score predicted significant ICH growth ($p<0.0001$) independent of ICH volume, blood pressure, INR, and time from onset to scan. The percentage of patients with significant ICH growth ranged from 2% for spot-negative patients to 94% for spot-positive patients with a spot sign score of 3 and 100% for those with a spot sign score of 4. Mean ICH growth for those with spot sign scores 3-4 was 21-36 ml (or 68%-72% volume increase) vs. 11 ml for spot-negative patients. Importantly, inter-observer agreement for identification of the spot sign was near-perfect among 3 readers (k=0.88-0.93). The presence of a spot sign (OR 2.5, 95% CI 1.3 to 4.7, $P<0.0052$) and the spot sign score (OR 1.5, 95% CI 1.2 to 1.9, $P<0.0002$) were each independent predictors of in-hospital mortality (in addition to patient age, admission GCS, and initial ICH and IVH volumes).[28] The spot sign (OR 2.4, 95% CI 1.1 to 4.9, $P<0.02$) and the spot sign score (OR 1.6, 95% CI 1.1 to 2.1, $P<0.0065$) were each independent predictors of poor outcome among survivors (mRS 4-5) at 3 months (in addition to patient age, admission GCS and MABP, as well as initial ICH and IVH volumes).[28] In this study, the highest spot sign scores were observed in patients with baseline ICH volumes 30-59.9 mL, CTA <3 hours of onset, baseline GCS 9-12, admission MABP >120 mm Hg, and deep gray matter ICH.[28]

In summary, the spot sign is considered the most accurate, reliable, and rapid imaging sign for predicting ICH growth.

<u>CT Angiography is an Ideal Emergency Imaging Tool for ICH</u>

CTA is a *non-invasive* test that can be performed quickly in any hospital with a helical CT scanner (acquisition time approx. *2 minutes*). CTA requires injection of contrast dye and can be obtained immediately following a routine non-contrast CT head scan, the standard initial investigation for ICH patients. The spot sign can be identified immediately on the source images usually before the patient is taken off the CT scan table (no image post-processing required), making it ideally suited for emergency decision-making. In addition to the *prognostic* value of the spot sign, CTA provides valuable *diagnostic* information about brain vascular anatomy. Combined with a post-contrast head CT, CTA is an excellent tool for diagnosis of serious secondary causes of ICH (aneurysm, AVM, venous thrombosis, tumour), as we have published.[29] Thus, independent of the spot sign, hyperacute CTA is beneficial for excluding structural pathology that could affect patient management.

How will the results of this trial be used?

SPOTLIGHT is intended to provide data necessary to inform the design of a future phase III trial, and represents an essential step toward the long-term objective of developing the first emergency treatment to improve outcomes from ICH. In addition to the anticipated feasibility and safety results, SPOTLIGHT will generate much-needed information about estimated treatment effect sizes, clinically important measures of ICH growth, and eligibility criteria for future studies. This trial will advance knowledge about ICH and has the potential to transform future ICH research. SPOTLIGHT will be a catalyst for related research aimed at improving ICH patient care, e.g. inspiring trials to evaluate the spot sign for predicting ICH growth and guiding treatment for patients presenting >5 hours of onset or with an unknown time of onset (e.g. those who awaken with deficits) and for anticoagulant-associated ICH. Our results will also have implications for patient selection for trials of other investigational ICH treatments, e.g. intensive blood pressure lowering and neurosurgical approaches for ICH evacuation.

2. AIM AND OBJECTIVES

Overall Aim

The ultimate goal of this research is to reduce death and disability caused by ICH. SPOTLIGHT is a focused phase II trial that tests an innovative ICH treatment protocol in the emergency department using CTA for patient selection. This type of image-guided targeted treatment approach for ICH is novel and aims to reduce hematoma expansion and improve outcomes in the highest-risk ICH subgroup (i.e., the spot-sign positive patients). The study is based upon solid biological rationale and a strong foundation of evidence from published studies, and goes beyond previous trials by using vascular imaging to guide treatment.

2.1 Primary Objective

The primary objective is to investigate the hemostatic effects of rFVIIa in spot-sign positive ICH patients. The study will compare the effects of rFVIIa vs. placebo on attenuating ICH growth, and identify variables that modify treatment response.

Hypothesis:
rFVIIa-treated patients will have significantly less ICH growth compared to placebo-treated patients, as measured by the average ICH volume on CT scan at 24 hours post-treatment and the average absolute change in ICH volume (ml) from baseline to 24 hours. We expect the greatest efficacy in patients treated early (<3 hours post-onset) and quickly (<40 min. after CTA), and without baseline intraventricular hemorrhage.

2.2 Secondary Objectives

1. To obtain feasibility data and safety data for this emergency rFVIIa treatment protocol in spot-sign positive ICH patients.

Hypotheses:

a) Recruitment targets will be achieved, with 50 eligible spot sign positive ICH patients enrolled during the first 18 months of active recruitment and 60 patients enrolled during the subsequent 18 months (sites are required to enroll a minimum of 2 patients per site per year over 3 years of recruitment). Site screening logs will be reviewed and barriers to recruitment will be identified and addressed during the course of the trial.

b) Sites will be able to scan patients with CTA rapidly, with >80% achieving a target time of <45 minutes from emergency department arrival to the start of the scan.

c) Enrolling physicians will interpret the presence/absence of a spot sign on CTA in the context of the trial with >90% accuracy, as compared to blinded over-read by the "gold standard" study neuroradiologist. All study investigators will undergo training beforehand with a certification program developed by Dr. Aviv, and recertification will be required periodically throughout the trial period. We will carefully assess any spot signs that are over-called (i.e. false positives) and provide feedback to sites during the course of the trial. Data from this study will determine whether future trials should rely solely on spot sign presence/absence as the main criterion for inclusion or whether enrolling physicians can also accurately calculate a 4-point spot sign score using a published rating scale.[28]

d) Sites will be able to randomize and treat patients rapidly, with >80% achieving a target time of <60 minutes from the end of the CT angiogram to administration of study drug. Sites will be required to rehearse mock enrollments prior to site activation, and delays to study drug administration will be identified and addressed during the course of the trial.

e) Sites will adhere to study protocol in terms of meeting inclusion/exclusion criteria and following treatment procedures, with a low rate of major protocol violations (<5%) during the first 18 months and thereafter.

f) Ability to control blood pressure acutely, defined as achieving systolic BP <180 mmHg within 1 hour post-randomization, will be achieved in >90% patients using a standard protocol (see Appendix). This will be an important demonstration that will have relevance for other future studies of ICH management.

g) The incidence of myocardial infarction and ischemic stroke within 4 days, and 90-day mortality rate, in the rFVIIa group will not exceed the rates observed in previous trials based on our stricter eligibility criteria.

Site performance on the above indicators in this study will be essential for guiding the design a future multicentre phase III trial of the proposed intervention that will be powered to assess clinical efficacy. The results of this trial will be used to determine whether modifications are needed to the inclusion/exclusion criteria, and will assist with sample size projections, site selection, recruitment strategies, ethical considerations, and local process of care issues for patient screening and scanning (especially to identify and minimize delays to scan time, randomization and drug administration).

2. To evaluate the acceptability and effects of implementing a waiver of consent for CTA in this emergency stroke trial, and to evaluate the applicability, acceptability and effects of a waiver of consent for randomization to treatment in this trial.

Hypotheses:

a) Site REBs will approve the proposed inclusion of a waiver of consent policy for CTA in the study protocol, and this waiver of consent policy will be acceptable to patients/LARs.
b) Sites in this trial will have significantly shorter door-to-CTA times and door-to-needle times and greater efficacy for this time-sensitive treatment vs. patients in other trials (e.g. STOP-IT) using standard consent for CTA and randomization.
c) The majority of site REBs will approve the proposed option of a waiver of consent for randomization to treatment in this trial, and the majority of patients/LARs surveyed will be in

favour of such a waiver of consent option for randomization to treatment in a future hypothetical trial. This study will estimate the proportion and characteristics of ICH patients who would qualify for a waiver of consent for treatment in future a trial (i.e., the proportion who not have the capacity to provide their own informed consent at the time of admission and for whom no LAR is immediately available, and for whom the investigator is able to obtain a complete and reliable medical history to determine that the patient fulfills the inclusion/exclusion criteria). These data will determine whether a waiver of consent for treatment should be used in the design of future emergency ICH trials.

3. To evaluate cognition and quality of life as endpoints in an ICH trial.

Hypothesis:
Survivors of ICH will have cognitive impairments and reduced quality of life, measurable on the Montreal Cognitive Assessment (MoCA) and Stroke Impact Scale at 90 days and 1 year.

4. To obtain preliminary clinical efficacy data for rFVIIa treatment in spot sign positive patients (a pooled analysis with other similar trials is planned).

Hypothesis:
Spot-sign patients treated with rFVIIa will have a lower probability of poor outcome compared to placebo-treated patients, as measured by the proportion with modified Rankin score 5-6 (death or severe disability) at 90 days and 1 year. ICH survivors who received rFVIIa will have a greater probability of good recovery compared to placebo, defined as the proportion with modified Rankin score 0-2 at 90 days and 1 year.

3. STUDY OVERVIEW

3.1 Study Design

SPOTLIGHT is a phase II multicentre, randomized, double-blind, placebo-controlled, investigator-led trial. The study will screen patients who present to the emergency department with acute spontaneous ICH and who can be randomized and treated within 6 hours of stroke onset. Eligible patients who have an acute ICH diagnosed by CT scan and a spot sign detected on CTA (ideally performed immediately after the routine plain CT scan) will be randomly assigned in a 1:1 ratio to a single dose of rFVIIa or placebo using a variable block randomization scheme. Study drug is to be administered as quickly as possible within 60 minutes (+ 10 minutes) of CTA and no later than 6 hours after stroke onset. Spot sign negative patients will not be randomized.

The study design improves upon published rFVIIa trials by using CTA for patient selection (previous trials did not assess spot sign status), and by aiming for *faster treatment times* by introducing assent-consent and waiver of consent procedures. Additionally, since cognitive outcomes have been understudied in ICH (and not included in previous rFVIIa trials), this study will assess cognitive (not just physical) disability using a bedside cognitive battery developed in Canada.

All patients will continue to receive standard stroke care and rehabilitation, and clinical ICH management should follow published guidelines [30]. It is anticipated that most patients will be admitted to an intensive care/close observation unit for 24 hours followed by stroke unit care, as is usual practice. In accordance with the 2010 American Heart Association Guidelines on Management of Intracerebral Hemorrhage, “Aggressive full care early after ICH onset and postponement of new DNR orders until at least the second full day of hospitalization is probably recommended (Class IIa; Level of Evidence: B)”,

unless a patient's preexisting advanced directives specify otherwise[new reference 30]. For participants in this study, DNR orders or withdrawal of support during the first 24 hours is therefore discouraged.

While rFVIIa is available in most tertiary care hospitals, it is not approved by Health Canada for ICH. A Clinical Trial Application will be submitted for Health Canada approval and the study will be submitted for REB approval at each site. The trial will be registered with an online clinical trials directory and will comply with GCP-ICH and reports will follow the CONSORT statement.

3.2 Study Population

3.2.1 Inclusion Criteria

1. Acute spontaneous primary supratentorial ICH diagnosed by CT scan.
2. Presence of a spot sign within the hematoma on CTA (single-phase, multi-phase, or dynamic CTA). [Note: CTA should ideally be performed immediately after the baseline CT scan. If CTA is going to be delayed more than 20 minutes after the baseline CT, then a new plain head CT must be obtained immediately prior to CTA which will serve as the baseline CT for the study]. A spot sign must meet the following criteria:
    - One or more foci of contrast enhancement within the margin of a parenchymal hematoma
    - Any size or morphology (shape may be spot-like, linear or serpiginous)
    - Spot sign(s) must not have any connection to vessels outside the hematoma
    - Hounsfield unit density greater than background hematoma density (density of spot sign is typically >120 Hounsfield units)
    - No corresponding density present within the hematoma on non-contrast CT
3. Baseline ICH volume 3-90 ml, estimated using the standard "abc/2" calculation on the baseline plain head CT.
4. Age ≥18 years.
5. Investigator is able to randomize and administer study drug as soon as possible within a target of 60 minutes after CT angiogram and no later than 6 hours after stroke symptom onset (using the "last seen normal" principle).
6. Plan to provide full medical care for at least 24 hours.
7. Consent from patient or LAR prior to enrolment (or a waiver of consent if patient/LAR assent-consent is not possible prior to enrolment, and if REB approved at your site). [Note: full informed consent to be obtained as soon as possible after study treatment administered].

3.2.2 Exclusion Criteria

Diagnostic/Imaging Exclusions

1. Brainstem or cerebellar hemorrhage.
2. ICH secondary to known or suspected trauma, aneurysm, vascular malformation, hemorrhagic conversion of ischemic stroke, venous sinus thrombosis, thrombolytic treatment, tumour, or infection; or an in-hospital ICH or ICH as a result of any in-hospital procedure or illness.
3. Baseline brain imaging shows evidence of acute or subacute ischemic stroke (chronic infarcts are not an exclusion).
4. Contrast administration within the previous 24 hours.

Clinical Exclusions

1. Evidence of thromboembolic risk factors, defined as any of the following: known history within the past 6 months of any of the following: (a) myocardial infarction, (b) coronary artery bypass surgery, (c) angina, (d) ischemic stroke, (e) transient ischemic attack, (f) carotid endarterectomy, (g) cerebral bypass surgery, (h) deep venous thrombosis, (i) pulmonary embolism, (j) vascular angioplasty, stenting (coronary, peripheral vascular or cerebrovascular) or filter (e.g. vena cava filter); (k) prosthetic cardiac valve; and/or (l) known history of a high-risk thrombophilia (e.g. antithrombin III deficiency, antiphospholipid antibody syndrome, protein C deficiency, etc.)
2. Known hereditary (e.g. hemophilia) or acquired hemorrhagic diathesis or coagulation factor deficiency.
3. Any condition known that the investigator feels would pose a significant hazard if rFVIIa were administered.
4. Planned surgery for ICH within 24 hours (placement of intraventricular catheter is not an exclusion).
5. Planned withdrawal of care before 24 hours post-ICH onset.
6. Known participation in another therapeutic trial.
7. Known allergy or other contraindication to iodinated contrast dye.
8. Known or suspected hypersensitivity to the trial product.

Medication Exclusions

1. Known unfractionated heparin use – must check PTT and exclude if elevated above upper limit of local lab's reference range.
2. Known low-molecular weight heparin, heparinoid, factor X inhibitor, or direct thrombin inhibitor use within previous 7 days.
3. Known GPIIb/IIIa antagonist use in previous 2 weeks.
4. Known warfarin (or other anticoagulant) therapy with INR >1.40. Note: if the patient is suspected to have cirrhosis, study staff are to wait for the INR value prior to dosing, and ensure not to enroll the patient if the INR value is >1.40. Otherwise the physician should use their discretion if they believe the patient is not at risk for elevated INR.
5. Concurrent or planned treatment with prothrombin complex concentrate, vitamin K, fresh frozen plasma, or platelet transfusion.

Clinical/Laboratory Exclusions

1. Pregnancy or lactation. Women of childbearing potential must have a negative pregnancy test prior to randomization.
2. Current clinical symptoms suggestive of acute coronary ischemia (e.g. chest pain).
3. Baseline ECG evidence of acute coronary ischemia (e.g. ST elevation in 2 contiguous leads, new LBBB, ST depression).
4. Baseline platelet count <50,000 or INR >1.40 or elevated PTT [Note: participants can be enrolled without awaiting these results unless a bleeding abnormality or thrombocytopenia is suspected, the participant is known to have been taking warfarin, heparin, or other anticoagulant, or anticoagulation use is uncertain.].

<u>Justification of Eligibility Criteria</u>

This study is targeting primary spontaneous, non-traumatic, non-anticoagulant-related ICH. The eligibility criteria reflect important refinements to previous rFVIIa trials intended to maximize efficacy and minimize harm. We have set a minimum ICH volume as very tiny ICH (<3 ml) tend to be benign. [31,32] The study is excluding patients with known thromboembolic events or vascular procedures within the past 6 months (the previous phase III trial only excluded patients with thromboembolic events within 30 days prior to enrollment). With these criteria, a lower incidence of SAEs is expected compared to prior

trials. This study is focusing on supratentorial bleeds, which account for the majority of ICH; brainstem/cerebellar bleeds have a different natural history and their inclusion would add too much heterogeneity. Cerebellar hemorrhages often require emergent surgery, which would also disqualify such patients.

Regarding baseline blood work, because time is critical enrollment should not be delayed while waiting for the results of INR, PTT, or platelet count unless a coagulopathy is suspected, the patient is known to have been taking warfarin or heparin, or anticoagulation use is uncertain. Baseline blood work must be checked for eligibility prior to enrollment for any patient being considered for enrollment with a waiver of consent. A serum creatinine value should ideally be obtained prior to CTA. However, because time is critical, CTA should not be delayed while waiting for the creatinine unless renal dysfunction is suspected (see Section 10.2 for further details).

Quick Screening Checklist for Potential Eligibility

A screening checklist has been developed to rapidly identify potential study candidates for whom the study team should come in to assess. This can be done by telephone, ideally between ED triage nurse and the on-call study nurse/coordinator/investigator. It lists automatic exclusions to study enrollment that can often be determined on admission/registration at ED triage desk (or from paramedic pre-notification available at some sites). Patients who fail this screening checklist need not undergo CTA if that is not standard clinical practice at some sites.

Automatic exclusions to study enrollment, assessed upon arrival to ED and prior to CT scanning:

- Patient cannot be scanned, randomized and treated within 6 hours after stroke symptom onset or "last seen normal time" (ED arrival >5 hours after onset is usually exclusionary).
- Age <18 years
- Currently on IV heparin or receiving low molecular weight heparin injections
- Known renal failure or known allergy to iodinated contrast dye

3.2.3 Concomitant Medications / Prohibited Medications and Procedures

As stated in the above eligibility criteria, the following are exclusions to enrollment:

- warfarin (or other anticoagulant) with INR >1.40
- unfractionated heparin use with abnormal PTT
- low-molecular weight heparin, heparinoid, factor X inhibitor, or direct thrombin inhibitor use within previous 24 hours (e.g. dabigatran, rivaroxaban, apixiban, enoxaparin, dalteparin). A complete list of prohibited medications will be provided to sites.
- GPIIb/IIIa antagonist use in previous 2 weeks
- Concurrent or planned treatment with prothrombin complex concentrate (e.g. Octaplex), vitamin K, fresh frozen plasma, or platelet transfusion

Metformin should be stopped at the time of CTA and should not be restarted for at least 48 hours and only then if renal function remains stable (<25% increase compared to baseline creatinine).[38] There are no restrictions placed on other medication use or procedures in this study. All medications, including OTC medications and herbal/natural remedies, taken by the subject are to be recorded on the concomitant medication form in the CRF at specified visits.

Concomitant medications will be captured for the duration of patient participation in the trial.

3.2.4 Imaging Procedures

Brain imaging with a non-contrast head CT scan is performed at baseline and will be repeated as soon after dosing as possible (+ 15 min) and at 24 hours +/- 3 hours post-dosing to assess the rate and degree of ICH growth. The baseline and 24-hour CT scans are standard clinical care for ICH. Patients transferred from outlying hospitals will have the baseline CT repeated with the CT angiogram. The local study investigator will use the baseline CT as part of the screening process for eligibility and will estimate ICH volume using the simple "abc/2" formula, which takes seconds to calculate and is familiar to stroke clinicians.[48] If there is a delay of more than 20 minutes between the baseline CT and the CT angiogram, then a plain head CT must be repeated at the time of the CT angiogram and this will be considered the baseline CT for study purposes.

The local investigator will determine the presence or absence of a spot sign by reviewing the CTA source images obtained immediately following the non-contrast CT scan. Rigorous pre-study training and certification, and recertification, of study investigators on spot sign interpretation is required and is an essential part of our study plan. Dr. Aviv has developed a web-based training module for certification of investigators. CTA is performed only once at baseline. A post-contrast head CT scan will be performed as part of the CTA protocol to assess for additional contrast leakage.[19] CT angiograms will be reported by the local radiologists and results will be available to the local clinicians because of the possibility of detecting pathology.

While planned surgical hematoma evacuation within 24 hours of enrollment is an exclusion criterion, some patients may experience clinical deterioration and be taken for emergent surgery at the discretion of treating clinicians. If this occurs before a 24-hour CT is obtained, a pre-operative CT should be requested and will be used as the study's outcome CT to assess ICH growth. Similarly, for any study patient who is not expected to survive long enough to be rescanned at the planned 24 hour CT scan time (e.g. due to significant early neurological deterioration or if a medical decision for withdrawal of care is made), then a plain head CT should be obtained earlier than 24 hours to ensure the patient has a follow-up outcome scan for study purposes.

3.2.5 Imaging Safety

CTA is widely available and routinely performed as standard care in the emergency evaluation of ischemic stroke and subarachnoid hemorrhage in many centres. For ICH, it is used to exclude secondary causes of ICH and many Canadian stroke centres use CTA in the acute phase of ICH as part of clinical routine. The potential risks of CTA are very small, well established, easily minimized, and virtually always treatable if they occur.

CTA involves a small amount of ionizing radiation. The radiation dose from a plain head CT is approximately 1.7 mSv, which is comparable to natural background whole-body radiation we are all exposed to over 8 months. The lifetime attributable risk of death from cancer from exposure to a head CT scan is less than 0.01% for patients aged 40-80 years.[51] The radiation dose delivered by CTA is slightly more than a non-contrast CT when centered on the intracranial vessels (1.9 mSv).[49] The CTA protocol for this study includes a CT angiogram and a post-contrast head CT scan for a radiation dose of 1.9 mSV + 1.7 mSv = 3.6 mSv). For comparison, the radiation dose from screening mammography is 3 mSv, chest CT 8 mSv, barium enema 15 mSv, abdomen and pelvis CT 15 mSv without contrast (31 mSv with contrast), coronary angiography 22 mSv.[51][52] Overall, then, the amount of radiation exposure for participants in this study is not excessive compared to other routine procedures and is considered to represent inconsequential risk relative to the information gained that may aid in the management of a life-threatening condition.

Radiographic iodinated contrast agents are used extensively in health care. Mild allergic reactions (hives, itching) occur in 2% with intravenous contrast dye; severe reactions occur in ≈0.1%. Contrast extravasation into a limb due to failure of intravenous access occurs in 0.25-0.6% of contrast-enhanced studies[50] and may result in local tissue damage.[53] Reported deaths from iodinated contrast agents range from 6.6 per million to 1 in 10,000.[45] The risk of contrast-induced nephropathy, (>25% increase in serum creatinine within 3 days of contrast administration),[38] is proportional to the amount of agent administered.[38] Only a single dose of contrast (75-100 ml) is required for this study. Chronic renal impairment is the main risk factor.[38] Patients with normal glomerular filtration rate (GFR) are at very low risk; with GFR 30-60, there is a low to moderate risk.[38] Guidelines recommend that patients be screened for risk factors associated with acute or chronic renal impairment, but acknowledge that this may not be possible in the acute setting.[38,54] The absence of risk factors effectively eliminates the probability of a given patient having renal impairment.[54] We and others have studied the renal safety of contrast CT studies in acute stroke patients. Our Calgary study found a low incidence of nephropathy (7/224; 3%) and no patients required dialysis.[34] Of patients who underwent CTA without knowledge of their creatinine, 2% developed nephropathy. Similarly, our Toronto study found elevated creatinine consistent with contrast-induced nephropathy in 5/175 (2.9%), and 1.8% of patients who were scanned before creatinine values were available; none required dialysis or had permanent renal sequelae.[35] A Boston study further supported the safety of emergency contrast CT studies before availability of renal function tests in code stroke patients who did not have a known history of renal disease.[56] A controlled study *(n=539)* reassuringly showed *no increase in risk of acute nephropathy in ICH patients who underwent CTA* (6%) vs. a control group who did not have CTA (10%).[57] Another controlled study showed *no increase in incidence of acute nephropathy in acute ischemic stroke patients who underwent a contrast-enhanced CT protocol (5%) vs. stroke patients who did not receive contrast studies (10%).*[55]

3.2.6 Randomization and Allocation Concealment

A computer-generated randomization schedule will be created for the trial by the study statistician such that there will be an equal number of patients assigned to each treatment. Randomization will be stratified by site using a variable block randomization scheme. Each site will identify an appropriate unblinded dispensing team (local Blood Bank, research pharmacy, or other appropriate team) who will hold the randomization list for that site, prepare the study drug in an unblinded manner, and dispense the blinded study drug to the investigator. The study statistician will provide the site dispensing team with the site randomization schedule, which includes the randomization numbers and the corresponding study drug assigned. The dispensing team will not be involved in any other aspect of the trial.

At the time that the informed consent form (or waiver of consent) is signed, a patient is considered to be enrolled in the study and will be assigned a patient number. Randomization should occur as quickly as possible after enrollment. The investigator will request the study drug STAT from the dispensing team. Upon request for study drug, the dispensing team will assign the patient a randomization number based on the next sequential randomization number on the site randomization list. The time of randomization is defined as the time that the study drug (NiaStase RT or saline) is allocated to the patient by the dispensing team from the site randomization list. The unblinded dispensing team will prepare the corresponding product (NiaStase RT or saline) in a blinded syringe ready for dosing (out of sight of the patient, investigator, and any other members of the blinded study team). Each site will use its own local supply of NiaStase RT and saline. In this trial, site standard sterile saline solution will be used for placebo (any brand is acceptable). Both saline and reconstituted Niastase RT are clear, colorless solutions identical in appearance and texture. The blinded syringe will be labeled according to Health Canada requirements including the randomization number, and provided to the site investigator for injection. Patients who are enrolled but not randomized are considered a screen failure. Once a patient has been randomized, study drug should be administered, and dosing should occur as soon as possible after randomization. Every

effort should be made to minimize any delays from enrollment to randomization, and from randomization to dosing.

3.3 Blinding and Unblinding

This is a double-blind study in which the identity of a patient's treatment will be unknown to the patient and the study personnel involved in the administration of study drug, evaluation of AEs and all other study outcomes.

There are no expected clinical situations in which unblinding of treatment allocation is anticipated to become necessary. The active drug, Factor VIIa, has a short half-life of approximately 2 hours. Any major complications are thought to be due to the active mechanism of the drug as a procoagulant molecule. Treatment of any subsequent arterial or venous thrombosis will follow the clinical standard of care. The ability to provide aggressive treatment (i.e. thrombolytic or antiocoagulant therapy) will be substantially attenuated by the underlying disease under consideration in this trial, i.e. intracerebral hemorrhage.

As unexpected events occur, the following unblinding policy has been established:

Unblinding will be possible for all participants in the trial. If a site requires unblinding, the site PI or local treating physician will call the study's Medical Monitor. Discussion of the case will ensue during which time the medical monitor will ascertain if there are any reasons to unblind. If it is agreed that unblinding is necessary, the local site PI will request that the local dispensing team provides the information. Date, time, reasons for unblinding and signature will be documented every time a blind is broken.

4. STUDY TREATMENT

4.1 Description of Investigational Product

NiaStase RT® (Recombinant activated coagulation factor VIIa - room temperature formulation) is the active comparator in this trial. Recombinant activated coagulation factor VII, rFVIIa, (NiaStase®, NovoSeven®; Novo Nordisk, Denmark) has been used worldwide for years as a treatment for life-threatening hemorrhage, and is approved in Canada and U.S. for the treatment of spontaneous and surgical bleeding in patients with hemophilia A or B and inhibitors to factors VIII or IX.[39] Coagulation factor VII is a naturally occurring initiator of hemostasis. Recombinant (r)FVIIa is functionally identical to naturally occurring FVIIa, binding to the surface of activated platelets where it generates activated Factor X allowing partial restoration of platelet surface thrombin generation.[40] Through its action of enhancing local hemostasis after binding to exposed tissue factors, rFVIIa is an effective initiator and amplifier of hemostasis in patients with normal coagulation.[37-41] It promotes hemostasis in central nervous system bleeding in patients with hemophilia.[42] With a relatively low frequency of systemic activation of coagulation, *rapid action at the site of bleeding, and a short half-life of 2.5 hours*, rFVIIa is an ideal agent for acute ICH.[43]

4.2 Dosage and Administration

The 80 μg/kg dose of rFVIIa chosen for this study is justified based on extensive preclinical testing, testing for non-stroke medical indications, dose-escalation ICH trials, and phase II and phase III RCTs in

ICH.[10,11,14,44] There is consensus among the Steering Committee that 80 µg/kg is the most appropriate dose, providing the best balance of efficacy and safety according to previous studies. Consultation with other experts concludes that this dose carries an acceptable safety profile as a therapy for ICH, especially for patients with a spot sign. A lower dose arm was considered but rejected because it offers less chance of efficacy and inclusion of a third randomization arm would not be feasible based on patient recruitment projections and budgetary considerations. The maximum dose per patient to be used in this study is 10 mg (corresponding to a maximum patient weight of 125 kg or 275 lbs). Sites will use locally available product. Reconstitution and administration should be performed using the following procedures (as per the NiaStase RT® Product Monograph dated March 18, 2010). Always use aseptic technique.

Reconstitution

For detailed instructions on how to reconstitute NiaStase RT® refer to PART III of the Product Monograph. NiaStase RT® powder and histidine solvent vials should be at room temperature at reconstitution. If not at room temperature, hold vials to bring contents to room temperature. The specified volume of diluents corresponding to the amount of NiaStase RT® is as follows:

Vial Size (mg)	Volume of Histidine Diluent to be Added to Vial (mL)	Concentration of rFVIIa After reconstitution (mg per mL)
1.0	1.1	1.0
2.0	2.1	1.0
5.0	5.2	1.0

Administration

Administration should take place immediately. If not used immediately after reconstitution, the vial may be stored at room temperature (below 30°C) or refrigerated for up to 3 hours. Any unused solution should be discarded. Do not freeze reconstituted NiaStase RT® or store in syringes. NiaStase RT® is intended for intravenous bolus injection only and should not be mixed with infusion solutions or be given in a drip. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever the solution and container permit. Do not use if particulate matter or discolouration is observed. Remove and discard the transfer needle from the syringe; attach a suitable intravenous injection needle and administer over 2 minutes. For detailed instructions on how to administer NiaStase RT® refer to PART III of the Product Monograph.

Storage

Prior to reconstitution, keep NiaStase RT® powder and the histidine solvent refrigerated or store between 2° to 30°C. Do not freeze. Protect powder and solvent from light. Do not use past the expiration date.

4.3 Drug Safety

Over 800 ICH patients have received rFVIIa in RCTs. The main safety concern is its prothrombotic potential, i.e., arterial (myocardial infarction, ischemic stroke) or venous (deep venous thrombosis, pulmonary embolism) thrombotic events. In the published phase IIb trial there was no difference in the overall rate of thromboembolic events between groups (7% in the rFVIIa groups vs. 2% in the placebo group, p=0.12) but there was an excess of arterial thrombotic events with rFVIIa vs. placebo (5% vs. 0%, p=0.01).[10] These included 7 myocardial ischemic events and 9 cerebral infarctions within 4 days of dosing. In the phase III trial, 293 patients were in the 80 µg/kg rFVIIa group. Safety data are available from the published paper of investigator-reported events[11] and a retrospective blinded DSMB review of all ECGs and centrally-measured troponin levels.[33] There was no difference in the rates of venous

thromboembolic events between rFVIIa and placebo. There was an increased incidence of arterial thromboembolic events in patients receiving 80 μg/kg rFVIIa vs. placebo. The frequency of myocardial infarction was 12.1% (rFVIIa) vs. 6.4% (placebo), p=0.015. These consisted of ST-elevation myocardial infarctions (2.0% rFVIIa vs. 1.5% placebo) and non-ST-elevation myocardial infarctions (10.1% rFVIIa vs. 4.9% placebo). The rate of "biochemical events" (isolated troponin leak) was 9.4% (rFVIIa) vs. 8.6% (placebo). Most cardiac events were considered to have "minor clinical impact". The rate of ischemic stroke was 6% (rFVIIa) vs. 3% (placebo), although there was no difference in the rate of ischemic stroke events considered possibly related to study drug (2.7% vs. 2.6%). Other thromboembolic events occurred in 2.0% (rFVIIa) vs. 1.8% (placebo) and included renal artery thrombosis, intracardiac thrombus, retinal artery embolism, and thrombophlebitis. Risk factors for thromboembolic events identified in the phase III trial included advanced age, preadmission antiplatelet therapy, and signs of acute ischemia on baseline ECG or head CT. *Overall, the potential risks of rFVIIa are relatively small when compared to the much greater risks of death and disability due to (untreated) ICH itself.* Nevertheless, the potential risks further underscore the need for conducting a much more focused trial like the present proposal with stricter selection criteria than previous studies to maximize the benefit/risk ratio (see Section 5.13 for safety monitoring details).

4.4 Standardized Blood Pressure Protocol

Blood pressure (BP) control in acute ICH is highly variable in practice and may influence ICH outcomes. Previous rFVIIa trials did not standardize BP. In this study, a standardized BP protocol is to be followed (see Appendix B) to minimize confounding influences of hypertension and antihypertensive drug use. An intuitive potential benefit of BP reduction is attenuation of ICH growth, and a pilot study suggested a clinical benefit of BP reduction in acute ICH.[48]. The protocol aims to achieve a target systolic BP <180 mmHg using bolus doses of IV enalapril, labetalol and/or hydralazine, which are familiar to stroke clinicians and have been used safely in acute ICH.[31] BP and heart rate will be closely monitored, and drugs/dosages will be recorded.

Elevated BP is common in acute ICH and patients with higher BP at presentation have elevated early mortality rates. Some multivariate analyses indicate a strong correlation between elevated systolic BP and subsequent ICH expansion, and acute BP reduction has been associated with a decreased incidence of expansion in some studies.[49] An MRI study provides evidence that edema in acute ICH is plasma-derived.[50] It has been hypothesized that reduction of BP, and subsequently of capillary hydrostatic pressures, may decrease edema formation as a result of altered Starling forces around the hematoma. Some physicians are reluctant to aggressively reduce BP in the acute phase predicated on a belief that there is a zone of ischemia surrounding the acute hematoma, despite a lack of evidence of for this in many MRI and CT perfusion studies. In the absence of evidence favouring either treatment strategy, physicians have been forced to make empirical decisions, and clinical practice reflects this uncertainty. Therefore, based on current guidelines, this study specifies a conservative systolic BP target of <180 mmHg for this study. Although any BP treatment target will be associated with controversy, the potential interaction with ICH expansion necessitates a standardized management protocol be included in the study design.

5. ASSESSMENTS

The schedule of assessments is provided in Appendix A. The anticipated duration of patient participation is 1 year. The primary study endpoint is ICH volume on the 24 hour CT scan. The primary clinical endpoint is measured at the 90 day follow-up. All assessments are performed in-person, except the 30-day follow-up is allowed to be done by telephone. The physician should delegate neither the dosing, interpretation of spot sign nor the assessment of inclusion/exclusion criteria to other study staff.

5.1 Baseline Assessment

At the baseline (pre-treatment) assessment, patients will be assessed for eligibility and the following information will be collected in the CRF: patient demographics, medical history, pre-admission and concomitant medications, neurological examination, physical examination, pre-stroke mRS score, ECG, blood work (creatinine, CBC, INR, PTT, troponin, BUN), vital signs, CT scan, CTA scan, ICH volume calculation, spot sign characteristics, intraventricular hemorrhage rating, stroke onset time, hospital arrival time, scan times. Women of childbearing potential will have a pregnancy test performed. Women of childbearing potential and males must confirm double barrier contraception for the first 90 days after dosing. Concomitant medications and adverse event information will be collected and documented throughout the visit.

5.2 Randomization/Dosing

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized and will receive a bolus injection of the study drug over a 2 minute period. Within 15 minutes before dosing, the NIHSS and GCS will be scored. Vital signs will be recorded at the time of dosing or within 5 minutes before dosing. The time of dosing will trigger the blood pressure protocol to begin (see Appendix B).

5.3 Immediate Post-Dose Follow Up

Immediately (+ 15 minutes) after study drug administration, a repeat CT head scan will be obtained to assess for early ICH expansion.

5.4 24 Hour Follow Up

At 24 hours (+/- 3 hours) post-dosing, a repeat plain CT head scan, vital signs, ECG, bloodwork (creatinine, BUN, and troponin) will be obtained. The following clinical assessments will be obtained within a target of +/- 2 hours of the CT scan: GCS, NIHSS, and AE assessment. A brief questionnaire will be administered to the participant or LAR (approximately 15-30 minutes in duration) about the consent process used in this trial (see section 5.12) within approximately 4 days, and again at approximately 90 days.

5.5 Day 2, 3, 4 Follow Up

On days 2 (48 hours +/- 6 hours post-dose), 3 (72 hours +/- 6 hours post-dose) and 4 (96 hours +/- 6 hours post-dose), the following assessments will be made: vital signs, creatinine, BUN, troponin, ECG, updated concomitant medications, and AE assessment. Also on day 4, the GCS and NIHSS will be assessed.

5.6 Day of Discharge Follow Up

If the day of discharge is on a day other than day 4, a separate AE assessment will be made. Also on the day of discharge, information will be documented regarding patient disposition and interventions such as the hospital stay, ICU admissions, rehabilitation services, any neurosurgical interventions, intubation and ventilator use. Concomitant medications will be updated.

5.7 Day 30 Follow Up (may be in person or by telephone)

On day 30 (+/- 7 days) days post-dosing, the following assessments will be made: mRS, Barthel Index and AE assessment. Updates to patient disposition, interventions and concomitant medications will be documented. The day 30 visit may be done by telephone or in-person.

5.8 Day 90 Follow Up

At 90 days (+/- 7 days) post-dosing, the following assessments will be made: NIHSS, mRS, Barthel Index, MoCA, Stroke Impact Scale, EQ-5D, consent questionnaire, CES-D depression scale, clinical brain MRI scan (at sites where this is feasible), AE assessment, and updates to patient disposition, concomitant medications and interventions will be documented. To facilitate scheduling the 90 day clinical brain MRI scan may be scheduled on a different day +/- 30 days of the 90 day follow up visit date. Subjects who had a 25% or more increase in baseline creatinine within 72 hours of the baseline imaging will have their creatinine and BUN measured. The day 90 follow up visit should be done in-person.

5.9 1 Year Follow Up

At 1 year (+/- 14 days) post-dosing, the following assessments will be made: NIHSS, mRS, Barthel Index, MoCA, Stroke Impact Scale, EQ-5D and CES-D depression scale. Updates to patient disposition, concomitant medications and interventions will be documented

The 1 year follow up visit should be done in person.

5.10 Clinical Scales (Neurological Impairment, Disability and Quality of Life)

a) Modified Rankin Scale (mRS)
The modified Rankin scale (see Appendix C) a clinician-reported measure of global disability, is a standard disability outcome in stroke trials. It is predominantly a physical disability, mobility and ambulation index ranging from 0 (no symptoms) to 1 (symptoms; no disability), 2 (mild disability), 3 (moderate disability; independent), 4 (dependent), 5 (severe disability, bedridden, incontinent), 6 (death).

b) Glasgow Coma Scale (GCS)
The Glasgow Coma Scale (see Appendix D) is a neurological scale to assess the level of consciousness.

c) NIH Stroke Scale (NIHSS)
The NIH Stroke Scale (see Appendix E) is a standard neurological deficit rating scale for acute stroke. It will document impairments (e.g. hemiparesis, aphasia, neglect) and overall stroke severity and facilitate comparison with other trials.

d) Barthel Index
The Barthel Index (see Appendix F) is a widely used 100-point scale assessing level of assistance stroke patients require in activities of daily living.

e) Montreal Cognitive Assessment (MoCA)
The Montreal Cognitive Assessment (see Appendix G) is a bedside cognitive test battery developed in Canada and available in 26 languages.[58].The NINDS-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards recommends MoCA as the test of choice for brief assessments.[59] It is preferred over others (e.g. Folstein MMSE) that are less sensitive to executive dysfunction and mild

memory impairment. It takes about 10 minutes to administer. The maximum score is 30 points. Given that ICH is a major cause of cognitive impairment and dementia (and previous rFVIIa trials did not measure cognition), it is important to assess cognition as an outcome in this study.

f) Stroke Impact Scale (SIS)
The Stroke Impact Scale (see Appendix H) is a stroke-specific assessment that evaluates quality of life dimensions (emotion, communication, memory, social participation).[60,61]

g) European Quality of Life Scale EQ-5D
The EQ-5D (see Appendix I) is a standardized instrument for use as a measure of health outcomes. It includes measures of mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

h) Center for Epidemiologic Studies Depression Scale (CES-D)
The CES-D (see Appendix J) is a 20-item instrument developed by NIMH to detect major or clinical depression, and is recommended by the NINDS-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards. [59]

5.11 Laboratory Evaluations / Specimen Collection

Standard Laboratory tests will be obtained. At the baseline assessment the following will be measured: CBC, INR, PTT, serum creatinine, BUN, troponin. At the 24 hour and days 2, 3 and 4 follow up visits the following will be measured: troponin, creatinine, BUN. Patients who had a 25% or more increase in baseline creatinine within 72 hours of baseline imaging will have their creatinine and BUN measured again at day 90.

5.12 Waiver of Consent Evaluation

A structured consent questionnaire will probe patient and family attitudes regarding consent and acceptability regarding the use of a waiver of consent for study randomization and treatment. This will be offered to patients or LAR of patients who are enrolled in SPOTLIGHT, and also to patients or LAR of patients who qualify for SPOTLIGHT but do not consent to participate.

The questionnaire will be administered within approximately 4 days. The duration will be approximately 15-30 minutes. The questionnaire will be administered again after approximately 90 days of the original visit.

5.13 Safety Assessments

Safety assessments consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs). In developing this protocol, we have consulted with cardiologists and other expert clinicians and have been extra-cautious in addressing the safety aspects. Our strict eligibility criteria aim to exclude patients at elevated risk for cardiac or other thromboembolic complications. Clinical safety assessments, ECG, and troponin will be obtained daily for 4 days post-treatment to monitor for adverse events possibly related to study drug. Four days is an appropriate timeframe given the very short duration of study drug exposure (single dose, short half-life) and ongoing or long-term risks beyond 4 days are not expected. Serum creatinine on days 1, 2, 3, 4 and 90 will monitor for nephropathy following contrast CTA. Each site is advised to appoint a local emergency room physician as a sub-investigator to facilitate smooth implementation of the protocol including arrangements for enrolling physicians to obtain real-time consultation on baseline ECG interpretation from a staff emergency physician prior to subject

randomization. If there is any suspicion of a cardiac AE/SAE, the site investigator is encouraged to obtain a clinical cardiology consultation and 2D echocardiogram.

The relationship of adverse events to study drug will be defined as probable, possible, or unlikely. Options for "definite" and "unrelated" will not be available to the investigator on the CRF, as the investigator will be blinded. Because there is only a single dose, there is a short half-life of approximately 2 hours, and there will be no difference in treatment for adverse events between arms, it is expected that the investigator will not require unblinding. See section 3.3. Outcomes will be rated as: recovered, recovering, recovered with sequelae, or fatal. The clinical importance of events will be rated. Detailed AE/SAE reporting procedures will be outlined in the study's procedure manual and a summary is provided in section 7. Sites will be required to report all fatal events, unanticipated problems and other SAEs to the Coordinating Centre within 24 hours and reportable AEs within 5 days. Site PIs are responsible for promptly informing their local REB of SAEs. All events will be independently reviewed by an Adjudication Committee (see Section 9.1.6).

6 SAFETY OUTCOMES

Primary
- Composite endpoint: Rate of myocardial infarction within 4 days post-dose, ischemic stroke within 4 days post-dose, or pulmonary embolism within 4 days post-dose

Secondary
- Unstable angina within 4 days
- Troponin rise above upper limit of normal within 4 days (without clinical symptoms or ECG evidence of acute coronary syndrome)
- Transient ischemic attack within 4 days
- Deep venous thrombosis (DVT) within 4 days
- Pulmonary embolism (PE) within 30 days
- Any other arterial or venous thromboembolic SAEs within 4 days (detailed in the operations manual)
- 90-day mortality
- Acute nephropathy, defined as a 25% or more increase in baseline creatinine within 72 hours of contrast administration [38]

7 ADVERSE EVENTS

7.1 Adverse Events and Adverse Drug Reactions

An adverse event is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. AEs include those reported spontaneously by the subject and those noted incidentally or as observed by the investigator or study personnel.

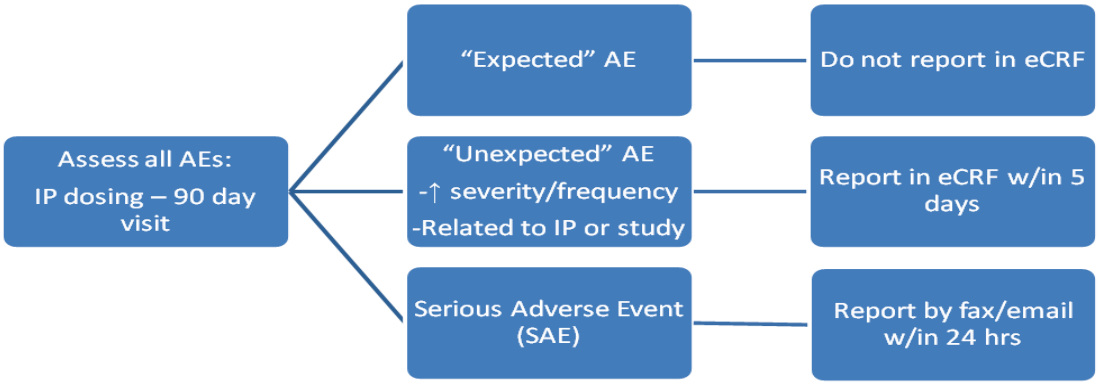
Study staff will assess all adverse events that occur during the period from dosing up to and including the day 90 follow up visit and document these in the source. Investigators will evaluate any changes in laboratory values and physical symptoms/signs and will determine if the change is clinically important and different from what is expected in the course of treatment for patients being treated for ICH. If clinically important and unexpected adverse experiences occur, they will be recorded in the CRF.

Expected Adverse Events
Expected adverse events are untoward clinical occurrences that are perceived by the investigator to occur with reasonable frequency in the day to day care of patients being treated for ICH. Adverse events that are expected in the course of this study may include (but are not limited to) headache, vomiting, seizure, cerebral edema, hydrocephalus, impaired consciousness, pneumonia, and urinary tract infection. These events will not be considered reportable adverse events unless the event is considered by the investigator to be associated with the study drug or procedures, or unexpectedly severe or frequent for an individual patient being treated for ICH or are of a Grade 3, 4 or 5 as defined by the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

Reportable Adverse Events
Reportable adverse events will be those AEs which are considered by the Investigator to be unexpected or of greater severity than expected or of greater frequency than usually found in the day to day care of patients being treated for ICH. Additionally, any AE that in the opinion of the Investigator is probably or possibly related to the investigational product or study procedures will be reported. As well, AEs of a grade 3, 4 or 5 severity as defined by the CTCAE version 4.0 are considered reportable.

Reportable AEs must be reported to the coordinating centre (i.e. entered into the eCRF) within 5 days of becoming aware of the event.

Figure 1. Schematic of AE Reporting Procedures



7.2 Serious Adverse Events (SAEs) and Serious Adverse Drug Reactions (SADRs)

A Serious Adverse Event is defined as any untoward medical occurrence that at any dose:
- results in death
- is life-threatening (an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or prolongation of an existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Medical and scientific judgment should be exercised in deciding whether other conditions should also be considered serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above. These should also be considered serious. Follow up information

regarding SAEs will be pursued until the event has resolved (with or without sequelae), until death, or until 30 days after the 90 day visit (whichever comes first.), as drug related events are not expected to occur after this period of time given the short half-life of the rFVIIa. For any deaths where there is uncertainty about the cause of death, site investigators may request an autopsy if appropriate.

7.2.1 Reporting Serious Adverse Events (SAE)

Any SAE, including death due to any cause, which occurs between dosing and the 90 day follow up visit whether or not related to the study drug, must be reported immediately (within 24 hours of the study site's knowledge of the event) by email or fax to the SPOTLIGHT Coordinating Centre. The report will contain as much available information concerning the SAE to enable the Coordinating Centre to file a report that satisfies regulatory reporting requirements. Criteria for documenting the relationship to study drug as well as severity and outcome will be the same as those previously described. Additionally**,** any arterial or venous thromboembolic event and/or death occurring within 30 days of dosing will be reported as an SAE.

<u>Definitions of Thromboembolic Adverse Events of Special Interest</u>

1. Acute myocardial infarction (AMI)

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

• Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

- Symptoms of ischaemia.
- New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
- Development of pathological Q waves in the ECG.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Identification of an intracoronary thrombus by angiography or autopsy.

• Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB,but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

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 embolism (PE)

   Clinically suspected and confirmed by contrast-enhanced CT (CTPA) as a constant intraluminal filling defect in one or segmental or larger pulmonary arteries or by high probability ventilation/perfusion (V/Q) lung scan (defined as one or more segmental mismatched defect). If the largest filling defect on CTPA is at the subsegmental level or if a V/Q scan is abnormal but not high probability, these results are considered nondiagnostic. Proven fatal pulmonary

embolism: death with autopsy proven major PE that was the likely direct or indirect cause of death. Possible fatal pulmonary embolism: sudden death in a patient with no autopsy in whom there is no more likely alternate diagnosis.

4. Deep venous thrombosis (DVT)
   Clinically suspected and confirmed by positive result on compression ultrasound in a proximal deep leg vein (popliteal, femoral or iliac) [symptomatic proximal DVT] or clinically suspected and confirmed by positive result on compression ultrasound in a deep calf leg vein [symptomatic calf DVT].

5. Myocardial damage with enzyme leak, defined as a troponin rise without ECG changes from baseline or clinical evidence to suggest myocardial dysfunction.

6. Other arterial or venous thromboembolic SAEs (please refer to the study's operations manual for a complete list).

7. Incidental asymptomatic DWI lesions on brain MRI. Such lesions, compatible with acute cerebral ischemia, have been recently reported in the literature to occur in 14-41% of acute ICH patients who undergo brain MRI within one week of ICH onset. Such lesions are typically tiny, asymptomatic, and located in topographically remote areas from the hematoma. Their pathophysiology and clinical significance are uncertain at this time. For proper AE classification and interpretation, this MR imaging observation should be distinguished from a clinically overt ischemic stroke.

7.2.2 Recording of AEs and SAEs

Reportable AEs and SAEs will be recorded in the electronic case report form (eCRF) and in the source documents. To avoid vague, ambiguous, or colloquial expressions, the AE should be recorded using standard medical terminology that is as specific as possible, rather than the subject's own words. Whenever the investigator is confident in making a unifying diagnosis, all related signs, symptoms, and abnormal test results should be grouped together and recorded as a single AE (e.g. cough and rhinitis may be reported as an "upper respiratory tract infection"). Each AE is to be evaluated for duration, severity, seriousness and causal relationship to the investigational drug and the outcome of the AE will be assessed.

<u>Severity</u>
The severity of the AE will be graded according to the CTCAE Version 4.0 guidelines:
- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

<u>Drug-Event Relationship</u>
The causal relationship between the study drug and the AE should be characterized according to the following:

- Unlikely – suggests that only a remote connection exists between the study drug and the event. Other conditions, including concurrent illness, progression or expression of the disease state or reaction to concomitant medication, appear to explain the AE.
- Possible – suggests that the association of the AE with the study drug is unknown, however the event is not reasonably supported by other conditions.
- Probable – suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator's clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and other conditions (concurrent illness, progression or expression of the disease state, or concomitant medication reactions) do not appear to explain the AE.

Outcome

The outcome of the adverse event should be classified according to the following definitions:

- Recovered / resolved: the event has resolved (no further symptoms are present and no treatment is being received by the subject)
- Recovered / resolved with sequelae: the event has resolved but there may be lingering effects present (e.g., a scar following a cut or abrasion).
- Recovering: the event may have resolved, the patient is returning to health
- Fatal: the subject died as a result of the event. This code should only be used for the event that caused the death, not any event that was present at the time of the subject's death. Fatal events require immediate reporting to the Sponsor (or an authorized representative).
- Unknown: may only be used in the event that the subject is lost to follow-up and no reliable data can be obtained.

All efforts should be made to classify the AE according to the above categories.

7.2.3 Follow-up of AEs and SAEs

All AEs and SAEs occurring during the study are to be followed up in accordance with good medical practice until resolved, judged no longer clinically significant, study completion, or if a chronic condition, until fully characterized. All follow-up results are to be recorded in the CRF as necessary. The outcome of any pregnancies occurring during the first 90 days of the study will be followed until the birth of the child and the child will be followed until one month of life.

7.2.4 Reporting of Serious Unexpected Adverse Drug Reactions (SUADRs)

The PI (or an authorized representative) is responsible for submitting reports of SUADRs to Health Canada within the required reporting period. All investigators participating in ongoing clinical studies with the study drug will be notified by the Coordinating Centre (or an authorized representative) of all SUADRs that require prompt submission to the REB/IRB. Investigators are responsible for notifying the REB/IRBs in writing of the SUADRs within the required reporting timelines. Copies of the notification will be maintained by the investigator in the study documentation files. Sites will receive detailed reporting guidelines for the SAE reporting process.

8. STATISTICAL METHODS

8.1 Sample Size

Sample size calculations are based on data from the ongoing PREDICT study regarding the expected baseline and 24-hour ICH volumes in spot-sign positive patients. The standard deviation of ICH volume at 24 hours is about 41 ml. Since all data to date indicate that rFVIIa reduces bleeding and does not increase bleeding, calculations are based on a one-sided Type I error chance of 5%. We believe a 20 ml difference in final ICH volume between groups would be highly clinically significant based on the literature, and we wish to have 80% power to detect this difference. With a 1:1 allocation ratio, a sample size of 53 rFVIIa and 53 placebo patients is required.

8.2 Details of Statistical Analysis

Baseline characteristics will be summarized by descriptive statistics as appropriate (mean and SD for continuous variables; frequencies and percentages for categorical variables).

The primary outcome of ICH growth within 24 hours will be compared between the 2 treatment groups by analyzing the final ICH volume on CT scan at 24 hours, adjusting for baseline ICH volume, by means of linear regression. The 24 hour ICH volume will be summarized for each group by descriptive statistics and the adjusted treatment effect and 95% confidence interval will be obtained from the regression model. Although absolute change or percent change in ICH volume between baseline and 24 hours has been the traditional method of analysis in prior studies, the proposed approach is more methodologically sound.[62] However, change and percent change will be summarized with descriptive statistics to allow comparison with other studies. Similar analyses will be performed for intraventricular hemorrhage volume and total volume (ICH plus intraventricular hemorrhage). We will calculate the minimum clinically important difference for ICH growth, adjusted for baseline ICH volume and anatomical location.

The feasibility parameters will be analyzed using descriptive statistics with the aim of determining if the spot sign can be assessed and treatment begun within an acceptable time period to conduct a larger trial of clinical outcomes. We expect the trained enrolling physicians will accurately interpret the presence of a spot sign in this trial, and we will carefully assess any spot signs that were over-called (i.e. false positives) compared to blinded over-read by the "gold standard" study neuroradiologist. Qualitative analysis of the waiver of consent questionnaire will examine feasibility and acceptability of a consent waiver for future trials. We will describe the characteristics of patients enrolled with a waiver and compare their median treatment times (and ICH volumes) with those enrolled with standard consent.

The frequency of adverse events will be compared between the treatment groups. Since the sample is small and adverse events are not expected to be common, expected frequencies (under the assumption of no difference) may be too low for chi-square tests, so Fisher's exact test will be employed. For safety, stopping rules have been developed based on data from the phase III trial demonstrating a 12% rate of myocardial infarction associated with 80 μg/kg rFVIIa (see below).

8.3 Imaging Analyses

De-identified CT and CTA images will be transferred to the Imaging Core Labs for central blinded interpretation. ICH size will be calculated by volumetric analysis. We will assess ICH location, intraventricular hemorrhage volume, edema volume, presence of hydrocephalus, mass effect, spot sign

patterns (number, morphology) and score. Segmented volumes are obtained 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. The operator places seed-points within the volume of interest and adjusts lower and upper intensity HU thresholds until the entire volume is correctly selected. Where ICH volume cannot be differentiated from intraventricular hemorrhage volume, the operator uses freehand drawing tools to remove intraventricular hemorrhage. In this situation, intraventricular hemorrhage volume will be determined using the original over-segmented volume that includes the combined ICH and intraventricular hemorrhage volumes, V_{total}, as intraventricular hemorrhage volume = V_{total} - ICH. This limitation is unavoidable as intraventricular hemorrhage has the same density as ICH and the 2 volumes are often contiguous. The volume (ml), mean (HU), standard deviation (HU) and the affected part(s) of the brain will be measured from the segmented volume. CT data will be transferred to a research PACS system and analyzed on a personal workstation using Quantomo software developed at University of Calgary. User-selected parameters used to segment the volumes (i.e., seed-points, HU intensity thresholds) 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 be saved in XML files. Statistical analysis will be performed off-line using the data collected in XML files. We will also collect MRI scans for blinded centralized volumetric analysis at the Sunnybrook Brain Imaging Analysis Laboratory.[63-64] As our sites typically obtain MRI as part of clinical routine for ICH survivors, we will not mandate MRI as a study-related investigation (to minimize budget), but will acquire these scans by a standardized protocol at day 90 to allow tissue segmentation. MRI analysis will yield regional tissue compartment volumes, including white matter disease (which may affect outcomes), residual lesion volumes and microhemorrhages [63-64]

8.4 Frequency of Statistical Analysis and Stopping Rules

Myocardial infarction, ischemic stroke, pulmonary embolism and all thromboembolic SAEs will be monitored on a continuous basis by the DSMB, which includes an unblinded statistician.

The medical monitor will review all SAEs and provide adjudicated reports to the DSMB. The DSMB will review and assess each SAE against the suggested stopping rules that are detailed in the DSMB charter.

8.5 Planned Subgroup Analyses

We will assess treatment in subgroups based on onset-to-treatment time (<3 vs. >3 hours); baseline ICH volume (<30 vs. >30 ml); anatomical location (deep vs. lobar); intraventricular hemorrhage (present vs. absent, and by Graeb score); spot sign score (1-2 vs. 3-4)[27] and morphological pattern,[13] and presence or absence of contrast leakage on post-contrast head CT performed as part of the baseline CT angiogram.[65]

8.6 Planned Pooled Analysis

A pooled analysis is planned with other similar trials, including the STOP-IT study based at the University of Cincinnati that received NIH (NINDS) funding and FDA approval and plans to begin recruitment in 2010, and STOP-AUST, an Australian trial that is proposed. SPOTLIGHT and these other studies will run independently as separate trials. The Executive Steering Committees of these studies have collaborated on a harmonized core study protocol to enable a future pooled analysis after completion

of each study. The benefits of pooling individual patient data from small RCTs have been exemplified by other key stroke trials (e.g. hemicraniectomy, carotid endarterectomy). A pooled analysis will enable analyses of clinical efficacy. The proportion of patients in each group achieving a 90-day modified Rankin score 5-6 (death or severe disability) will be compared in an adjusted analysis. A generalized linear mixed model with log-link will assess the relative risk of poor outcome in the two groups, adjusting for site, age, baseline ICH volume, treatment times, intraventricular hemorrhage, Glasgow Coma score, and pre-stroke Rankin score. Similar analyses will be performed for mortality and the other clinical scales. A shift analysis across the full range of mRS scores will be performed using the methodology of Saver to estimate the number of patients needed to treat for 1 additional patient to improve by 1 or more levels of disability on the mRS.[66]

9. TRIAL MANAGEMENT

9.1 Study Group Members

A list of study group members will be maintained and stored at the Coordinating Centre.

9.1.1 Coordinating Centre

The Study Headquarters is Sunnybrook Health Sciences Centre, University of Toronto. The SPOTLIGHT Coordinating and Data Management Centre is located in the Applied Health Research Centre (AHRC), Li Ka Shing Knowledge Institute of St. Michael's Hospital (www.stmichaelshospital.com/research), University of Toronto. This comprehensive clinical trials unit employs expert project management staff and uses state of the art, secure, encrypted, web-based data management software (Medidata RAVE™) with sophisticated data validation rules. The Coordinating Centre will be responsible for developing and programming the electronic CRFs, trial procedure manual, data monitoring, regulatory documents, data management and analysis, and providing progress and data reports to the Executive Steering Committee, DSMB, Health Canada and participating sites.

9.1.2 DSMB

The DSMB will provide oversight and monitoring of the conduct of the trial to ensure safety of participants and validity and integrity of the data. A Charter will outline roles, responsibilities and processes to be followed. The DSMB is an independent group not otherwise associated in any way with the trial, and will make ongoing recommendations concerning the continuation, modification and termination of the trial.

9.1.3 Executive Steering Committee

An advisory committee, has advised in the study planning and protocol development, and will provide ongoing direction during the course of the study.

9.1.4 Steering Committee

The Steering Committee consists of members of the Executive Committee and the Coordinating Centre, plus site PIs from each participating centre, and expert external advisors.

9.1.5 Imaging Core Labs

The Imaging Core Lab for all the CT analyses is at the Seaman Family MR Research Centre, University of Calgary, under the direction of Dr. Andrew Demchuk. All CTA spot sign analyses will be performed by Dr. Richard Aviv at Sunnybrook Health Sciences Centre in Toronto. MRI scans will be analyzed at Sunnybrook Health Sciences Centre under the direction of Dr. Sandra Black.

9.1.6 Adjudication Committee

An Internal Medical Monitor will independently review all SAEs in real time and submit opinions to the PIs, Independent Adjudication Committee, and DSMB regarding the relationship of events to study drug. A blinded Neuroradiologist will independently adjudicate the imaging aspects of suspected cerebrovascular SAEs. An independent Adjudication Committee will review all reported AE/SAE events and prepare summary reports for the DSMB.

9.1.7 Ethics Committee

The Ethics Committee will review the enrolment of every incapacitated patient for whom a waiver of consent has been used, and report to the DSMB, Steering Committee, and local REBs. The committee will be chaired by the trial ethicist, Dr. Julie Spence, an emergency physician at the University of Toronto, and a former Chair of the St. Michael's Hospital Research Ethics Board.

9.2 Research Ethics Board/Institutional Review Board

A copy of the protocol (including protocol amendments), all versions of informed consent forms, other information to be completed by participants such as survey instruments or questionnaires, and any proposed advertising/ recruitment materials must be reviewed and approved by the REB/IRB of each participating centre prior to implementation of the trial. The investigator will be responsible for obtaining REB/IRB approval and annual Continuing Review throughout the duration of the study.

9.3 Early Termination

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified, and without penalty or loss of benefits to which the subject is otherwise entitled. Study patients will be informed of the possibility to withdraw consent without giving any reason. Subjects may be withdrawn for specific reasons during the study, which include: ineligibility, non-compliance or for administrative reasons (including study closure). Before a subject is declared lost to follow-up, all efforts should have been made to contact the patient for a final assessment.

9.4 Monitoring

Annual monitoring visits will be conducted at each site by a member(s) of the SPOTLIGHT Coordinating Centre to inspect all study related documentation and records, including, but not limited to, study data, patient medical records, and source documents.

9.5 Source Documents and Access to Source Data/Documents

Each participating site must maintain appropriate medical and research records for this trial and regulatory/institutional requirements for the protection of confidentiality of study subjects. Source documentation should support the data collected on the CRF. The Principal Investigator is responsible for assuring that the data collected are complete, accurate, and recorded in a timely manner. Access to the source documentation will be as per regulatory/institutional guidelines.

9.6 Data Management

Electronic data capture (Medidata RAVE™) will be used for this trial, meaning that all study data will be entered in electronic forms (eCRF) at the investigational site. Data collection will be completed by authorized study site personnel designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorized study site personnel prior to the study being initiated and any data being entered into the system for any study subjects.

The study data will be housed on a secure in-house server at St. Michael's Hospital in Toronto throughout the duration of study, and up to 10 years after the study is complete. A copy of the tabulated raw study data will be stored at Sunnybrook Health Sciences Centre for 25 years after completion of the study.

9.7 Participant Confidentiality

All subject related information including Case Report Forms, evaluation forms, reports, etc. will be kept strictly confidential. All records will be kept in a secure, locked location and only research staff will have access to the records. Subjects will be identified only by means of a coded number specific to each subject. All computerized databases will identify subjects by numeric codes only, and will be password protected.

9.8 Disclosure and Publication Policy

The study will be registered on clinicaltrials.gov after REB approval is obtained from at least one site. Study results will be published upon completion of the study, and authorship will be in line with ICMJE guidelines.

10 INFORMED CONSENT PROCESS

This study is predicated on the ability to provide ultra-rapid study drug administration, as rFVIIa is a highly time-sensitive treatment. Given the time constraints necessary for this emergency treatment protocol and the nature of ICH (many potential participants are expected to be incapacitated during the hyperacute phase of a spot-sign positive ICH), obtaining timely prospective fully informed consent prior to enrolment is not feasible. Family members or representatives may or may not be present at the moment the CT scan diagnosis of ICH is made. Even if present, they may have difficulty understanding and appreciating the full Informed Consent Form. Thus, this study is designed to streamline consent procedures to allow eligible participants the opportunity to be treated as quickly as possible to maximize the benefit/risk ratio of this study protocol. Any delay to study drug administration is expected to significantly diminish, or even negate, the potential benefits of rFVIIa.

Therefore, a two-phase consent process is proposed. A short summary form has been developed and will be used to seek *assent* for randomization and study drug administration from a patient with capacity to consent and/or the patient's legally authorized representative (LAR). The full consent document will subsequently be reviewed with either the patient or the patient's LAR at the earliest possible time, to ensure that all research-related questions are addressed. Both the assent and consent documents are signed and copies are provided to the patient or LAR.

However, because ICH patients are frequently incapacitated and LAR consent may not be possible to obtain immediately, a waiver of informed consent option has been developed for this study to enable enrolment of eligible patients without delay. In Canada, there is REB allowance to approve a consent waiver in emergency situations when patient consent is not possible and a LAR is not immediately available. Ethical justification to waive informed consent prior to study-related procedures is provided below in accordance with the criteria of the Tri-Council Policy Statement for ethical conduct of research involving humans in individual medical emergencies (Article 3.8). [67] These criteria are similar to U.S. federal regulations that allow emergency consent to be conducted without informed consent; in contrast to U.S. regulations, community consultation is not mandated in Canada.

10.1 Justification for the Use of a Waiver of Consent in Individual Medical Emergencies (Tri-Council Policy Statement Article 3.8)

1. A serious threat to the prospective participant requires immediate intervention.

As outlined in the protocol, acute ICH is a life-threatening emergency that requires immediate management (40% 30-day mortality; half of deaths occurring within 48 hours). Bleeding may increase minute by minute, and the majority of ICH expansion occurs very early. [1] Therefore, treatment to stop active bleeding must be applied as soon as possible. Delaying study drug administration to obtain consent is expected to significantly diminish, or even negate, the potential benefits of rFVIIa, and may potentially expose patients to unnecessary harm if patients are treated late (after intracerebral bleeding has stopped). Indeed, the failure of other acute stroke trials to demonstrate efficacy may in some cases relate directly to the fact that study drug was administered too late. [68]

2. Either no standard efficacious care exists or the research offers a realistic possibility of direct benefit to the participant in comparison with standard care.

At present, there are no specific acute medical or surgical treatments for ICH that are approved or have proven efficacious in a randomized trial. The published phase IIb and phase III rFVIIa trials suggest the first real possibility of direct benefit to patients compared to standard care alone. According to post-hoc analysis of the phase III trial, a subgroup that derived significant clinical benefit from rFVIIa consisted of patients who could be treated very quickly (within 2.5 hours of stroke onset), aged ≤70 years, with baseline ICH size ≤60 ml and intraventricular hemorrhage volume ≤5 ml.[11] While encouraging, we estimate that such results would only apply to a minority (<7%) of ICH patients who meet these criteria (data on file, Registry of the Canadian Stroke Network, May 2008). Our approach (using image-guided patient selection with the CTA spot sign) offers a way to potentially help many more patients.

3. Either the risk is not greater than that involved in standard efficacious care, or it is clearly justified by the prospect for direct benefits to the participant.

rFVIIa in the ICH population is associated with an increased incidence of arterial thromboembolic complications (the major risks are myocardial infarction and ischemic stroke). With the 80 μg/kg dose, the potential risks are offset by a realistic chance of benefit for patients who otherwise have very high morbidity and mortality (i.e. spot sign positive patients). Our trial design and strict eligibility criteria aim to minimize harm by excluding patients at elevated risk for adverse events and those unlikely to respond

to hemostatic therapy (i.e. spot sign negative patients). Careful clinical and laboratory monitoring for potential thromboembolic adverse events is an essential component of this study. Indeed, we expect that using a waiver of consent to expedite treatment may maximize the benefit/risk ratio of rFVIIa. In some centres, rFVIIa is already being used "off-label" for ICH, which may expose some patients to potential risk without expected benefit if active bleeding has already stopped. In this study, hemostatic therapy is being tailored to individual patients in a rational way. By stratifying patients according to CTA findings, spot-sign negative patients in this study (who are not at high risk for ICH expansion) would not be enrolled. With respect to CT angiography, this is already a widely used diagnostic test for patients with acute ICH because it provides information about treatable pathologies (e.g. aneurysm, arteriovenous malformation, etc.). Early identification of unsuspected secondary causes of ICH may have an important impact on subsequent patient care. Many ICH patients undergo CT angiography at some point during their hospitalization; in this study CT angiography is simply being performed as part of the initial assessment. Intravenous contrast may be associated with nephrotoxicity or allergic reaction, but these are uncommon; patients with known renal disease are excluded and we will monitor for renal toxicity.

4. The prospective participant is unconscious or lacks capacity to understand the risks, methods, and purposes of the research project.

In all but those with the smallest hemorrhages, ICH patients are rendered incapable of making informed decisions in the acute stage due to altered level of consciousness or cognitive impairment (e.g., aphasia, anosognosia). Because most stroke patients are rendered acutely incompetent to make personal medical decisions by their stroke (ischemic or ICH), restricting enrolment only to patients who are fully alert, cooperative, and capable to provide consent is not feasible. Without a waiver option, there will be an obvious selection bias (according to who is able to provide consent), which undermines the study's external validity, i.e. skewed toward patients with milder ICH and failing to represent those with moderate and severe ICH. For our study results to have true generaliazability, we must enroll a representative sample of patients. The ethical principle of justice may be considered to be violated if experimental therapies can only be offered to selected patients. Waiver of consent suspends the principle of autonomy in favour of the principle of justice: unless such patients can be studied, effective treatments for future similar patients will never be advanced. Guidance for assessing capacity is noted in Appendix K of this document: Suggested Framework for evaluating capacity for consent in an emergency setting.

5. Third party authorization cannot be secured in sufficient time, despite diligent and documented efforts to do so.

In the emergency setting associated with ultra-early treatment of ICH, LARs may not be immediately available at the time of the baseline imaging. Without a waiver of consent option, these patients would be excluded from the study or included after significant delay. Based on experience from another emergency stroke trial (IMS study), we estimate a LAR may not be present in about 20-25% of eligible candidates.

6. No relevant prior directive by the participant is known to exist.

If advance directives are available, either in writing or from a LAR, the treating physician will be responsible for informing the study team of only those patients who are potentially eligible for study enrolment.

10.2 Description of Proposed Consent Procedures

There are 3 versions of the consent form:

- Document A: Brief Study Summary/Informed Consent Form for participants and/or LAR from whom two-staged *assent-consent* will be sought prior to enrolment
- Document B: Long version of the Information Sheet/Informed Consent Form to be used either on its own or after enrolment as a follow-up to Document A if the brief assent-consent is used.

- Document C: Letter of Information/Informed Consent Form for continued participation in the study for participants who are enrolled with a waiver of consent.

There are two possible routes for study enrolment:

- *Assent-Consent*

  For eligible patients who have capacity to consent or for eligible incapacitated patients with a Legally Authorized Representative (LAR) present, a short study summary (Document A) can be presented prior to the full consent form if the site receives the required local ethics approval. A consent discussion based on the study summary will take place and *assent* for randomization and study drug administration will be sought. If the LAR is not present but can be reached by telephone, then telephone assent-consent from the LAR will be permitted to enable enrolment without delay. After study drug administration, full informed consent will then be sought from the patient or LAR using the more detailed, longer version information sheet and consent form (Document B).
- *Waiver of Consent*

  In the event that assent-consent cannot be obtained (i.e. for eligible patients who are incapacitated and for whom a LAR is not immediately available), a waiver of consent will be invoked to enable randomization and study drug administration without delay. An additional screening form for potential contraindications to rFVIIa must be completed for those who are considered for enrolment with waived consent. After study drug administration, every effort must be made by the investigator to promptly identify and contact the LAR to provide full explanation of the study and seek informed consent for continued study participation using Document C.

Additional Eligibility Screening Requirement for Incapacitated Patients with No LAR

If an incapacitated participant appears to be a good study candidate and there is no LAR available in person or by telephone, then a waiver of consent option may be invoked by the investigator. In this situation, the investigator must first determine eligibility by obtaining information about the participant's past medical history from all available sources, i.e. medical information should be sought from the patient, paramedics, electronic medical records, medic alert card/bracelet, primary care physician or other physicians, etc., and inferred from the patient's medication list, physical examination findings, and laboratory tests, with particular emphasis on identifying any exclusions to study participation. A second physician will confirm subject incapacity.

If any of the following additional features are present, in addition to the exclusion criteria listed above, the patient is not eligible for enrolment using a waiver of consent.

- Preadmission medications: ASA plus clopidogrel
- Preadmission medication: warfarin
- Known hospital admission or emergency department visit (for any reason) within past 3 months
- Physical examination findings to suggest previous stroke (chronic neurological deficits), cardiac surgery (sternotomy scar), carotid endarterectomy (neck incision), recent stenting/catherization procedure (femoral or radial artery puncture)
- Baseline troponin T or troponin I $\leq$0.1 ng/ml ($\leq$0.1 µg/L).

Procedures for Obtaining Patient Consent After Enrolment

In all cases, informed consent from the patient must be actively pursued by the investigator after daily assessments to determine if the previously incapacitated patient has regained capacity. If the patient is discharged or leaves the hospital prior to patient or LAR contact, attempts will be made using registered letter and documented phone calls weekly for a minimum of 28 days post-discharge. When the patient regains capacity, the investigator will inform him/her about enrolment in the study and will seek consent for continued participation. Despite LAR consent, the investigator must continue to seek informed

consent from the patient for continuation in the study. In the event that capacity is regained, patient consent supersedes the authority of the consent provided by the LAR.

Investigators are advised to use the CURVES method of Chow et al. to assess and document capacity (see Appendix K).[67]

All processes for obtaining consent must be in compliance with local sites' REB guidelines. All participants or LAR will be given detailed oral and written information about the trial. Consent forms describing in detail the study intervention, study procedures and risks will be given to each participant or LAR. All participants or LAR must sign informed consent document B or C that have been approved by a participating centre's REB. Participants or LAR may withdraw consent at any time during the course of the trial. The informed consent form will be signed and dated by the participant or LAR and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the participant's study files and a copy of the signed form will be provided to the participant or LAR.

Please see Figure 2 for a schematic of the consent procedures.

Waived Consent for CT Angiography

CTA is a widely used diagnostic test for patients with ICH because it provides information about treatable pathologies (e.g. aneurysm, arteriovenous malformation, etc.). Early identification of unsuspected secondary causes of ICH may have an important impact on subsequent patient care. As such, many ICH patients undergo CTA at some point during their hospitalization. In this study CTA is being performed as part of the initial assessment, ideally within the first half-hour of arrival at the emergency department. When performed acutely, CTA also provides important prognostic information for patient care based on the presence and characteristics of a spot sign(s).[12,28] The 2010 American Heart Association Guideline on Management of Intracerebral Hemorrhage recommends CTA: "CT angiography and contrast-enhanced CT may be considered to help identify patients at risk for hematoma expansion (Class IIb; Level of Evidence: B), and CT angiography,…contrast-enhanced CT,…can be useful to evaluate for underlying structural lesions, including vascular malformations and tumors when there is clinical or radiological suspicion (Class IIa; Level of Evidence: B)".[30]

All of the stroke centres selected as participating sites in this trial already perform CTA as part of standard clinical care for many patients with ICH. The emergency use of CTA for acute ICH assessment is becoming a leading practice at designated stroke centres. Many, but not all, of the participating Canadian sites in this trial already routinely obtain CTA acutely as part of standard clinical care for "code stroke" cases in the emergency department, including acute ICH and acute ischemic stroke.

Therefore, for sites that are already performing CTA acutely as part of their standard clinical care acute stroke imaging protocols, consent for participation in this trial will be sought following CTA. For sites that are not already routinely performing acute CTA as standard clinical care for ICH, site REB approval for a waiver of consent policy for CTA is requested to enable CTA to be performed without delay for ICH patients who are potential study candidates after passing the Quick Screening Checklist for Eligibility. Consent for study enrollment for eligible patients will then be sought after CTA has been completed.

Local radiology protocols at each site are to be followed for excluding patients with known contraindications to CTA, i.e. known allergy to iodinated contrast dye, known renal insufficiency or creatinine clearance <30 ml/min), and administration of a low-osmolar or iso-osmolar contrast agent (e.g. Visipaque) for patients whose serum creatinine is not known prior to scanning or creatinine clearance is 30-60 ml/min.[34,35,38] Site PIs will be responsible for preparing a written standard operating procedure

specific to their site in conjunction with their local site neuroradiologist co-investigator to describe the local criteria/contraindications for CTA.

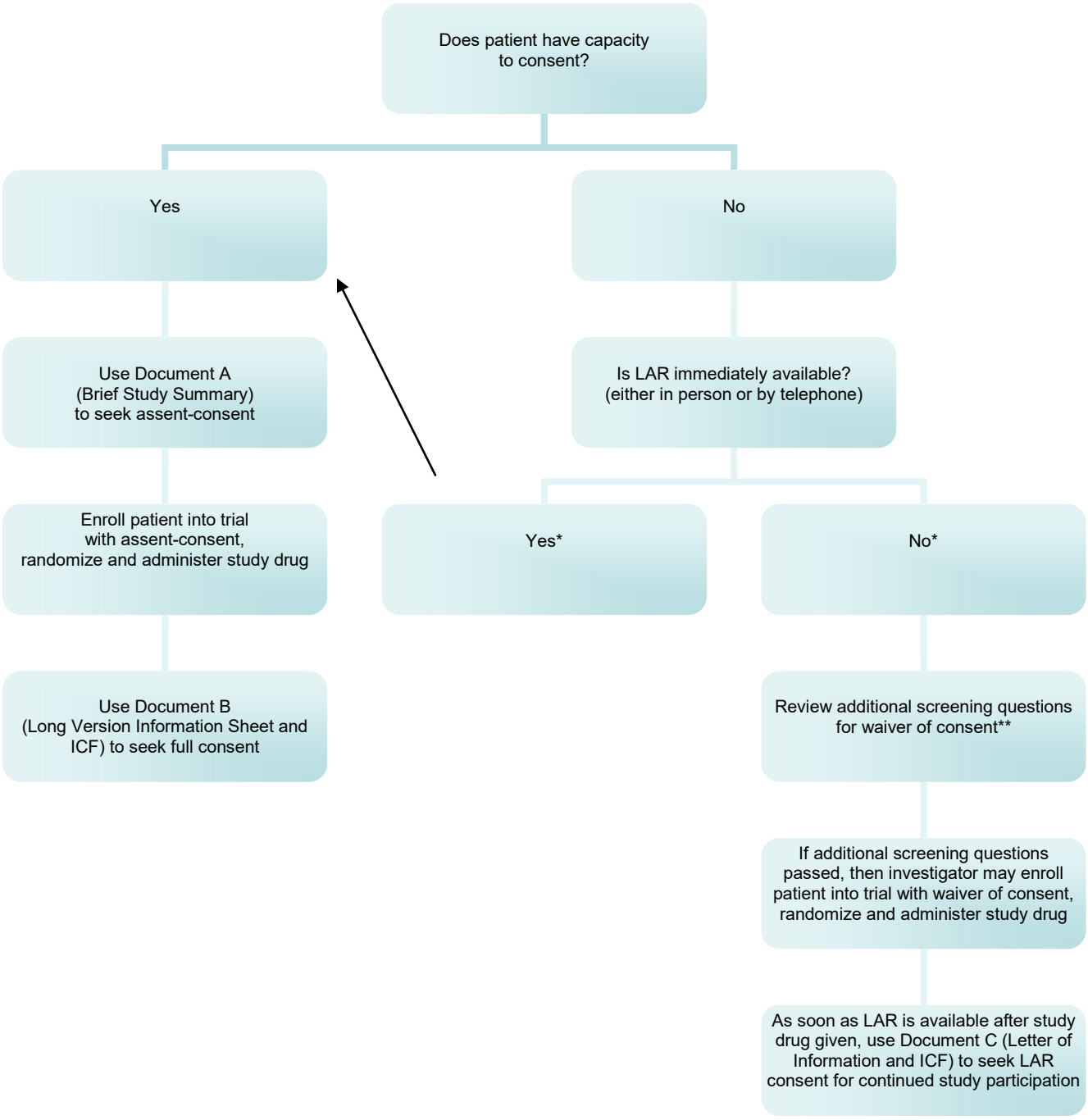
A serum creatinine value should ideally be obtained prior to CTA. However, turnaround time for stat blood work at sites is variable and serum creatinine measurement is frequently waived in the emergency situation. The European Society of Urogenital Radiology guideline states that "in emergency situations serum creatinine measurement can be waived". [36] If a baseline serum creatinine result is not available at the time of the proposed CTA, the investigator should check for any available previous creatinine levels or documentation of renal insufficiency in the patient's electronic medical record, and assess for risk factors for renal failure (see the list below). In the absence of a recent creatinine value, it will be up to the investigator's judgment to proceed with CTA or not based on the individual patient profile and situation. According to the Canadian Association of Radiologists, "the absence of risk factors [see below] for renal disease effectively eliminates the likelihood of a patient having renal impairment" and states that "delays whilst awaiting serum creatinine results may adversely affect patient care".[38] They recommend the use of iso-osmolar or low-osmolar agents rather than high osmolar agents, plus fluid administration, e.g. intravenous normal saline (0.9% NaCl) 1 ml/kg/h for 12 hours post-CTA.[38]

Screening for Contraindications to CT Angiography

According to the Canadian Association of Radiologists Consensus Guidelines for the Prevention of Contrast Induced Nephropathy, patients should be screened for the following risk factors for renal impairment or development of contrast-induced nephropathy:

- Diabetes mellitus
- Renal disease or solitary kidney
- Sepsis or acute hypotension
- Dehydration or volume contraction
- Age >70 years
- Previous chemotherapy
- Organ transplant
- Cardiovascular disease (hypertension, congestive heart disease, cardiac or peripheral vascular disease)
- Nephrotoxic drugs (loop diuretics, amphotericin B, aminoglycosides, vancomycin, non-steroidal anti-inflammatory drugs, cancer and immune suppressant chemotherapy)
- HIV or AIDS

Figure 2. Schematic of Consent Procedures



* For all incapacitated patients who are enrolled, the investigator must do daily reassessments of patient capacity, and seek patient consent with Document C if/when patient regains capacity
** See protocol

References

1. 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):1-5.
2. Leira R, Davalos A, Silva Y, Gil-Peralta A, Tejada J, Garcia M, Castillo J. Early neurologic deterioration in intracerebral hemorrhage: predictors and associated factors. *Neurology* 2004 August 10;63(3):461-7
3. Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, Begtrup K, Steiner T. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology* 2006 April 25;66(8):1175-81.
4. Flaherty ML, Haverbusch M, Sekar P, Kissela B, Kleindorfer D, Moomaw CJ, Sauerbeck L, Schneider A, Broderick JP, Woo D. Long-term mortality after intracerebral hemorrhage. *Neurology* 2006 April 25;66(8):1182-6
5. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage: incidence and time course. *Stroke* 1996;27(10):1783-7.
6. Fujii Y, Takeuchi S, Sasaki O, Minakawa T, Tanaka R. Multivariate analysis of predictors of hematoma enlargement in spontaneous intracerebral hemorrhage. *Stroke* 1998;29(6):1160-6.
7. Cheung RT. Predictors of hematoma growth? Stroke 29[11], 2442-2443. 1998.
8. Gladstone D, Rodan LH, Fang J, Linday P, Hill MD, Silver FL, Kapral MK. Incidence and outcomes of warfarin-associated intracerebral hemorrhage compared to spontaneous intracerebral hemorrhage in a prospective stroke registry. (submitted)
9. Kissela B, Schneider A, Kleindorfer D, Khoury J, Miller R, Alwell K, Woo D, Szaflarski J, Gebel J, Moomaw C, Pancioli A, Jauch E, Shukla R, Broderick J. Stroke in a biracial population: the excess burden of stroke among blacks. *Stroke* 2004 February;35(2):426-31.
10. 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. *New England Journal of Medicine* 2005;352:777-85.
11. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2008;358(20):2127-37.
12. 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 April;38(4):1257-62.
13. Thompson AL, Kosior JC, Gladstone DJ, Hopyan JJ, Symons SP, Romero F, Dzialowski I, Roy J, Demchuk AM, Aviv RI. Defining the CT angiography 'spot sign' in primary intracerebral hemorrhage. *Can J Neurol Sci* 2009 July;36(4):456-61.
14. Mayer SA, Brun NC, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T. Safety and feasibility of recombinant factor VIIa for acute intracerebral hemorrhage. *Stroke* 2005 January;36(1):74-9.
15. Yamaki T, Yoshino E, Higuchi T. Extravasation of contrast medium during both computed tomography and cerebral angiography. *Surg Neurol* 1983;19(3):247-50.
16. Yamamoto T, Muraki M, Oishi H, Uemura K. [Contrast-enhanced MRI of hypertensive intracerebral hemorrhage in the peracute stage--extravasation of contrast medium as detector of growing hematoma]. *Nippon Rinsho* 1993;51 Suppl:48-54.
17. Wolpert SM, Schatzki SC. Extravasation of contrast material in the intracerebral basal ganglia. *Radiology* 1972;102(1):83-5.
18. Huckman MS, Weinberg PE, Kim KS, Davis DO. Angiographic and clinico-pathologic correlates in basal ganglionic hemorrhage. *Radiology* 1970;95(1):79-92.

19. 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(10):2025-32.
20. Kowada M, Yamaguchi K, Matsuoka S, Ito Z. Extravasation of angiographic contrast material in hypertensive intracerebral hemorrhage. *J Neurosurg* 1972;36(4):471-3.
21. 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(4):650-5.
22. Yamaguchi K, Uemura K, Takahashi H, Kowada M, Kutsuzawa T. [Extravasation of contrast media in hypertensive cerebral hemorrhage]. *Rinsho Hoshasen* 1972;17(4):257-63.
23. Gazzola S, Aviv RI, Gladstone DJ, Mallia G, Li V, Fox AJ, Symons SP. Vascular and nonvascular mimics of the CT angiography "spot sign" in patients with secondary intracerebral hemorrhage. *Stroke* 2008 April;39(4):1177-83.
24. 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 March 20;68(12):889-94.
25. Aviv RI, Gladstone D, Goldstein J, Flaherty M, Broderick J, Demchuk A. Contrast extravasation predicts hematoma growth: where to now? *AJNR Am J Neuroradiol* 2008.
26. Kim J, Smith A, Hemphill JC, III, Smith WS, Lu Y, Dillon WP, Wintermark M. Contrast extravasation on CT predicts mortality in primary intracerebral hemorrhage. *AJNR Am J Neuroradiol* 2008 March;29(3):520-5.
27. Delgado Almandoz JE, Yoo AJ, Stone MJ, Schaefer PW, Goldstein JN, Rosand J, Oleinik A, Lev MH, Gonzalez RG, Romero JM. Systematic characterization of the computed tomography angiography spot sign in primary intracerebral hemorrhage identifies patients at highest risk for hematoma expansion: the spot sign score. *Stroke* 2009 September;40(9):2994-3000.
28. Delgado Almandoz JE, Yoo AJ, Stone MJ, Schaefer PW, Oleinik A, Brouwers HB, Goldstein JN, Rosand J, Lev MH, Gonzalez RG, Romero JM. The spot sign score in primary intracerebral hemorrhage identifies patients at highest risk of in-hospital mortality and poor outcome among survivors. *Stroke*. 2010 Jan;41(1):54-60. Epub 2009 Nov 12.
29. Yeung R, Ahmad T, Aviv RI, de Tilly LN, Fox AJ, Symons SP. Comparison of CTA to DSA in determining the etiology of spontaneous ICH. *Can J Neurol Sci* 2009 March;36(2):176-80.
30. Morgenstern LB, Hemphill JC 3rd, Anderson C, Becker K, Broderick JP, Connolly ES Jr, Greenberg SM, Huang JN, Macdonald RL, Messé SR, Mitchell PH, Selim M, Tamargo RJ; on behalf of the American Heart Association Stroke Council and Council on Cardiovascular Nursing. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage. A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2010 Jul 22. [Epub ahead of print]
31. Dowlatshahi D, Smith EE, Flaherty M, Ali M, Lyden P, Demchuk A, VISTA collaborators. Small intracerebral hemorrhages are associated with less hematoma expansion and better outcomes. (submitted)
32. Demchuk A, Kosior J, Tymchuk S, Molina C, Dzialowski I, Boulanger J-M. Multicentre prospective study demonstrates validity of CTA spot sign for hematoma expansion prediction in noncoagulopathic primary ICH patients. *Cerebrovasc Dis* 2008;25(Suppl 2):52.
33. Diringer MN, Skolnick BE, Mayer SA, Steiner T, Davis SM, Brun NC, Broderick JP. Thromboembolic events with rFVIIa in spontaenous ICH: results from the FAST trial. (manuscript under review)
34. 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 August;38(8):2364-6.
35. Hopyan JJ, Gladstone DJ, Mallia G, Schiff J, Fox AJ, Symons SP, Buck BH, Black SE, Aviv RI. Renal safety of CT angiography and perfusion imaging in the emergency evaluation of acute stroke. *AJNR Am J Neuroradiol* 2008 November;29(10):1826-30.

36. Tomsen HS, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR). In which patients should serum creatinine be measured before iodinated contrast medium administration? Eur Radiol 2005; 15: 749-754
37. American College of Radiology. Manual on Contrast Media. http://www.acr.org/secondarymainmenucategories/quality_safety/contrast_manual.aspx
38. Benko A, Fraser-Hill M, Magner P, Capusten B, Barrett B, Myers A, Owen RJ. Canadian Association of Radiologists: consensus guidelines for the prevention of contrast-induced nephropathy. *Can Assoc Radiol J* 2007 April;58(2):79-87.
39. Hedner U. Recombinant activated factor VII as a universal haemostatic agent. *Blood Coagul Fibrinolysis* 1998 March;9 Suppl 1:S147-S152.
40. Hedner U, Ingerslev J. Clinical use of recombinant FVIIa (rFVIIa). *Transfus Sci* 1998 June;19(2):163-76.
41. Friederich PW, Henny CP, Messelink EJ, Geerdink MG, Keller T, Kurth KH, 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 January 18;361(9353):201-5.
42. Rice KM, Savidge GF. NovoSeven (recombinant factor VIIa) in centeral nervous systems bleeds. *Haemostasis* 1996;26 Suppl 1:131-4.
43. Fewel ME, Park P. The emerging role of recombinant-activated factor VII in neurocritical care. *Neurocrit Care* 2004;1(1):19-29.
44. Roberts HR, Monroe DM, White GC. The use of recombinant factor VIIa in the treatment of bleeding disorders. *Blood* 2004 December 15;104(13):3858-64.
45. GE Healthcare Inc.Visipaque (iodixanol) injection package insert. 2006.
46. Kazuhiro Ohwaki, et al. Blood Pressure Management in Acute Intracerebral Hemorrhage: Relationship Between Elevated Blood Pressure and Hematoma Enlargement. Stroke. 2004;35:1364-1367
47. Ken S. Butcher, Tracey Baird, Lachlan MacGregor, Patricia Desmond, Brian Tress, and Stephen Davis. Perihematomal Edema in Primary Intracerebral Hemorrhage Is Plasma Derived. Stroke. 2004;35:1879-1885
48. Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, Khoury J. The ABCs of measuring intracerebral hemorrhage volumes. *Stroke* 1996 August;27(8):1304-5.
49. Cohnen M, Wittsack HJ, 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 September;27(8):1741-5.
50. Cochran ST, Bomyea K, Sayre JW. Trends in adverse events after IV administration of contrast media. *AJR Am J Roentgenol* 2001 June;176(6):1385-8.
51. Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. *NEJM* 2007 Nov 29;357(22):2277-84
52. Smith-Bindman R, Lipson J, Marcus R, et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. *Arch Intern Med* 2009;169:2078–86
53. Bellin MF, Jakobsen JA, Tomassin I, Thomsen HS, Morcos SK, Thomsen HS, Morcos SK, Almen T, Aspelin P, Bellin MF, Clauss W, Flaten H, Grenier N, Idee JM, Jakobsen JA, Krestin GP, Stacul F, Webb JA. Contrast medium extravasation injury: guidelines for prevention and management. *Eur Radiol* 2002 November;12(11):2807-12.
54. 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 January;47(1):254-61.
55. Lima FO, Lev MH, Levy RA, Silva GS, Ebril M, de Camargo EC, Pomerantz S, Singhal AB, Greer DM, Ay H, González RG, Koroshetz WJ, Smith WS, Furie KL. Functional contrast-

enhanced CT for evaluation of acute ischemic stroke does not increase the risk of contrast-induced nephropathy. *AJNR Am J Neuroradiol.* 2010 May;31(5):817-21. Epub 2009 Dec 31.
56. Mehdiratta M, Schlaug G, Kumar S, Caplan LR, Selim M. Reducing the delay in thrombolysis: is it necessary to await the results of renal function tests before computed tomography perfusion and angiography in patients with code stroke? *J Stroke Cerebrovasc Dis*. 2008 Sep;17(5):273-5.
57. Oleinik A, Romero JM, Schwab K, Lev MH, Jhawar N, gado Almandoz JE, Smith EE, Greenberg SM, Rosand J, Goldstein JN. CT angiography for intracerebral hemorrhage does not increase risk of acute nephropathy. *Stroke* 2009 July;40(7):2393-7.
58. www.mocatest.org. Accessed Sept. 1,2009.
59. Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, Powers WJ, DeCarli C, Merino JG, Kalaria RN, Vinters HV, Holtzman DM, Rosenberg GA, Wallin A,Dichgans M, Marler JR, Leblanc GG. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. *Stroke* 2006 September;37(9):2220-41.
60. Lai SM, Perera S, Duncan PW, Bode R. Physical and social functioning after stroke: comparison of the Stroke Impact Scale and Short Form-36. *Stroke* 2003 February;34(2):488-93.
61. Duncan PW, Wallace D, Lai SM, Johnson D, Embretson S, Laster LJ. The stroke impact scale version 2.0. Evaluation of reliability, validity, and sensitivity to change. *Stroke* 1999 October;30(10):2131-40.
62. Vickers AJ, Altman DG. Statistics notes: Analysing controlled trials with baseline and follow up measurements. *BMJ* 2001 November 10;323(7321):1123-4.
63. Pettersen JA, Sathiyamoorthy G, Gao FQ, Szilagyi G, Nadkarni NK, St George-Hyslop P, Rogaeva E, Black SE. Microbleed topography, leukoaraiosis, and cognition in probable Alzheimer disease from the Sunnybrook dementia study. *Arch Neurol* 2008 June;65(6):790-5.
64. Levy-Cooperman N, Ramirez J, Lobaugh NJ, Black SE. Misclassified tissue volumes in Alzheimer disease patients with white matter hyperintensities: importance of lesion segmentation procedures for volumetric analysis. *Stroke* 2008 April;39(4):1134-41.
65. Ederies A, Demchuk A, Chia T, Gladstone DJ, Dowlatshahi D, Bendavit G, Wong K, Symons SP, Aviv RI. Postcontrast CT extravasation is associated with hematoma expansion in CTA spot negative patients. *Stroke* 2009 May;40(5):1672-6.
66. Saver JL. Novel end point analytic techniques and interpreting shifts across the entire range of outcome scales in acute stroke trials. *Stroke* 2007;38(11):3055-62.
67. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada. Tri-Council Policy Statement : Ethical conduct for research involving humans, December 2010.
68. Gladstone DJ, Black SE, Hakim, SE. Toward Wisdom From Failure: Lessons From Neuroprotective Stroke Trials and New Therapeutic Directions. *Stroke* 2002;33;2123-2136
69. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third Universal Definition of Myocardial Infarction. *European Heart Journal* 2012;33, 2551–2567

Appendix A: Schedule of Events

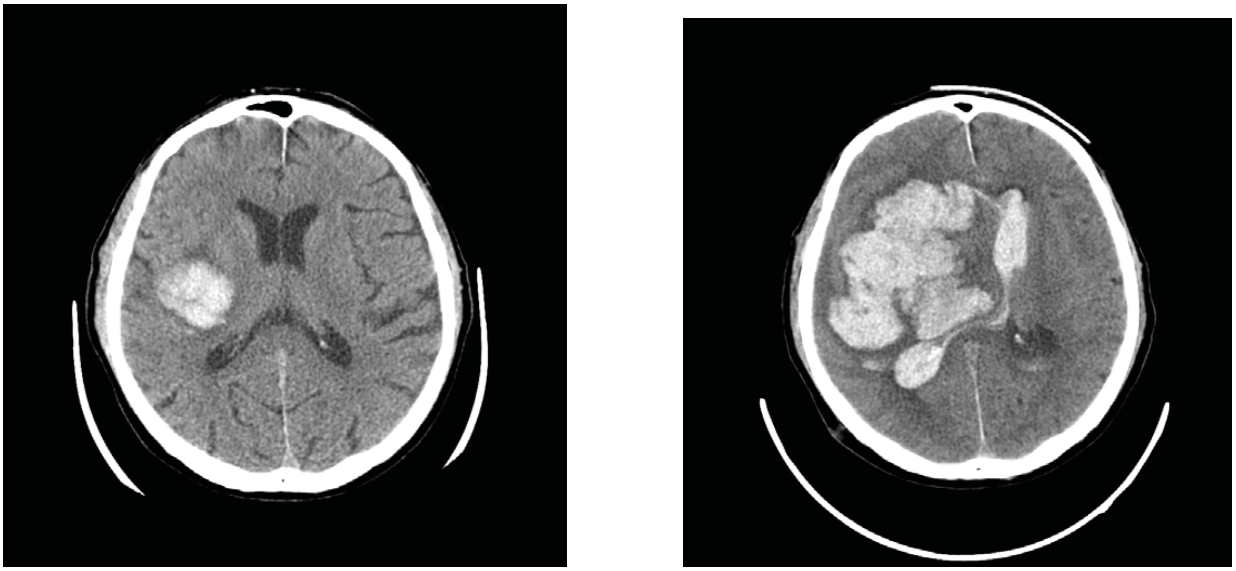
	Baseline	Immediate Post-Dose (+ 15 min)	24 hours (+/- 3 hrs)	Day 2 (48 +/- 6 hrs)	Day 3 (72 +/- 6 hrs)	Day 4 (96 +/- 6 hrs)	Day of Discharge	Day 30 (+/- 7 days)	Day 90 (+/- 7 days)	1 year (+/- 2 wks)
Consent	X									
Medical History	X									
Physical Exam	X									
Vital Signs	X	X***	X	X	X	X				
Demographic Information	X									
Creatinine	X		X	X	X	X			X**	
Pregnancy Test *	X									
CBC, INR, PTT	X									
Glasgow Coma Scale	X		X			X				
NIH Stroke Scale	X		X			X			X	X
Barthel Index								X	X	X
Modified Rankin Score	X							X	X	X
MoCA cognitive assessment									X	X
Stroke Impact Scale									X	X
EQ-5D									X	X
Consent Questionnaire			X						X	
CT head scan	X	X	X							
CT angiogram	X									
Clinical brain MRI									X	
Electrocardiogram	X		X	X	X	X				
Troponin, BUN	X		X	X	X	X			X**	
Adverse Event Assessment		X	X	X	X	X	X	X	X	
Patient Disposition							X	X	X	X
Interventions							X	X	X	X
Preadmission/Concomitant Medications	X		X	X	X	X			X	X
CES-D									X	X

* Women of childbearing potential
** Subjects who had a 25% or more increase in baseline creatinine within 72 hours of baseline imaging will have their creatinine and BUN measured.
*** Follow blood pressure protocol per Appendix B
Note: All assessments are done in-person except the 30-day visit can be done in-person or by telephone

Appendix B: Standardized Blood Pressure Protocol to Achieve a Target Systolic BP <180 mmHg within One Hour of Randomization

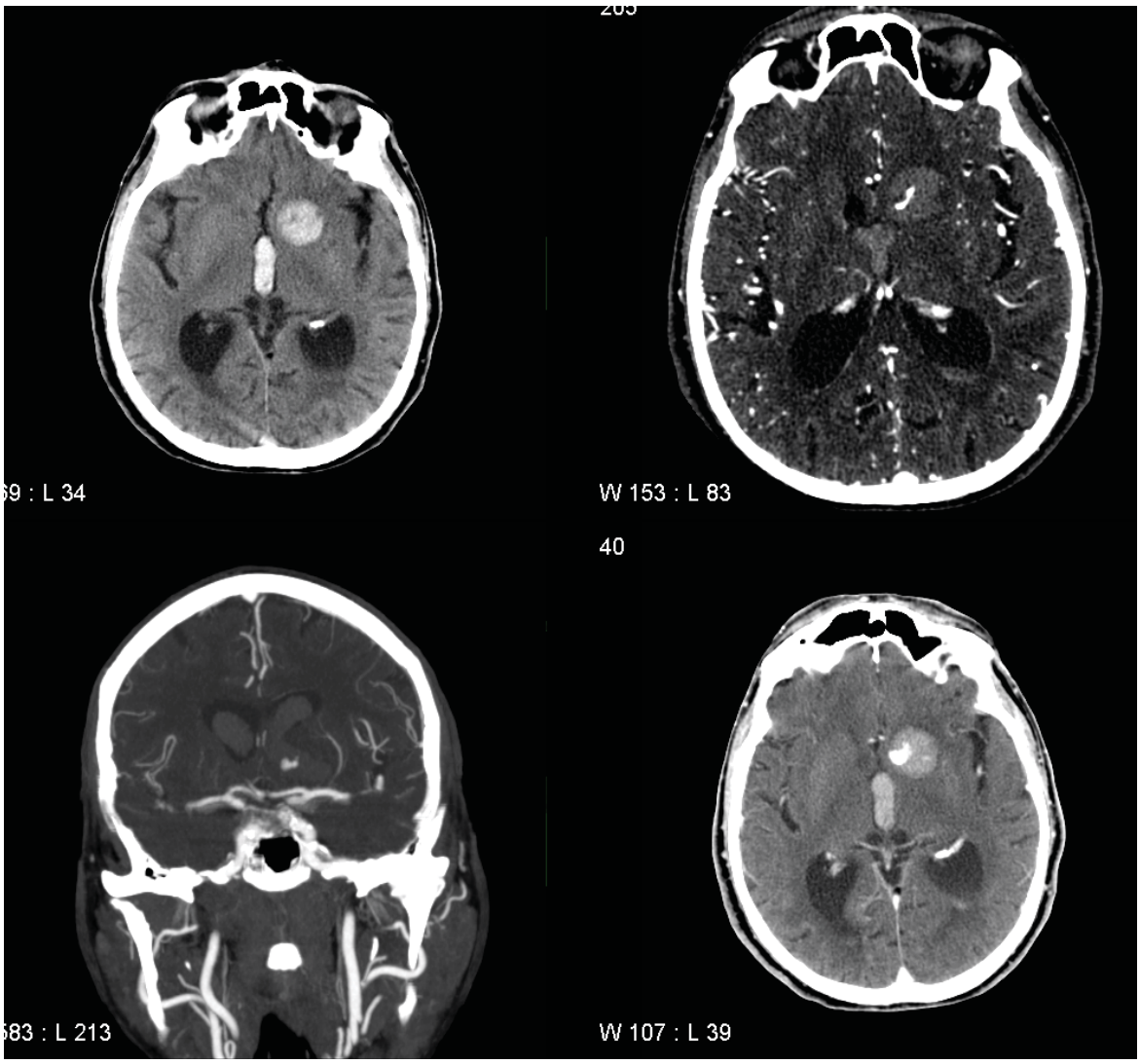
SPOTLIGHT Blood Pressure Protocol	
Target Systolic BP	Target SBP < 180 mmHg x 24 h minimum
Monitoring	● Continuous HR monitoring × 24 h minimum ● Record BP/HR q 15 min × 1 h, q 30 min × 5 h and q 1 h × 18 h
Initial Therapy	
Enalapril (IV; if available)	● Enalapril 1.25 mg bolus if initial SBP >180 mmHg
Labetalol (IV)	● Labetalol test dose: 10 mg bolus over 1 min ● If SBP ≥ 180 mmHg and HR > 55 BPM, repeat 10 mg bolus in 5 minutes. ● 10-20 mg IV push q 5 min until SBP < 180 mmHg or HR < 55 BPM ● Maximum labetalol dose: 300 mg / 24 h
Hydralazine (IV)	If BP persistently > 180 mmHg: ● Hydralazine test dose: 5 mg IV bolus over 1 min ● If SBP ≥ 180 mmHg, repeat 5 mg IV bolus in 5 min ● 10-20 mg IV bolus q 5 min until SBP < 180 mmHg ● Maximum hydralazine dose = 240 mg/24 h
Maintenance Therapy	
IV treatment prn	If SBP > 180 mmHg at any point: ● Labetalol (20 mg) / hydralazine (10–20 mg) boluses. BP and HR should then be recorded 5 and 15 minutes later ● Enalapril 1.25 mg may be repeated q 6 h if SBP >180 mmHg ● If SBP ≤ 180 mmHg or HR < 55 BPM, hold IV antihypertensives

Figure 2. Example of ICH Growth



This patient presented to the emergency department with an initially mild hemiparesis and the baseline CT scan performed at approximately 2 hours post-onset shows an acute ICH in the right basal ganglia region (left image). Within hours, the patient deteriorated neurologically, progressing to complete hemiplegia and coma requiring intubation. A repeat CT scan about 6 hours later showed massive expansion of the hematoma with intraventricular extension (right image). The patient died 48 hours later.

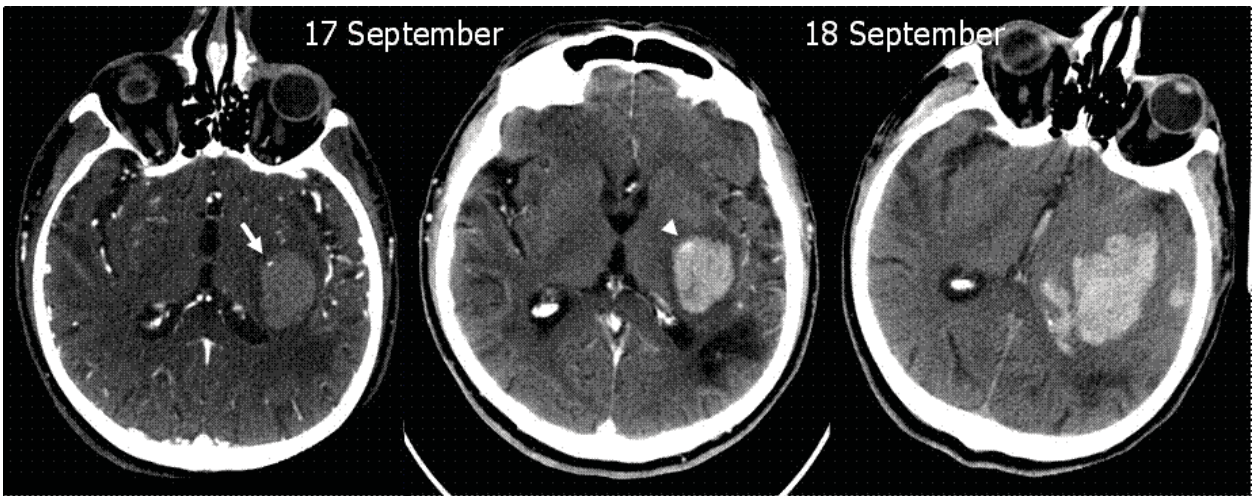
Figure 3. The CT Angiography Spot Sign



Axial non-contrast head CT scan (top left image) demonstrating a left putaminal hematoma and third ventricular hemorrhage. The axial CT angiography source images (top right image) and coronal maximum intensity projection (bottom left image) demonstrate a prominent spot sign (bright white density within the hematoma), which also shows active extravasation on post-contrast head CT scan (bright white density within the hematoma; bottom right image).

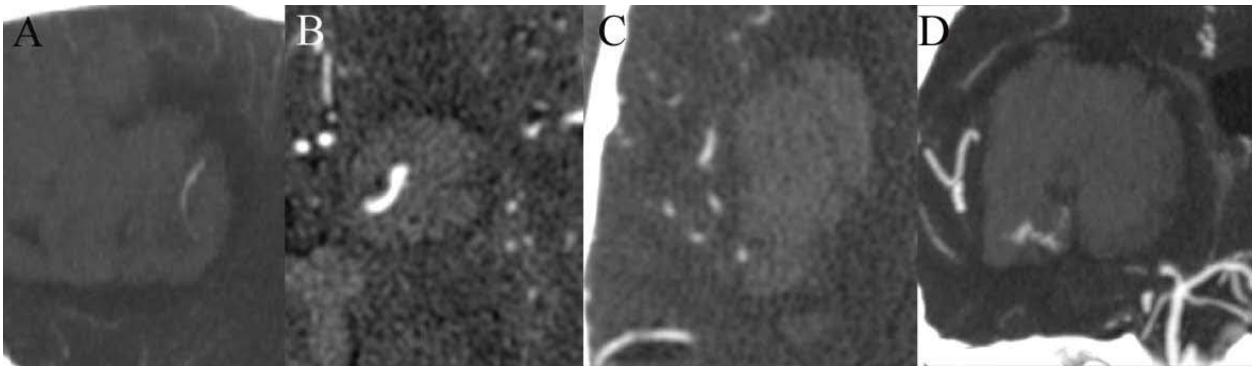
The defining criteria of a spot sign are: (1) shape: spot-like, serpiginous, or linear; (2) location: within the margin of a parenchymal hematoma without connection to an outside vessel; (3) size: >1.5 mm diameter in at least one dimension; (4) density: at least double the density (Hu) of the hematoma; (5) number: single or multiple; and (6) it is not caused by hyperdensity in same location on noncontrast CT.

Figure 4. Another Example of the CT Angiography Spot Sign



The spot sign appears as a tiny bright dot (arrow) within the larger parenchymal hematoma on the CT angiogram source image (left image). A repeat non-contrast head CT scan the next day reveals expansion of the hematoma (right) compared to the baseline volume (centre).

Figure 5. Four Different Spot Sign Patterns



CTA sagittal (a), axial (b, c) and coronal (d) images demonstrating 4 spot sign patterns. Pattern 1 – line only; pattern 2 - line and spot; pattern 3 - single spot; pattern IV -confluent branching spots and lines.

Appendix C. Modified Rankin Scale

Modified Rankin Scale[3]	Structured Interview for the Modified Rankin Scale
5=Severe disability: bedridden, incontinent, and requiring constant nursing care and attention.	5=Severe disability; someone needs to be available at all times; care may be provided by either a trained or an untrained caregiver. Question: Does the person require constant care?
4=Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance.	4=Moderately severe disability; need for assistance with some basic ADL, but not requiring constant care. Question: Is assistance essential for eating, using the toilet, daily hygiene, or walking?
3=Moderate disability; requiring some help, but able to walk without assistance.	3=Moderate disability; need for assistance with some instrumental ADL but not basic ADL. Question: Is assistance essential for preparing a simple meal, doing household chores, looking after money, shopping, or traveling locally?
2=Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance.	2=Slight disability; limitations in participation in usual social roles, but independent for ADL. Questions: Has there been a change in the person's ability to work or look after others if these were roles before stroke? Has there been a change in the person's ability to participate in previous social and leisure activities? Has the person had problems with relationships or become isolated?
1=No significant disability despite symptoms; able to carry out all usual duties and activities.	1=No significant disability; symptoms present but not other limitations. Question: Does the person have difficulty reading or writing, difficulty speaking or finding the right word, problems with balance or coordination, visual problems, numbness (face, arms, legs, hands, feet), loss of movement (face, arms, legs, hands, feet), difficulty with swallowing, or other symptom resulting from stroke?
0=No symptoms at all.	0=No symptoms at all; no limitations and no symptoms.

References

Wilson JTL, Hareendran A, Grant M, Baird T, Schulz UGR, Muir KW, Bone I "**Improving the Assessment of Outcomes in Stroke: Use of a Structured Interview to Assign Grades on the Modified Rankin Scale"** *Stroke* 2002;33;2243-2246

Appendix D. Glasgow Coma Scale

GLASGOW COMA SCALE

Patient Name: _____

Rater Name: _____

Date: _____

Activity		Score
EYE OPENING		
None	1 = Even to supra-orbital pressure	
To pain	2 = Pain from sternum/limb/supra-orbital pressure	
To speech	3 = Non-specific response, not necessarily to command	
Spontaneous	4 = Eyes open, not necessarily aware	_____
MOTOR RESPONSE		
None	1 = To any pain; limbs remain flaccid	
Extension	2 = Shoulder adducted and shoulder and forearm internally rotated	
Flexor response	3 = Withdrawal response or assumption of hemiplegic posture	
Withdrawal	4 = Arm withdraws to pain, shoulder abducts	
Localizes pain	5 = Arm attempts to remove supra-orbital/chest pressure	
Obeys commands	6 = Follows simple commands	_____
VERBAL RESPONSE		
None	1 = No verbalization of any type	
Incomprehensible	2 = Moans/groans, no speech	
Inappropriate	3 = Intelligible, no sustained sentences	
Confused	4 = Converses but confused, disoriented	
Oriented	5 = Converses and oriented	_____
		____
	TOTAL (3–15):	

References

Teasdale G, Jennett B. “Assessment of coma and impaired consciousness. A practical scale.” The Lancet 13:2(7872):81-4,1974

Appendix E. NIH Stroke Scale (NIHSS)

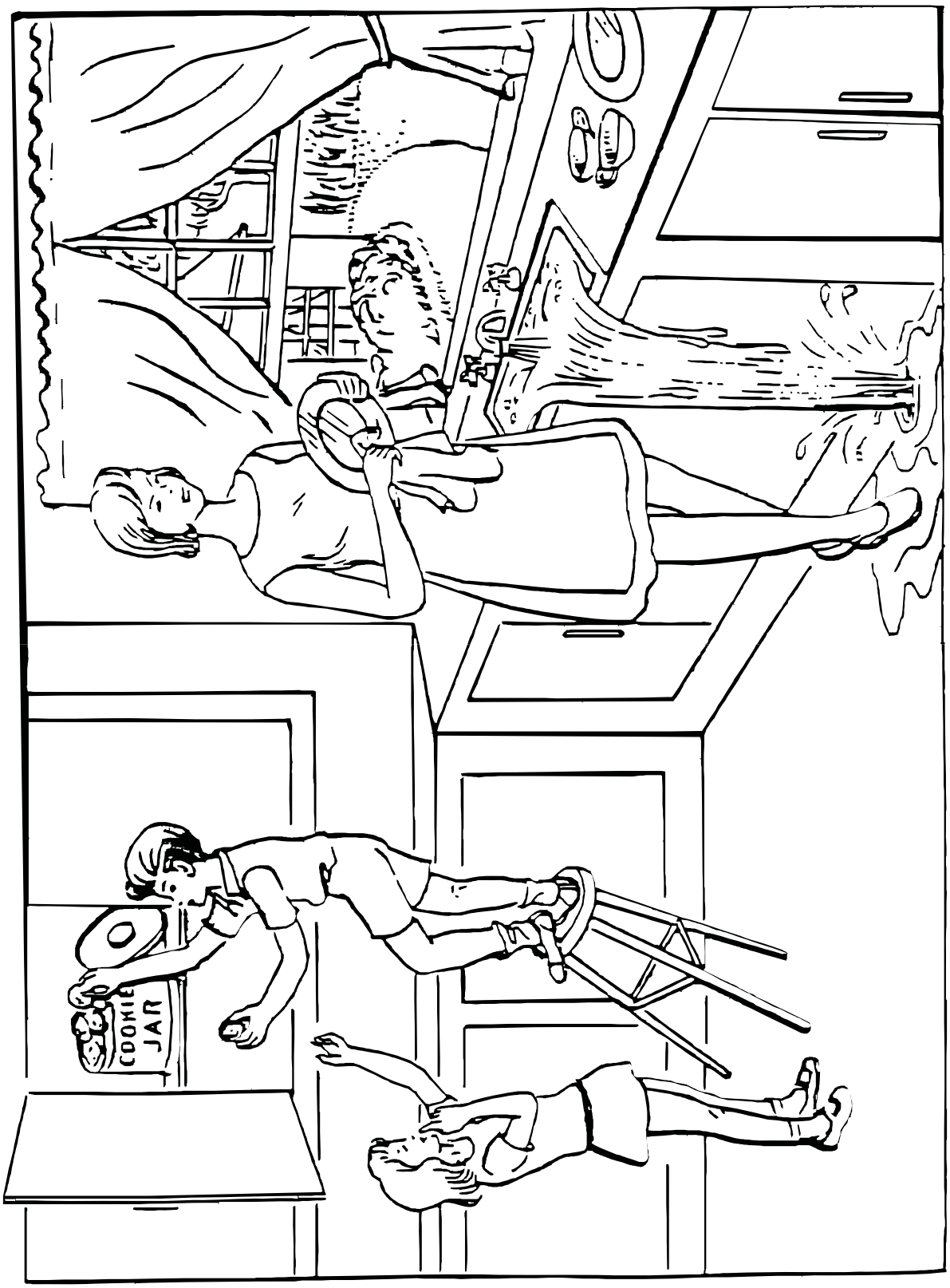
Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician 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.

NIH Stroke Scale			
NIH Stroke Scale Item	**Function**	**Scores**	**Exam**
1a. Level of Consciousness (Alert, drowsy, etc.)	Alert Drowsy Stuporous (requires repeated stimuli) Comatose (reflex responses only)	0 1 2 3	
1b. LOC Questions (Month, age)	Both Correct One correct Incorrect	0 1 2	
1c. LOC Commands (Open, close eyes, make fist, let go)	Obeys both correctly Obeys one correctly Incorrect	0 1 2	
2. Best Gaze (Eyes open – patient follow examiner's finger or face)	Normal Partial gaze palsy Forced deviation	0 1 2	
3. Visual (Introduce visual stimulus/threat to patient's visual field quadrants)	No loss Partial hemianopia Complete hemianopia Bilateral hemianopia	0 1 2 3	
4. Facial Palsy (show teeth, raise eyebrows and squeeze eyes shut)	Normal Minor asymmetry Partial (lower face paralysis) Complete	0 1 2 3	
5a. Motor Arm - Left (Elevate extremity 90° and score drift/movement)	No drift Drift Some effort against gravity No effort against gravity No movement Amputation, joint fusion	0 1 2 3 4 9	
5b. Motor Arm - Right (Elevate extremity 90° and score drift/movement)	No drift Drift Some effort against gravity No effort against gravity No movement Amputation, joint fusion	0 1 2 3 4 9	
6a. Motor Leg – Left (Elevate extremity 30° and score drift/movement)	No drift Drift Some effort against gravity No effort against gravity No movement Amputation, joint fusion	0 1 2 3 4 9	
6b. Motor Leg - Right (Elevate extremity 30° and score drift/movement)	No drift Drift Some effort against gravity No effort against gravity No movement Amputation, joint fusion	0 1 2 3 4 9	
7. Limb Ataxia (Finger-nose, heel down shin)	Absent Present in upper or lower Present in both	0 1 2	

8. Sensory (Pin prick to face, arm, trunk, and leg – compare side to side)	Normal Partial loss Dense loss	0 1 2	
9. Best Language (Name items, describe a picture and read sentences)	No aphasia Mild - moderate aphasia Severe aphasia Mute	0 1 2 3	
10. Dysarthria (Evaluate speech clarity by patient repeating listed words)	Normal articulation Mild - moderate slurring Severe, nearly unintelligible or worse	0 1 2	
11. Extinction and Inattention (Use information from prior testing to identify neglect or double simultaneous stimuli testing)	No neglect Partial neglect Profound neglect	0 1 2	
		NIH Stroke Scale TOTAL:	

The "Quick & Easy" NIHSS Authored by: Judith A. Spilker, RN, BSN, Dept. of Emergency Medicine & Laura R. Sauerbeck, RN, BSN, Dept. of Neurology University of Cincinnati


COOKIE
JAR

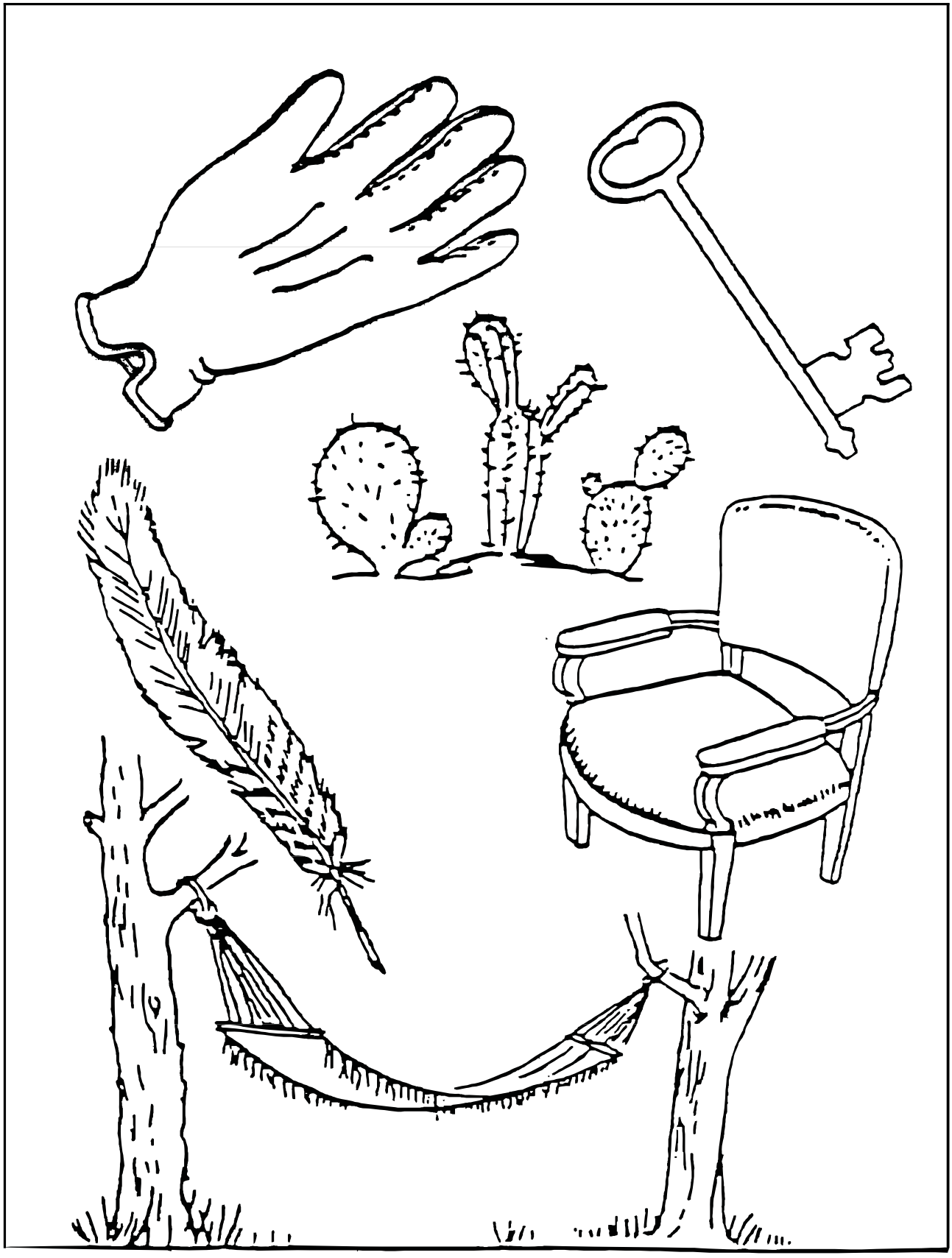
You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.



MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

Appendix F. Barthel Index

THE BARTHEL INDEX

Patient Name: _____
Rater Name: _____
Date: _____

Activity	Score
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	_____
BATHING 0 = dependent 5 = independent (or in shower)	_____
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	_____
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 = continent	_____
TOILET USE 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	_____
TRANSFERS (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	_____
MOBILITY (ON LEVEL SURFACES) 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 any aid; for example, stick) > 50 yards	_____
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	_____
TOTAL (0–100):	_____

Provided by the Internet Stroke Center — www.strokecenter.org

The Barthel ADL Index: Guidelines

1. The index should be used as a record of what a patient does, not as a record of what a patient could do.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. The need for supervision renders the patient not independent.
4. A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives and nurses are the usual sources, but direct observation and common sense are also important. However direct testing is not needed.
5. Usually the patient's performance over the preceding 24-48 hours is important, but occasionally longer periods will be relevant.
6. Middle categories imply that the patient supplies over 50 per cent of the effort.
7. Use of aids to be independent is allowed.

References

Mahoney FI, Barthel D. "Functional evaluation: the Barthel Index."
Maryland State Medical Journal 1965;14:56-61. Used with permission.

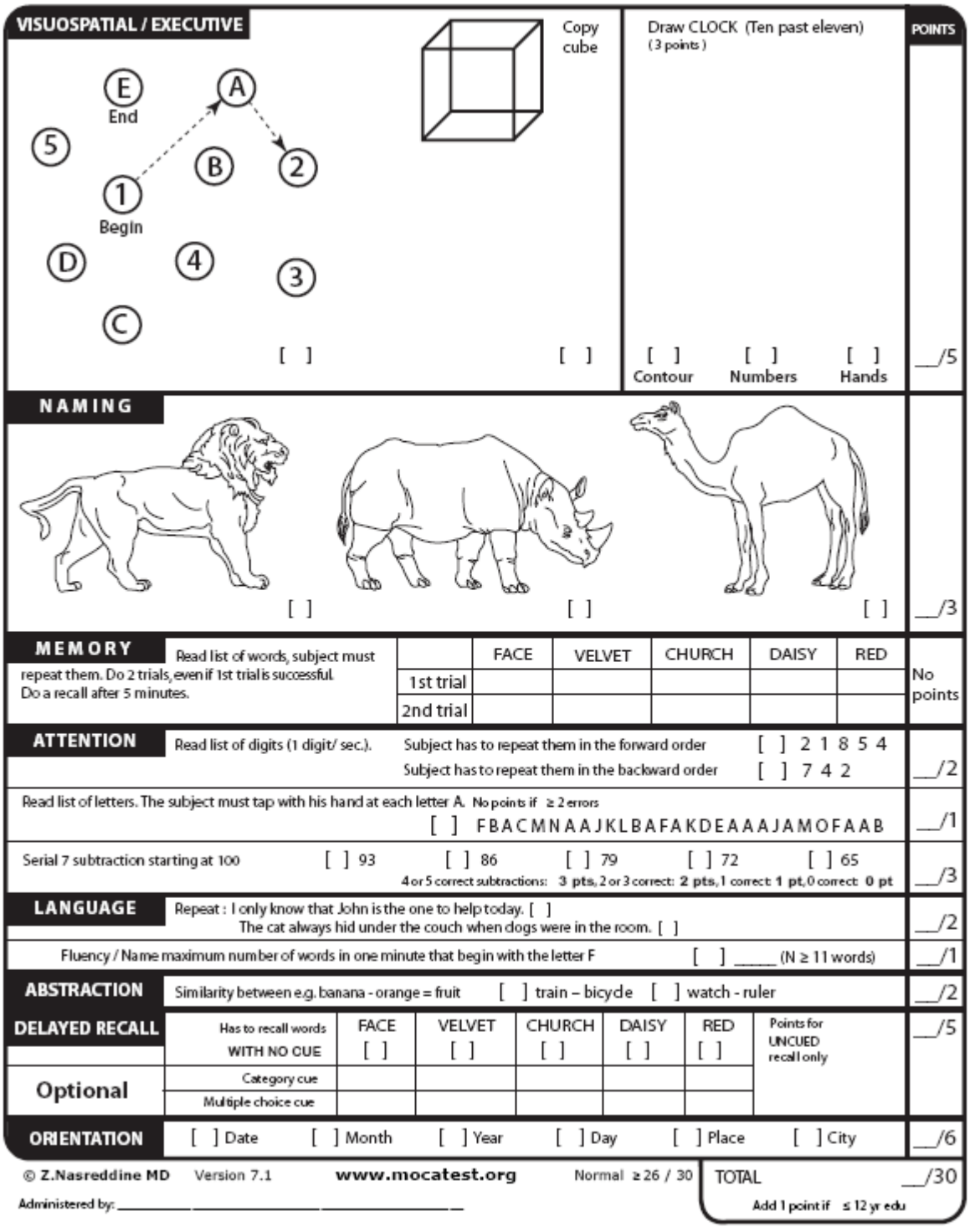
Loewen SC, Anderson BA. "Predictors of stroke outcome using objective measurement scales."
***Stroke.* 1990;21:78-81.**

Gresham GE, Phillips TF, Labi ML. "ADL status in stroke: relative merits of three standard indexes."
***Arch Phys Med Rehabil.* 1980;61:355-358.**

Collin C, Wade DT, Davies S, Horne V. "The Barthel ADL Index: a reliability study."
***Int Disability Study.*1988;10:61-63.**

Copyright Information

Appendix G. Montreal Cognitive Assessment (MoCA)



Appendix H. Stroke Impact Scale (SIS)

Stroke Impact Scale

VERSION 3.0

The purpose of this questionnaire is to evaluate how stroke has impacted your health and life. We want to know from **YOUR POINT OF VIEW** how stroke has affected you. We will ask you questions about impairments and disabilities caused by your stroke, as well as how stroke has affected your quality of life. Finally, we will ask you to rate how much you think you have recovered from your stroke.

Stroke Impact Scale

These questions are about the physical problems which may have occurred as a result of your stroke.

1. In the past week, how would you rate the strength of your....	**A lot of strength**	**Quite a bit of strength**	**Some strength**	**A little strength**	**No strength at all**
a. Arm that was most affected by your stroke?	5	4	3	2	1
b. Grip of your hand that was most affected by your stroke?	5	4	3	2	1
c. Leg that was most affected by your stroke?	5	4	3	2	1
d. Foot/ankle that was most affected by your stroke?	5	4	3	2	1

These questions are about your memory and thinking.

2. In the past week, how difficult was it for you to...	**Not difficult at all**	**A little difficult**	**Somewhat difficult**	**Very difficult**	**Extremely difficult**
a. Remember things that people just told you?	5	4	3	2	1
b. Remember things that happened the day before?	5	4	3	2	1
c. Remember to do things (e.g. keep scheduled appointments or take medication)?	5	4	3	2	1
d. Remember the day of the week?	5	4	3	2	1
e. Concentrate?	5	4	3	2	1
f. Think quickly?	5	4	3	2	1
g. Solve everyday problems?	5	4	3	2	1

These questions are about how you feel, about changes in your mood and about your ability to control your emotions since your stroke.

3. In the past week, how often did you...	**None of the time**	**A little of the time**	**Some of the time**	**Most of the time**	**All of the time**
a. Feel sad?	5	4	3	2	1
b. Feel that there is nobody you are close to?	5	4	3	2	1
c. Feel that you are a burden to others?	5	4	3	2	1
d. Feel that you have nothing to look forward to?	5	4	3	2	1
e. Blame yourself for mistakes that you made?	5	4	3	2	1
f. Enjoy things as much as ever?	5	4	3	2	1
g. Feel quite nervous?	5	4	3	2	1
h. Feel that life is worth living?	5	4	3	2	1
i. Smile and laugh at least once a day?	5	4	3	2	1

The following questions are about your ability to communicate with other people, as well as your ability to understand what you read and what you hear in a conversation.

4. In the past week, how difficult was it to...	**Not difficult at all**	**A little difficult**	**Somewhat difficult**	**Very difficult**	**Extremely difficult**
a. Say the name of someone who was in front of you?	5	4	3	2	1
b. Understand what was being said to you in a conversation?	5	4	3	2	1
c. Reply to questions?	5	4	3	2	1
d. Correctly name objects?	5	4	3	2	1
e. Participate in a conversation with a group of people?	5	4	3	2	1
f. Have a conversation on the telephone?	5	4	3	2	1
g. Call another person on the telephone, including selecting the correct phone number and dialing?	5	4	3	2	1

The following questions ask about activities you might do during a typical day.

5. In the past 2 weeks, how difficult was it to...	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Could not do at all
a. Cut your food with a knife and fork?	5	4	3	2	1
b. Dress the top part of your body?	5	4	3	2	1
c. Bathe yourself?	5	4	3	2	1
d. Clip your toenails?	5	4	3	2	1
e. Get to the toilet on time?	5	4	3	2	1
f. Control your bladder (not have an accident)?	5	4	3	2	1
g. Control your bowels (not have an accident)?	5	4	3	2	1
h. Do light household tasks/chores (e.g. dust, make a bed, take out garbage, do the dishes)?	5	4	3	2	1
i. Go shopping?	5	4	3	2	1
j. Do heavy household chores (e.g. vacuum, laundry or yard work)?	5	4	3	2	1

The following questions are about your ability to be mobile, at home and in the community.

6. In the past 2 weeks, how difficult was it to...	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Could not do at all
a. Stay sitting without losing your balance?	5	4	3	2	1
b. Stay standing without losing your balance?	5	4	3	2	1
c. Walk without losing your balance?	5	4	3	2	1
d. Move from a bed to a chair?	5	4	3	2	1
e. Walk one block?	5	4	3	2	1
f. Walk fast?	5	4	3	2	1
g. Climb one flight of stairs?	5	4	3	2	1
h. Climb several flights of stairs?	5	4	3	2	1
i. Get in and out of a car?	5	4	3	2	1

The following questions are about your ability to use your hand that was MOST AFFECTED by your stroke.

7. In the past 2 weeks, how difficult was it to use your hand that was most affected by your stroke to...	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Could not do at all
a. Carry heavy objects (e.g. bag of groceries)?	5	4	3	2	1
b. Turn a doorknob?	5	4	3	2	1
c. Open a can or jar?	5	4	3	2	1
d. Tie a shoe lace?	5	4	3	2	1
e. Pick up a dime?	5	4	3	2	1

The following questions are about how stroke has affected your ability to participate in the activities that you usually do, things that are meaningful to you and help you to find purpose in life.

8. During the past 4 weeks, how much of the time have you been limited in...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Your work (paid, voluntary or other)	5	4	3	2	1
b. Your social activities?	5	4	3	2	1
c. Quiet recreation (crafts, reading)?	5	4	3	2	1
d. Active recreation (sports, outings, travel)?	5	4	3	2	1
e. Your role as a family member and/or friend?	5	4	3	2	1
f. Your participation in spiritual or religious activities?	5	4	3	2	1
g. Your ability to control your life as you wish?	5	4	3	2	1
h. Your ability to help others?	5	4	3	2	1

9. Stroke Recovery

On a scale of 0 to 100, with 100 representing full recovery and 0 representing no recovery, how much have you recovered from your stroke?

_____ 100 Full Recovery

_____ 90

_____ 80

_____ 70

_____ 60

_____ 50

_____ 40

_____ 30

_____ 20

_____ 10

_____ 0 No Recovery

Item Clarifications

1. If patient says "I don't have an affected side", then instruct them to score using their perceived weaker side. If they still insist there is no affected, or weaker, side instruct them to score using their dominant side.

4. If patient says s/he does not do any or all of the items listed, code item(s) as *Extremely Difficult.*
   (Item f) If patient does not call but is handed the phone this is OK.
   (Item g) If patient cannot hold a phone book, if they can read it this is OK. This item addresses whether the patient is able to initiate a phone call, look up the number, and dial this number correctly.

5. If patient says s/he does not do any or all of the items listed, code item(s) as *Cannot do at all.*
   (Item a) If person is on pureed food, even if they feel they could cut the food, code as *Cannot do at All* (1/5/98)
   (Item c) Bathing oneself does not include getting into the tub.
   (Item e) This question is associated with movement. Does the person have the physical ability to get to the bathroom quickly enough?
   (Item f) Losing a little urine/dribbling is considered an accident.
      If person has intermittent catheter and is having no leaking problems code them as per report. (1/5/98)
      If person has an in-dwelling Foley catheter, code as *Cannot do at all.* (1/5/98)
   (Item g) Constipation is not counted here, person has to have an accident.
   (Item i) "Shopping" means any type of shopping and does not include driving.

6. If patient hasn't done any of the items in the past two weeks code as *Cannot do at all.*
   (Item h) If patient hasn't "climbed several flights of stairs" in two weeks, they may be prompted by saying "have you gone up and down one flight of stairs a couple of times in a row." If they still say they have not done it then they must be coded as *Cannot do at all.*
   (Item i) If the patient wants to know what kind of car say "your car" or "the car you ride in most."

7. If patient says "I don't have an affected side", then instruct them to score using their perceived weaker side. If they still insist there is no affected, or weaker, side instruct them to score using their dominant side.
   (Item a) If the patient says s/he has not been to the grocery store say "have you carried anything heavy with that hand."
   (Item d) This item is to tie a shoelace/bow using both hands.

8. If patient does not do any of the specific items (and has never done), code interference as *None of the time.*

Appendix I. EQ-5D

By placing a check-mark in one box in each group below, please indicate which statements best describe your own state of health today.

Mobility

I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-Care

I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

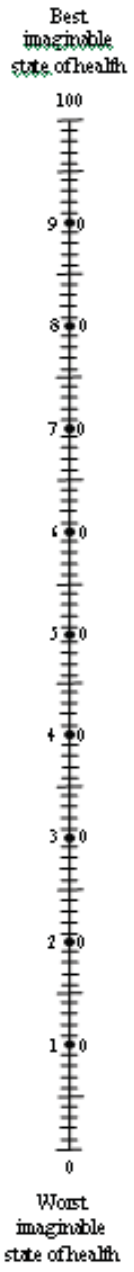
Anxiety/Depression

I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

To help people say how good or bad their state of health is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your state of health is today.

Your own state of health today



Appendix J: CES-D

CENTER FOR EPIDEMIOLOGIC STUDIES—DEPRESSION SCALE				
Circle the number of each statement which best describes how often you felt or behaved this way – DURING THE PAST WEEK.				
	Rarely or none of the time (less than 1 day)	**Some or a little of the time (1-2 days)**	**Occasionally or a moderate amount of the time (3-4 days)**	**Most or all of the time (5-7 days)**
During the past week:	0	1	2	3
1) I was bothered by things that usually don't bother me	0	1	2	3
2) I did not feel like eating; my appetite was poor	0	1	2	3
3) I felt that I could not shake off the blues even with help from my family and friends	0	1	2	3
4) I felt that I was just as good as other people	0	1	2	3
5) I had trouble keeping my mind on what I was doing	0	1	2	3
6) I felt depressed	0	1	2	3
7) I felt that everything I did was an effort	0	1	2	3
8) I felt hopeful about the future	0	1	2	3
9) I thought my life had been a failure	0	1	2	3
10) I felt fearful	0	1	2	3
11) My sleep was restless	0	1	2	3
12) I was happy	0	1	2	3
13) I talked less than usual	0	1	2	3
14) I felt lonely	0	1	2	3
15) People were unfriendly	0	1	2	3
16) I enjoyed life	0	1	2	3
17) I had crying spells	0	1	2	3
18) I felt sad	0	1	2	3
19) I felt that people disliked me	0	1	2	3
20) I could not get "going"	0	1	2	3

Appendix K: Suggested Framework for evaluating capacity for consent in an emergency setting

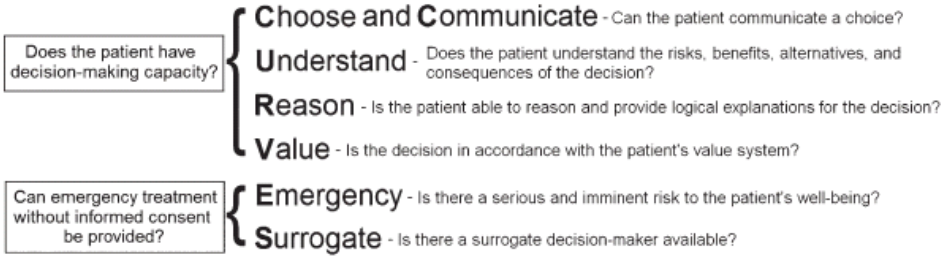


FIGURE 1. Mnemonic for the assessment of decision-making capacity and provision of emergency treatment. A patient lacks capacity if any of the prerequisite abilities (to choose and communicate, understand, reason, or value a decision) are absent. If a patient lacks capacity in an emergent situation and no surrogate decision maker is available, then emergency treatment without informed consent may be provided for a medically warranted course of action.

- **C** – Choose and Communicate. Patients must be able to choose from among the options before them. Furthermore, their choice must be made without coercion or manipulation, although appropriate persuasion is permitted.[1] Each patient must be able to communicate his or her preferences, whether verbally, in writing, or through the use of signals.
- **U** – Understand. The patient must understand the relevant risks, benefits, alternatives, and consequences of any planned intervention or course of action.
- **R** – Reason. The patient must be able to reason and provide adequate explanations for accepting or declining each intervention.
- **V** – Value. The patient's decision should be consistent with his or her value system. Physicians should strive to be aware of and understand the patient's values, and they must also be aware that patient values and goals may change with time.

- **E** – Emergency. A true emergency exists, meaning that there is serious and imminent risk to life or limb.
- **S** – Surrogate. No surrogate decision maker or legal document detailing the patient's desires is immediately available, and there is no time to obtain an ethics consultation.

Chow et al. Curves: A Mnemonic for Determining Medical Decision-Making Capacity and Providing Emergency Treatment in the Acute Setting. Chest 2010; 137; 421-427.

Change Log of Amendments to SPOTLIGHT Protocol
From Version 2.0 16Mar2011 to current working Version 3.0 10Mar2014

Protocol Section		Version 2.0 (16-Mar-2011)	Changed to or Added in for Version 3.0 (10-Mar-2014)	Reason
3.2.1	Inclusion Criteria	Presence of a spot sign within the hematoma on CTA source images. [Note: CTA should ideally be performed immediately after the baseline CT scan. If CTA is going to be delayed more than 20 minutes after the baseline CT, then a new baseline plain head CT must be obtained immediately prior to CTA]. A spot sign must meet the following criteria: • One or more foci of contrast enhancement within the margin of a parenchymal hematoma • Any size or morphology (shape may be spot-like, linear or serpiginous) • Spot sign(s) must not have any connection to vessels outside the hematoma • Hounsfield unit density at least double that of background hematoma density (density of spot sign is typically >120 Hounsfield units)	Presence of a spot sign within the hematoma on CTA **(single-phase, multi-phase, or dynamic CTA)**. [Note: CTA should ideally be performed immediately after the baseline CT scan. If CTA is going to be delayed more than 20 minutes after the baseline CT, then a new plain head CT must be obtained immediately prior to CTA **which will serve as the baseline CT for the study**]. A spot sign must meet the following criteria: • One or more foci of contrast enhancement within the margin of a parenchymal hematoma • Any size or morphology (shape may be spot-like, linear or serpiginous) • Spot sign(s) must not have any connection to vessels outside the hematoma • Hounsfield unit density **greater than** background hematoma density (density of spot sign is typically >120 Hounsfield units)	With improving imaging software, some hospital sites have upgraded their single phase CT angiography to a multiphase or dynamic imaging acquisition protocol. All methods are acceptable for identification of a spot sign in this trial.
3.2.1	Inclusion Criteria	Baseline ICH volume 3-70 ml, estimated using the standard "abc/2" calculation on the baseline plain head CT.	Baseline ICH volume 3-**90** ml, estimated using the standard "abc/2" calculation on the baseline plain head CT.	(see cover letter)
3.2.1	Inclusion Criteria	Age 18-85 years (participants must have had their 18th birthday and not their 86th birthday).	Age ≥18 years.	The protocol is structured to protect participant safety. Therefore the upper age limit will be removed in order to allow for patients who are healthy enough, to be offered participation in the study.
3.2.1	Inclusion Criteria	Investigator is able to randomize and administer study drug within 60 minutes after CT angiogram and no later than 6 hours after stroke symptom onset (using the "last seen normal" principle).	Investigator is able to randomize and administer study drug **as soon as possible within a target of 60 minutes after CT angiogram** and no later than 6 hours after	Clarifies that this criterion is a target which should be assessed prior to enrolling the participant, and that the patient does not

Change Log of Amendments to SPOTLIGHT Protocol
From Version 2.0 16Mar2011 to current working Version 3.0 10Mar2014

			stroke symptom onset (using the "last seen normal" principle).	become disqualified from study participation if this is not met.
3.2.1	Inclusion Criteria	n/a	Plan to provide full medical care for at least 24 hours.	Added an inclusion criterion to reiterate to enrolling physicians the importance of direct investigator involvement in managing participants' care until the primary outcome is obtained.
3.2.1	Inclusion Criteria	Assent-consent from patient or LAR prior to enrolment, or a waiver of consent if patient/LAR assent-consent is not possible prior to enrolment. [Note: full informed consent to be obtained as soon as possible after study treatment administered].	Consent from patient or LAR prior to enrolment (or a waiver of consent if patient/LAR assent-consent is not possible prior to enrolment, **and if REB approved at your site**). [Note: full informed consent to be obtained as soon as possible after study treatment administered].	Clarifies confusion for site REBs who have approved the protocol but rejected the waiver of consent process.
3.2.2	Clinical Exclusions	Glasgow Coma Scale score <8, at time of initial screening by the enrolling investigator/nurse.	Criterion removed	The GCS exclusion was originally intended to exclude patients with the largest hematomas, however this is a redundancy that is covered by the remaining exclusion criteria.
3.2.2	Clinical Exclusions	Known pre-existing dependence or moderate or severe disability, defined as pre-admission modified Rankin Scale score >2. [Note: Patients must be independent in all basic activities of daily living and are excluded if they cannot walk independently without the assistance of another SPOTLIGHT Protocol Version 2.0 - 16Mar2011 Page 16 of 75 person (use of a cane or walker is not an exclusion) or if they require assistance from another person for basic activities of daily living (e.g. dressing, transfers, feeding, bathing, toileting)]. Patients with advanced dementia or admitted from a nursing home are excluded (cognitive impairment alone, without dementia, is not an exclusion to enrollment).	Criterion removed	This assessment is not necessary for this phase II trial and is overly restrictive.
3.2.2	Clinical Exclusions	Evidence of thromboembolic risk factors, defined as any of the following: known history within the past 6 months of any of the following: (a) myocardial infarction, (b) coronary artery bypass	Evidence of thromboembolic risk factors, defined as any of the following: known history within the past 6 months of any of the following: (a) myocardial infarction, (b)	Added an exclusionary thromboembolic risk factor to increase patient safety.

Change Log of Amendments to SPOTLIGHT Protocol
From Version 2.0 16Mar2011 to current working Version 3.0 10Mar2014

		surgery, (c) angina, (d) ischemic stroke, (e) transient ischemic attack, (f) carotid endarterectomy, (g) cerebral bypass surgery, (h) deep venous thrombosis, (i) pulmonary embolism, (j) any vascular angioplasty, stenting (coronary, peripheral vascular or cerebrovascular) or filter (e.g. vena cava filter); and/or known history of a high-risk thrombophilia (e.g. antithrombin III deficiency, antiphospholipid antibody syndrome, protein C deficiency, etc.)	coronary artery bypass surgery, (c) angina, (d) ischemic stroke, (e) transient ischemic attack, (f) carotid endarterectomy, (g) cerebral bypass surgery, (h) deep venous thrombosis, (i) pulmonary embolism, (j) vascular angioplasty, stenting (coronary, peripheral vascular or cerebrovascular) or filter (e.g. vena cava filter); **(k) prosthetic cardiac valve;** and/or (l) known history of a high-risk thrombophilia (e.g. antithrombin III deficiency, antiphospholipid antibody syndrome, protein C deficiency, etc.)	
3.2.2	Clinical Exclusions	Known terminal illness or planned withdrawal of care or comfort care measures.	Planned withdrawal of care before 24 hours post-ICH onset.	Phrasing was clarified to be more specific.
3.2.2	Medical Exclusions	Known low-molecular weight heparin, heparinoid, factor X inhibitor, or direct thrombin inhibitor use within previous 24 hours.	Known low-molecular weight heparin, heparinoid, factor X inhibitor, or direct thrombin inhibitor use within previous **7 days**	To avoid confounding/inadvertent enrollment of patients with anticoagulant-related intracerebral hemorrhage associated with the newer direct-acting oral anticoagulants that could have a prolonged half-life with renal impairment, we have implemented stricter exclusion criterion: longer washout period.
3.2.2	Clinical/Laboratory Exclusions	Baseline troponin T or troponin I >0.1 ng/ml (>0.1 µg/L).	Criterion removed and requirement added to sec. 10.2 Additional Eligibility Screening Requirement for Incapacitated Patients with No LAR	Unnecessary given that patients are already being screened clinically and by EKG. Also, to reduce delays to treatment and thereby improve benefit/risk ratio of study treatment. Unless the patient is enrolled with the deferred consent model, the investigator will not be required to await the troponin result before randomization and treatment. The baseline troponin will still be drawn for data collection purposes and repeat

Change Log of Amendments to SPOTLIGHT Protocol
From Version 2.0 16Mar2011 to current working Version 3.0 10Mar2014

				troponin measurements are still mandatory as part of the secondary safety outcome assessments.
3.2.2	Quick Screening Checklist for Potential Eligibility	Automatic exclusions to study enrollment, assessed upon arrival to ED and prior to CT scanning: • Patient cannot be scanned, randomized and treated within 6 hours after stroke symptom onset or "last seen normal time" (ED arrival >5 hours after onset is usually exclusionary). • Age <18 years or >85 years • Moderate or severe pre-existing disability or dependence, requiring assistance in ADLs • Severe dementia • Living in a nursing home • Palliative or terminal illness with pre-stroke life expectancy <6 months • Currently on IV heparin or receiving low molecular weight heparin injections • Comatose (Glasgow Coma Scale score 3-7) • Known renal failure or known allergy to iodinated contrast dye	Automatic exclusions to study enrollment, assessed upon arrival to ED and prior to CT scanning: • Patient cannot be scanned, randomized and treated within 6 hours after stroke symptom onset or "last seen normal time" (ED arrival >5 hours after onset is usually exclusionary). • Age <18 years • Currently on IV heparin or receiving low molecular weight heparin injections • Known renal failure or known allergy to iodinated contrast dye	Reflects updated Criteria, see above.
5.	Assessments	The investigator should delegate neither the dosing nor the assessments which affect the inclusion/exclusion criteria to other study staff.	The physician should delegate neither the dosing, interpretation of spot sign nor the assessment of inclusion/exclusion criteria to other study staff.	Clarifies level of involvement of study staff.
5.1	Baseline Assessment	GCS Score	Moved to 5.2 Randomization and Dosing	Clarify that GCS will not be required for criteria, but remains as an assessment closer to dosing.
5.1	Baseline Assessment	… blood work (creatinine, CBC, INR, PTT, troponin, CK, CK-MB, BUN)…	Removed all CK and CK-MB from blood work assessments	CK and CK-MB are not necessary as troponin will be measured; some site labs have already phased out CK and CK-MB at the institutional level.
5.4	24-Hour Follow Up	… (creatinine, BUN, troponin, CK, CK-MB)…		
5.5	Day 2, 3, 4 Follow Up			
5.11	Laboratory			

Change Log of Amendments to SPOTLIGHT Protocol
From Version 2.0 16Mar2011 to current working Version 3.0 10Mar2014

	Evaluations / Specimen Collection			
5.13	Safety Assessments	Clinical safety assessments, ECG, and troponin, CK, CK-MB will be obtained…		
5.2	Randomizatio n/Dosing	Within 5 min before dosing, this NIHSS will be scored.	Within 15 minutes before dosing, the NIHSS and GCS will be scored.	Feasibility, and not crucial to have the measurement within 5 minutes.
5.3	Immediate Post-Dose Follow-up	From: Immediately (+ 15 minutes) after study drug administration, a repeat CT head scan will be obtained... **GCS and NIHSS assessments will be done within 15 minutes following this CT scan**.	Removed GCS and NIHSS assessments immediately post dose.	Redundancy in doing the GCS and NIHSS a few minutes apart; values in immediate post dose assessment not expected to change significantly; takes time away from staff performing more crucial procedures on the acute patient.
5.5	Day 4 Follow Up	Also on day 4, the GCS, NIHSS, **and mRS** will be assessed.	Also on day 4, the GCS and NIHSS will be assessed.	mRS at Day 4 is not expected to add value to final dataset, therefore extra data will not be collected.
5.8	Day 90 Visit	clinical brain MRI scan	clinical brain MRI scan **(at sites where this is feasible)**,	Some sites have advised that a clinical MRI at 90 days is not feasible, and this will not be considered a protocol deviation.
5.10	Clinical Scales (a) mRS (b) NIHSS	section (a) Certification for the NIHSS will be required every 2 years. section (c) Certification for the mRS will be required every 2 years.	Removed requirement.	Investigator feedback: It was felt that it takes a prohibitively long time to obtain re-certification, and these teams who are staff at regional stroke centres routinely perform these assessments on patients. Therefore it was decided that while evidence of training would be required for all individuals generating study data, the frequency of re-training will not

Change Log of Amendments to SPOTLIGHT Protocol
From Version 2.0 16Mar2011 to current working Version 3.0 10Mar2014

				be mandated.
7.2.1	Definitions of Thromboembolic Adverse Events of Special Interest	Definitions of Thromboembolic Serious Adverse Events (SAE) of Special Interest	Definitions of Thromboembolic Adverse Events of Special Interest	Clarifies that AEs and not just SAEs of special interest will be monitored.
7.2.1	Definitions of Thromboembolic Adverse Events of Special Interest	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	1. Acute myocardial infarction (AMI) The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for MI: • Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: - Symptoms of ischaemia. - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB). - Development of pathological Q waves in the ECG. - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. - Identification of an intracoronary thrombus by angiography or autopsy. • Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or	Per DSMB request, definition of Acute Myocardial Infarction was updated with new citation.

			new LBBB,but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased. • Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required. • Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL. • Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery	

Change Log of Amendments to SPOTLIGHT Protocol
From Version 2.0 16Mar2011 to current working Version 3.0 10Mar2014

			occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.	
7.2.1	Definitions of Thromboembolic Adverse Events of Special Interest	Added text.	7. Incidental asymptomatic DWI lesions on brain MRI. Such lesions, compatible with acute cerebral ischemia, have been recently reported in the literature to occur in 14-41% of acute ICH patients who undergo brain MRI within one week of ICH onset. Such lesions are typically tiny, asymptomatic, and located in topographically remote areas from the hematoma. Their pathophysiology and clinical significance are uncertain at this time. For proper AE classification and interpretation, this MR imaging observation should be distinguished from a clinically overt ischemic stroke. If an AE reported as Stroke was based on MRI assessment, the name of the AE should be updated to Incidental asymptomatic DWI lesions on brain MRI.	
9.16	Adjudication Committee	A Medical Monitor will independently review all SAEs in real time and submit opinions to the PIs and DSMB regarding the relationship of events to study drug. A blinded Neuroradiologist will independently adjudicate the imaging aspects of suspected cerebrovascular SAEs.	A**n Internal** Medical Monitor will independently review all SAEs in real time and submit opinions to the PIs**, Independent Adjudication Committee,** and DSMB regarding the relationship of events to study drug. A blinded Neuroradiologist will independently adjudicate the imaging aspects of suspected cerebrovascular SAEs. **An independent Adjudication Committee will review all reported AE/SAE events and prepare summary reports for the DSMB.**	As requested by the DSMB, an independent adjudication committee will be added to the current process of internal medical monitor review of AEs and SAEs.
10	Informed Consent Process	Wording in TCPS version 1998	Wording from TCPS version 2010	Section reflects wording and references to current version of the TCPS

Change Log of Amendments to SPOTLIGHT Protocol
From Version 2.0 16Mar2011 to current working Version 3.0 10Mar2014

10.1	Justification for the Use of a Waiver of Consent	Added wording	Guidance for assessing capacity is noted in Appendix K of this document: *Suggested Framework for evaluating capacity for consent in an emergency setting.*	Additional guidance to the reader of the protocol.
10.2	Additional Eligibility Screening Requirement for Incapacitated Patients with No LAR	Added wording	Baseline troponin T or troponin I ≤0.1 ng/ml (≤0.1 µg/L)	
	Appendix A: Schedule of Events			Updated to reflect changes to the main protocol.
Other spelling, grammar and minor wordsmithing throughout document.				

SPOTLIGHT Summary of Protocol Changes

Date: March 16, 2011

This document contains a summary of the minor updates to the SPOTLIGHT protocol between the original document named version 2.0 from October 15, 2010 to the current final document version 2.0 dated March 16, 2011. The version number will remain as the original until an amendment becomes necessary after Health Canada review has taken place. In this case, a detailed account of changes will be tracked and rationale for each item will be indicated. We anticipate submitting the Health Canada CTA immediately following receipt of your REB approval.

The primary purpose for this update was to change the source of the investigational product in light of the manufacturer's recent decision not to supply drug for this study; Novo Nordisk was expected to supply study drug, but the company is no longer able to do so. As a result, each participating site will use their own local supply of the drug, which is already supplied to hospitals for off-label use by Canadian Blood Services, and this agency has no objection to this plan. Sunnybrook's Blood Bank is supportive of this plan, confirmed by Dr. Yulia Lin. The relevant parts of the study protocol describing the source of study drug and procedure for randomization have now been updated accordingly to reflect this change.

A few additional items in the protocol were updated based on investigator meetings, DSMB and executive steering committee meetings and requests for further detail to facilitate feasibility and decision making for the sites, particularly for patient safety. The revisions mainly consist of rewording certain sentences to improve clarity.

Summary of changes:

- Update of protocol throughout document to remove operational and publication associations with Novo Nordisk, manufacturer of study drug NiaStase RT
- Update to Randomization and Allocation section and Disclosure and Publication Policy section to reflect absence of Novo Nordisk involvement in providing or blinding investigational product, and addition of the new procedure to use locally available product.
- Additional definitions and explanation to Safety Assessments section, Safety Outcomes section and Safety Reporting section to clarify the procedures for reporting AEs and SAEs
- Minor adjustments to the phrasing of the inclusion and exclusion criteria for clarity
- Change of exclusion criterion INR > 1.50 to > 1.40
- Addition of CES-D Depression Scale, developed by NIMH to detect major or clinical depression, and is recommended by the NINDS-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards. This very brief questionnaire will be administered to patients at the 90 day and 1 year follow up visit, and is a standard scale used clinically in the Sunnybrook Stroke Clinic and in research studies. Assessment for post-stroke depression is considered an important outcome to capture in this trial.
- Addition of a statement of the necessity for periodic investigator recertification for the web-based spot sign imaging training module (in addition to the initial imaging certification, we are planning for recertification of enrolling physician investigators to be repeated at intervals during the course of the study).
-

- Update to the explanation of site procedures in section 5 to clarify the details, and harmonization with Appendix A: Schedule of Events

- Further explanation was included regarding the consent questionnaire, and confirmation of timeline for this administration

- Removal of individual steering committee member names and some details from some sections of the document referring to SPOTLIGHT–affiliated committees. These details will be kept in separate documents and filed.

- Removal of the suggested stopping rules for the DSMB, as this is now inserted into the DSMB Charter as a guideline for the DSMB

- Corrections throughout the document to general formatting and grammar, and typographical errors

CONFIDENTIAL

"Spot Sign" Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT): A Randomized Controlled Trial

Principal Investigator
Dr. David Gladstone, University of Toronto

Co-Principal Investigators
Dr. Richard Aviv, University of Toronto
Dr. Andrew Demchuk, University of Calgary

Version Number: 2.0

Date: March 16, 2011

Study funded by a peer-reviewed operating grant from the Canadian Institutes of Health Research (CIHR)

Address for correspondence:
David Gladstone MD, PhD, FRCPC
Division of Neurology, Department of Medicine
University of Toronto
Sunnybrook Health Sciences Centre
2075 Bayview Avenue, Room A442
Toronto, Ontario, Canada M4N 3M5
Tel 416-480-4866; FAX 416-480-5753
Email david.gladstone@sunnybrook.ca

Approval of Final Protocol

David Gladstone, MD, PhD, FRCPC
Principal Investigator

21 MAR 2011
Date

Richard Aviv, MD
Co-Principal Investigator

24 March 11
Date

Andrew Demchuk, MD, FRCPC
Co-Principal Investigator

March 23/11
Date

Site Investigator Agreement Page

"Spot Sign" Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT): A Randomized Controlled Trial

I have read and understand this protocol and concur with the study design. I agree to participate as an Investigator and to follow the protocol as outlined.

_____ _____

Site Investigator Signature Date

_____

Site Investigator Name (Please Print)

Table of Contents

List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
CTA	Computed Tomography Angiography
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic Data Capture
GCS	Glasgow Coma Scale
GCP	Good Clinical Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	Intracerebral Hemorrhage
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IVH	Intraventricular Hemorrhage
LAR	Legally Authorized Representative
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
N	Number (typically refers to participants)
NIHSS	National Institutes of Health Stroke Scale
NDA	New Drug Application
OTC	Over-the-counter
PI	Principal Investigator
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
RCT	Randomized Controlled Trial
rFVIIa	Recombinant Activated Coagulation Factor VII
REB	Research Ethics Board
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
WHO	World Health Organization

Protocol Summary

Full Title	"Spot Sign" Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT): A Randomized Controlled Trial
Short Title	SPOTLIGHT
Principal Investigators	Drs. David Gladstone, Richard Aviv, Andrew Demchuk
Funding	Canadian Institutes of Health Research (CIHR)
Primary Objective	To investigate the hemostatic effects of rFVIIa in spot-sign positive ICH patients. The study will compare the effects of rFVIIa vs. placebo on attenuating ICH growth, and explore variables that modify treatment response.
Secondary Objectives	1. To obtain feasibility and safety data for this emergency rFVIIa treatment protocol in spot-sign positive ICH patients. 2. To evaluate the applicability, acceptability and effects of implementing a waiver of consent policy in an emergency stroke trial. 3. To evaluate cognition and quality of life as endpoints in an ICH trial. 4. To obtain preliminary clinical efficacy data for rFVIIa treatment in spot-sign positive patients (a pooled analysis with other trials is planned).
Study Population	Acute spontaneous (non-traumatic) supratentorial ICH diagnosed by CT scan within 6 hours of onset, with evidence of active contrast extravasation within the hematoma as defined by the presence of a spot sign on CT angiography performed immediately after the baseline CT scan.
Study Design	Phase II multicentre, two-arm, double blind, placebo controlled, randomized trial
Sample Size	N = 110 (55 patients per group)
Accrual Period	48 months recruitment + 1 year follow-up
Study Duration	May 1, 2011 | End Date: 1 October 2016
Outcomes	*Primary Efficacy Outcome:* Difference between the 2 groups in ICH growth on CT scan within 24 hours. *Secondary Outcomes:* 1. Recruitment rates 2. Scan times (door to CT angiogram) 3. Treatment times (door to needle; CT angiogram to needle) 4. Accuracy of spot sign interpretation 5. Protocol adherence 6. Waiver of consent use, acceptability, and effect on treatment times 7. Acute blood pressure control 8. Total ICH growth at 24 hours (ICH plus IVH) 9. Cognitive function and quality of life *Exploratory Outcomes:* Difference between the 2 treatment groups in the proportion of patients with poor clinical outcome (mRS 5-6, i.e. death or severe disability) and the proportion of survivors achieving good clinical outcome (mRS 0-2; i.e. independent recovery/no disability) at 90 days

	Primary Safety Endpoint: Myocardial infarction within 4 days; ischemic stroke within 4 days; pulmonary embolism within 4 days. *Secondary Safety Endpoints:* Unstable angina within 4 days; troponin rise above upper limit of normal within 4 days (without clinical symptoms or ECG evidence of acute coronary syndrome); TIA within 4 days, deep venous thrombosis within 4 days, other arterial or venous thromboembolic SAEs within 4 days; pulmonary embolism within 30 days; acute nephropathy, 90-day mortality
Study Intervention Description	Patients randomized (1:1) to receive either a single intravenous bolus of 80 ug/kg rFVIIa (intervention group) or placebo (control group)
Assessments	Baseline assessment, post-dose assessments, 24 hours, days 2,3,4,day of discharge, days 30,90, and 1 year.

Abstract

Background – Intracerebral hemorrhage (ICH) is a devastating type of stroke (case fatality 40%). Patients frequently deteriorate within hours of hospital arrival due to continued bleeding in the brain resulting in hematoma expansion. For every 10% increase in ICH size, the risk of death increases by 5% and patients are 16% more likely to worsen by 1 point on the Rankin disability scale. There currently are no emergency treatments proven to improve patient outcomes. The most promising investigational treatment to date is hemostatic therapy with recombinant activated factor VII (rFVIIa), which significantly reduced ICH expansion (≈50% reduction) in 2 RCTs. Despite its ability to reduce bleeding, rFVIIa did not improve clinical outcomes in an unselected (heterogeneous) population of a phase III trial (*NEJM* 2008). We believe efficacy was diluted by inclusion of patients without active ICH expansion (rFVIIa will not help if bleeding has already stopped). Previous trials did not select patients for treatment based on any markers of active bleeding. Therefore, we propose a *focused trial* targeting only the "active bleeders" as the most logical next step. Based on our previous work, we now have a way for clinicians in the emergency department to predict which patients are at greatest risk of worsening due to ICH expansion. We described a radiographic sign ("spot sign") on CT angiography, a non-invasive X-ray of the intracranial blood vessels (*Stroke* 2007). This sign, present in 1/3 of acute ICH patients, refers to contrast extravasation within a hematoma and appears as foci of bright contrast enhancement, easily identified by visual inspection of CT angiography source images. This sign readily distinguishes 2 types of ICH patients: "spot sign positive" patients represent the active bleeders (extravasating contrast) who are destined to deteriorate and should theoretically benefit most from hemostatic therapy, whereas "spot sign negative" patients have stopped bleeding and are not expected to respond to treatment. Encouraging pilot data from our multicentre prospective PREDICT study (*Stroke* 2008) confirm the feasibility of performing hyperacute CT angiography and validate the prognostic value of the spot sign (mean ICH growth 34 ml with a spot sign vs. 6 ml without a spot sign). Image-guided stroke therapy is becoming the way of the future and now is the time to test the spot sign for guiding treatment in a trial.

Objectives – The primary objective is to test the ability of rFVIIa treatment to reduce ICH growth in ICH patients who have a spot sign (the highest risk ICH subgroup). Secondary objectives are to collect key feasibility data and additional safety data necessary to guide the design of a future phase III trial. We will assess applicability of a waiver of consent policy designed to minimize door-to-needle times, adherence to a standardized blood pressure protocol, and cognition, quality of life, and MRI outcomes. The tertiary objective is to explore preliminary clinical efficacy.

Methods – This phase II double blind RCT will enroll 110 patients from approximately 15 leading Canadian stroke centres. Acute ICH patients who can be treated within 6 hours of onset will undergo CT angiography using standard CT scanners (scan time 2 minutes). Those with a spot sign will be randomly assigned in a 1:1 ratio to a single injection of rFVIIa 80 μg/kg or placebo; patients without a spot sign will not be treated. Because ICH growth is highly time-sensitive and informed consent cannot always be immediately obtained, a waiver of consent protocol has been developed for this study and is justified on ethical grounds. The primary endpoint is ICH expansion within 24 hours. Secondary endpoints are scan-to-needle times, safety outcomes (thromboembolic SAEs), neurological impairment (NIHSS), cognition (MoCA), and global recovery measure (Stroke Impact Scale). Preliminary clinical endpoints (day 90 modified Rankin scale) will be explored through a planned pooled analysis with an independent (NIH-funded) U.S. study that will run in parallel with this trial.

Significance – The ultimate goal of this research is to reduce death and disability from ICH. SPOTLIGHT capitalizes on Canadian strengths in stroke imaging research and fosters international collaboration. rFVIIa deserves further investigation and this proposal for image-guided patient selection is the most rational way forward. By combining CT angiography to predict ICH growth, and rFVIIa to stop ICH growth, this trial offers a plausible means to improve patient outcomes. SPOTLIGHT will advance knowledge about ICH and is an essential step toward developing an efficacious emergency treatment protocol for this life-threatening condition.

1. BACKGROUND AND RATIONALE

The Problem of Intracerebral Hemorrhage

This study addresses the management of intracerebral hemorrhage (ICH), the most deadly and disabling type of stroke. ICH is caused by sudden bleeding into the brain from a ruptured blood vessel, most often related to hypertension and amyloid angiopathy. It accounts for about 10-30% of all strokes worldwide, often afflicting young people. Many ICH patients arrive at hospital early with initially modest deficits that then rapidly worsen, minute by minute, due to ongoing bleeding in the brain[1,2] Figure 1). Such ICH expansion during the first few hours is an independent predictor of neurological deterioration and mortality: for each 10% increase in ICH size, the risk of death increases by 5% and patients are 16% more likely to have an increase of 1 disability level on the 7-point modified Rankin scale.[3] Significant ICH growth (>33% volume increase from baseline) occurs in 18-38% of patients scanned within 3 hours of symptom onset[1,4,5,6] and 8-16% scanned within 3-6 hours, indicating this phenomenon is time-dependent.[5,6,7] The clinical consequences are dire: Canadian data on spontaneous ICH in the Registry of the Canadian Stroke Network (n=1546) reveals a 39% in-hospital mortality.[8] In other studies, the 30-day mortality is 30-50%, half of deaths occur within 48 hours, and most survivors are left with serious long-term disability.[4,9] Unfortunately, there are currently no proven hyperacute medical treatments for this life-threatening condition.

The Opportunity

Treatment aimed at preventing ICH expansion, if administered early enough and to the right patient, should translate into improved recovery and reduced disability. The most promising investigational treatment to date is hemostatic therapy with recombinant activated Factor VII (rFVIIa), which has been in clinical use for many years for other life-threatening bleeding conditions. Two landmark trials recently showed that rFVIIa can significantly reduce bleeding in the brain (about 50% reduction in ICH growth vs. placebo).[10,11] However, clinical efficacy was not demonstrated when studied in a heterogeneous (unselected) group of ICH patients in a phase III trial.[10,11] Now, with the discovery of a new imaging sign that is present in about 1/3 of acute ICH patients (termed the "**spot sign**"),[12] ICH trials can now be designed with a much more rational treatment approach. Using the spot sign, it has become possible for the first time for clinicians in the emergency department to rapidly and accurately predict the patients who are at highest risk for imminent deterioration due to ICH expansion and might, therefore, benefit most from rFVIIa treatment.

The spot sign is defined as tiny bright foci of enhancement within a parenchymal hematoma, detected by visual inspection of CT angiography source images[13] (Figure 2 and 3).

With a 2-minute non-invasive CT angiogram (CTA), 2 types of ICH patients are readily distinguished:

1. ***"Spot sign positive" patients*** are the active bleeders who are at highest risk for deterioration and should, we hypothesize, be the best candidates to respond to hemostatic therapy.
2. ***"Spot sign negative" patients*** are at low risk for ICH expansion and are not expected to benefit from hemostatic therapy.

Previous rFVIIa trials did not use CTA to assess spot sign status and, thus, failed to target only the patients with active bleeding. SPOTLIGHT will test the ability of the spot sign to guide rFVIIa treatment in a clinical trial.

Literature Review, Previous Trials, Pilot Data, and the Need for This Trial

rFVIIa Stops Bleeding in the Brain

Hemostatic therapy with rFVIIa (intravenous injection) is the first intervention proven to significantly reduce ICH growth, and has opened the exciting prospect that this devastating condition can be treated in selected patients. rFVIIa for ICH has been tested in dose-escalation, phase IIb, and phase III trials.[10,11,14] The phase IIb trial (n=399) randomized patients within 4 hours of onset to placebo or rFVIIa 40 µg/kg, 80 µg/kg or 160 µg/kg.[10] The mean percentage increase in ICH volume was 29% with placebo vs. 16%, 14% and 11% in the rFVIIa 40, 80 and 160 µg/kg groups, respectively (p=0.01). Mean absolute growth in ICH volume was reduced by 3.3 ml, 4.5 ml, and 5.8 ml with the 3 doses, respectively (p=0.01). A phase III trial (n=841) confirmed rFVIIa reduces ICH expansion in a dose-dependent fashion.[11] This trial randomized patients within 4 hours of onset to placebo, rFVIIa 20 µg/kg or 80 µg/kg. The placebo group had a 26% mean increase in ICH volume vs. 18% in the 20 µg/kg group and 11% in the 80 µg/kg group (p<0.001).[11] While 74% of placebo patients had some ICH growth, only 28% had growth >33%. Thus, the overall treatment effect is reduced considerably by patients with little or no ICH expansion. *If patients destined to have significant ICH growth can be identified right away and other patients excluded from treatment, the difference in ICH growth (and clinical outcomes) between treatment and placebo groups is expected to be magnified.*

Treatment with rFVIIa is Time-Sensitive

The treatment effect of rFVIIa is maximal within the first 3 hours. Among patients in the phase IIb trial treated within 3 hours (n=269), the mean percentage increase in ICH volume was 34% (placebo) vs. 13% (rFVIIa) (p=0.004). The absolute increase in ICH volume was 10.7 ml (placebo) vs. 4.4 ml (rFVIIa) (p=0.009). The phase III trial provided further evidence that earlier treatment is associated with greater reduction in ICH growth: 5.6 ml less growth for patients treated within 2 hours vs. 4.5 ml less for those treated within 3 hours and 3.8 ml less for those treated up to 4 hours. [11] There was a significant reduction in death or severe disability at day 15 with rFVIIa vs. placebo (33% vs. 47%, p=0.03) in the subgroup treated under 2 hours (S. Mayer, personal communication). Thus, like ischemic stroke, the concept of *"time is brain"* applies to ICH treatment.

Improved Patient Selection in RCTs is Necessary to Achieve Clinical Efficacy

Despite the significant reductions in ICH growth with rFVIIa, clinical efficacy remains to be proven. In the phase IIb trial, 90-day mortality was 29% (placebo) vs. 18% (rFVIIa), a relative mortality reduction of 38% (p=0.02). Clinical outcomes at 90 days all favoured rFVIIa treatment. However, in the phase III trial there were no significant differences in 90-day mortality or functional outcomes in the overall (heterogeneous) population. Baseline imbalances in intraventricular hemorrhage may have contributed, but we believe that clinical efficacy in that trial was most likely diluted by the inclusion of patients who were never at risk for ICH expansion (rFVIIa will not help if bleeding has already stopped). None of the previous trials selected patients based on any markers of active bleeding. Thus, a focused trial targeting only the "active bleeders" is now the next logical step in the investigation of this promising therapy.

Image-Guided Patient Selection is the Way Forward: The Spot Sign Story

Contrast extravasation (leakage of radiographic contrast dye) within an intracerebral hematoma can be visualized by CTA, MR angiography or catheter angiography, and correlates with an actively bleeding vessel and ICH growth.[15-22] Initial work on the spot sign in Toronto and Calgary has stimulated major international interest in the value of CTA for predicting ICH growth. Dr. Aviv's group at Sunnybrook in Toronto described the spot sign in 2007,[12] and along with Dr. Demchuk's group published a radiographic definition of the sign, characterized different morphological patterns[13] (Figure 4), and distinguished the spot sign from its radiographic mimics (e.g. calcification, tumour).[23] In the Toronto Sunnybrook study, CT angiograms were analyzed from ICH patients scanned within 3 hours of onset.[12]

A spot sign was identified in 33% and predicted ICH growth >30% or 6 ml with 91% sensitivity and 89% specificity. The positive and negative predictive values for growth were 77% and 96%. ICH expansion was more common in patients with a spot sign than those without ($p<0.001$), and the spot sign independently predicted ICH enlargement ($p<0.001$). The outcome of death or severe disability occurred in 50% of those with a spot sign vs. 35% in those without. Inter-observer agreement was high (k=0.92-0.94). Becker et al. found contrast extravasation on CTA to be an independent predictor of in-hospital mortality: extravasation was present in 46% of 113 patients and was associated with higher mortality (64%) vs. patients without extravasation (16%). [19] Goldstein et al. (2007) reported CT angiograms from 104 patients that corroborated our spot sign findings. [24] Contrast was present within the ICH in 56% and this finding was the single most powerful predictor of ICH expansion. Sensitivity and specificity of extravasation for predicting ICH growth was 93% and 50%, with a 98% negative predictive value. There was a trend toward earlier time to patient presentation in those with extravasation and ICH expansion, and increased mortality in those with extravasation ($p=0.04$). Multivariable analysis confirmed an independent effect of extravasation on ICH growth (OR 18, 95% CI 2.1-162, $p=0.009$). Kim et al. (2007) added further evidence that contrast extravasation independently predicts ICH growth and mortality: 30-day mortality was 53% in those with extravasation vs. 19.5% without. [25,26]

A large Harvard study (n=367) provided very strong validation of the spot sign. [27] The PPV for significant ICH growth was highest for spot signs with the certain characteristics: ≥3 spots (PPV 96%), axial dimension ≥5mm (PPV 91%), and attenuation ≥180 HU (PPV 84%). The authors developed a 4-point "spot sign score" based on the number of spots, maximal axial dimension and attenuation, and this score predicted significant ICH growth ($p<0.0001$) independent of ICH volume, blood pressure, INR, and time from onset to scan. The percentage of patients with significant ICH growth ranged from 2% for spot-negative patients to 94% for spot-positive patients with a spot sign score of 3 and 100% for those with a spot sign score of 4. Mean ICH growth for those with spot sign scores 3-4 was 21-36 ml (or 68%-72% volume increase) vs. 11 ml for spot-negative patients. Importantly, inter-observer agreement for identification of the spot sign was near-perfect among 3 readers (k=0.88-0.93). The presence of a spot sign (OR 2.5, 95% CI 1.3 to 4.7, $P<0.0052$) and the spot sign score (OR 1.5, 95% CI 1.2 to 1.9, $P<0.0002$) were each independent predictors of in-hospital mortality (in addition to patient age, admission GCS, and initial ICH and IVH volumes).[28] The spot sign (OR 2.4, 95% CI 1.1 to 4.9, $P<0.02$) and the spot sign score (OR 1.6, 95% CI 1.1 to 2.1, $P<0.0065$) were each independent predictors of poor outcome among survivors (mRS 4-5) at 3 months (in addition to patient age, admission GCS and MABP, as well as initial ICH and IVH volumes).[28] In this study, the highest spot sign scores were observed in patients with baseline ICH volumes 30-59.9 mL, CTA <3 hours of onset, baseline GCS 9-12, admission MABP >120 mm Hg, and deep gray matter ICH.[28]

In summary, the spot sign is considered the most accurate, reliable, and rapid imaging sign for predicting ICH growth.

<u>CT Angiography is an Ideal Emergency Imaging Tool for ICH</u>

CTA is a *non-invasive* test that can be performed quickly in any hospital with a helical CT scanner (acquisition time approx. *2 minutes*). CTA requires injection of contrast dye and can be obtained immediately following a routine non-contrast CT head scan, the standard initial investigation for ICH patients. The spot sign can be identified immediately on the source images usually before the patient is taken off the CT scan table (no image post-processing required), making it ideally suited for emergency decision-making. In addition to the *prognostic* value of the spot sign, CTA provides valuable *diagnostic* information about brain vascular anatomy. Combined with a post-contrast head CT, CTA is an excellent tool for diagnosis of serious secondary causes of ICH (aneurysm, AVM, venous thrombosis, tumour), as we have published.[29] Thus, independent of the spot sign, hyperacute CTA is beneficial for excluding structural pathology that could affect patient management.

How will the results of this trial be used?

SPOTLIGHT is intended to provide data necessary to inform the design of a future phase III trial, and represents an essential step toward the long-term objective of developing the first emergency treatment to improve outcomes from ICH. In addition to the anticipated feasibility and safety results, SPOTLIGHT will generate much-needed information about estimated treatment effect sizes, clinically important measures of ICH growth, and eligibility criteria for future studies. This trial will advance knowledge about ICH and has the potential to transform future ICH research. SPOTLIGHT will be a catalyst for related research aimed at improving ICH patient care, e.g. inspiring trials to evaluate the spot sign for predicting ICH growth and guiding treatment for patients presenting >5 hours of onset or with an unknown time of onset (e.g. those who awaken with deficits) and for anticoagulant-associated ICH. Our results will also have implications for patient selection for trials of other investigational ICH treatments, e.g. intensive blood pressure lowering and neurosurgical approaches for ICH evacuation.

2. AIM AND OBJECTIVES

Overall Aim

The ultimate goal of this research is to reduce death and disability caused by ICH. SPOTLIGHT is a focused phase II trial that tests an innovative ICH treatment protocol in the emergency department using CTA for patient selection. This type of image-guided targeted treatment approach for ICH is novel and aims to reduce hematoma expansion and improve outcomes in the highest-risk ICH subgroup (i.e., the spot-sign positive patients). The study is based upon solid biological rationale and a strong foundation of evidence from published studies, and goes beyond previous trials by using vascular imaging to guide treatment.

2.1 Primary Objective

The primary objective is to investigate the hemostatic effects of rFVIIa in spot-sign positive ICH patients. The study will compare the effects of rFVIIa vs. placebo on attenuating ICH growth, and identify variables that modify treatment response.

Hypothesis:
rFVIIa-treated patients will have significantly less ICH growth compared to placebo-treated patients, as measured by the average ICH volume on CT scan at 24 hours post-treatment and the average absolute change in ICH volume (ml) from baseline to 24 hours. We expect the greatest efficacy in patients treated early (<3 hours post-onset) and quickly (<40 min. after CTA), and without baseline intraventricular hemorrhage.

2.2 Secondary Objectives

1. To obtain feasibility data and safety data for this emergency rFVIIa treatment protocol in spot-sign positive ICH patients.

Hypotheses:

a) Recruitment targets will be achieved, with 50 eligible spot sign positive ICH patients enrolled during the first 18 months of active recruitment and 60 patients enrolled during the subsequent 18 months (sites are required to enroll a minimum of 2 patients per site per year over 3 years of recruitment). Site screening logs will be reviewed and barriers to recruitment will be identified and addressed during the course of the trial.

b) Sites will be able to scan patients with CTA rapidly, with >80% achieving a target time of <45 minutes from emergency department arrival to the start of the scan.

c) Enrolling physicians will interpret the presence/absence of a spot sign on CTA in the context of the trial with >90% accuracy, as compared to blinded over-read by the "gold standard" study neuroradiologist. All study investigators will undergo training beforehand with a certification program developed by Dr. Aviv, and recertification will be required periodically throughout the trial period. We will carefully assess any spot signs that are over-called (i.e. false positives) and provide feedback to sites during the course of the trial. Data from this study will determine whether future trials should rely solely on spot sign presence/absence as the main criterion for inclusion or whether enrolling physicians can also accurately calculate a 4-point spot sign score using a published rating scale.[28]

d) Sites will be able to randomize and treat patients rapidly, with >80% achieving a target time of <60 minutes from the end of the CT angiogram to administration of study drug. Sites will be required to rehearse mock enrollments prior to site activation, and delays to study drug administration will be identified and addressed during the course of the trial.

e) Sites will adhere to study protocol in terms of meeting inclusion/exclusion criteria and following treatment procedures, with a low rate of major protocol violations (<5%) during the first 18 months and thereafter.

f) Ability to control blood pressure acutely, defined as achieving systolic BP <180 mmHg within 1 hour post-randomization, will be achieved in >90% patients using a standard protocol (see Appendix). This will be an important demonstration that will have relevance for other future studies of ICH management.

g) The incidence of myocardial infarction and ischemic stroke within 4 days, and 90-day mortality rate, in the rFVIIa group will not exceed the rates observed in previous trials based on our stricter eligibility criteria.

Site performance on the above indicators in this study will be essential for guiding the design a future multicentre phase III trial of the proposed intervention that will be powered to assess clinical efficacy. The results of this trial will be used to determine whether modifications are needed to the inclusion/exclusion criteria, and will assist with sample size projections, site selection, recruitment strategies, ethical considerations, and local process of care issues for patient screening and scanning (especially to identify and minimize delays to scan time, randomization and drug administration).

2. To evaluate the acceptability and effects of implementing a waiver of consent for CTA in this emergency stroke trial, and to evaluate the applicability, acceptability and effects of a waiver of consent for randomization to treatment in this trial.

Hypotheses:

a) Site REBs will approve the proposed inclusion of a waiver of consent policy for CTA in the study protocol, and this waiver of consent policy will be acceptable to patients/LARs.
b) Sites in this trial will have significantly shorter door-to-CTA times and door-to-needle times and greater efficacy for this time-sensitive treatment vs. patients in other trials (e.g. STOP-IT) using standard consent for CTA and randomization.
c) The majority of site REBs will approve the proposed option of a waiver of consent for randomization to treatment in this trial, and the majority of patients/LARs surveyed will be in

favour of such a waiver of consent option for randomization to treatment in a future hypothetical trial. This study will estimate the proportion and characteristics of ICH patients who would qualify for a waiver of consent for treatment in future a trial (i.e., the proportion who not have the capacity to provide their own informed consent at the time of admission and for whom no LAR is immediately available, and for whom the investigator is able to obtain a complete and reliable medical history to determine that the patient fulfills the inclusion/exclusion criteria). These data will determine whether a waiver of consent for treatment should be used in the design of future emergency ICH trials.

3. To evaluate cognition and quality of life as endpoints in an ICH trial.

Hypothesis:
Survivors of ICH will have cognitive impairments and reduced quality of life, measurable on the Montreal Cognitive Assessment (MoCA) and Stroke Impact Scale at 90 days and 1 year.

4. To obtain preliminary clinical efficacy data for rFVIIa treatment in spot sign positive patients (a pooled analysis with other similar trials is planned).

Hypothesis:
Spot-sign patients treated with rFVIIa will have a lower probability of poor outcome compared to placebo-treated patients, as measured by the proportion with modified Rankin score 5-6 (death or severe disability) at 90 days and 1 year. ICH survivors who received rFVIIa will have a greater probability of good recovery compared to placebo, defined as the proportion with modified Rankin score 0-2 at 90 days and 1 year.

3. STUDY OVERVIEW

3.1 Study Design

SPOTLIGHT is a phase II multicentre, randomized, double-blind, placebo-controlled, investigator-led trial. The study will screen patients who present to the emergency department with acute spontaneous ICH and who can be randomized and treated within 6 hours of stroke onset. Eligible patients who have an acute ICH diagnosed by CT scan and a spot sign detected on CTA (ideally performed immediately after the routine plain CT scan) will be randomly assigned in a 1:1 ratio to a single dose of rFVIIa or placebo using a variable block randomization scheme. Study drug is to be administered as quickly as possible within 60 minutes (+ 10 minutes) of CTA and no later than 6 hours after stroke onset. Spot sign negative patients will not be randomized.

The study design improves upon published rFVIIa trials by using CTA for patient selection (previous trials did not assess spot sign status), and by aiming for *faster treatment times* by introducing assent-consent and waiver of consent procedures. Additionally, since cognitive outcomes have been understudied in ICH (and not included in previous rFVIIa trials), this study will assess cognitive (not just physical) disability using a bedside cognitive battery developed in Canada.

All patients will continue to receive standard stroke care and rehabilitation, and clinical ICH management should follow published guidelines [30]. It is anticipated that most patients will be admitted to an intensive care/close observation unit for 24 hours followed by stroke unit care, as is usual practice. In accordance with the 2010 American Heart Association Guidelines on Management of Intracerebral Hemorrhage, "Aggressive full care early after ICH onset and postponement of new DNR orders until at least the second full day of hospitalization is probably recommended (Class IIa; Level of Evidence: B)",

unless a patient's preexisting advanced directives specify otherwise[new reference 30]. For participants in this study, DNR orders or withdrawal of support during the first 24 hours is therefore discouraged.

While rFVIIa is available in most tertiary care hospitals, it is not approved by Health Canada for ICH. A Clinical Trial Application will be submitted for Health Canada approval and the study will be submitted for REB approval at each site. The trial will be registered with an online clinical trials directory and will comply with GCP-ICH and reports will follow the CONSORT statement.

3.2 Study Population

3.2.1 Inclusion Criteria

1. Acute spontaneous primary supratentorial ICH diagnosed by CT scan.
2. Presence of a spot sign within the hematoma on CTA source images. [Note: CTA should ideally be performed immediately after the baseline CT scan. If CTA is going to be delayed more than 20 minutes after the baseline CT, then a new baseline plain head CT must be obtained immediately prior to CTA]. A spot sign must meet the following criteria:
    - One or more foci of contrast enhancement within the margin of a parenchymal hematoma
    - Any size or morphology (shape may be spot-like, linear or serpiginous)
    - Spot sign(s) must not have any connection to vessels outside the hematoma
    - Hounsfield unit density at least double that of background hematoma density (density of spot sign is typically >120 Hounsfield units)
    - No corresponding density present within the hematoma on non-contrast CT
3. Baseline ICH volume 3-70 ml, estimated using the standard "abc/2" calculation on the baseline plain head CT.
4. Age 18-85 years (participants must have had their 18th birthday and not their 86th birthday).
5. Investigator is able to randomize and administer study drug within 60 minutes after CT angiogram and no later than 6 hours after stroke symptom onset (using the "last seen normal" principle).
6. Assent-consent from patient or LAR prior to enrolment, or a waiver of consent if patient/LAR assent-consent is not possible prior to enrolment. [Note: full informed consent to be obtained as soon as possible after study treatment administered]. (see section on Ethics and Consent Procedures below for explanation)

3.2.2 Exclusion Criteria

Diagnostic/Imaging Exclusions

1. Brainstem or cerebellar hemorrhage.
2. ICH secondary to known or suspected trauma, aneurysm, vascular malformation, hemorrhagic conversion of ischemic stroke, venous sinus thrombosis, thrombolytic treatment, tumour, or infection; or an in-hospital ICH or ICH as a result of any in-hospital procedure or illness.
3. Baseline brain imaging shows evidence of acute or subacute ischemic stroke (chronic infarcts are not an exclusion).
4. Contrast administration within the previous 24 hours.

Clinical Exclusions

1. Glasgow Coma Scale score <8, at time of initial screening by the enrolling investigator/nurse.
2. Known pre-existing dependence or moderate or severe disability, defined as pre-admission modified Rankin Scale score >2. [Note: Patients must be independent in all basic activities of daily living and are excluded if they cannot walk independently without the assistance of another

person (use of a cane or walker is not an exclusion) or if they require assistance from another person for basic activities of daily living (e.g. dressing, transfers, feeding, bathing, toileting)]. Patients with advanced dementia or admitted from a nursing home are excluded (cognitive impairment alone, without dementia, is not an exclusion to enrollment).

3. Evidence of thromboembolic risk factors, defined as any of the following: known history within the past 6 months of any of the following: (a) myocardial infarction, (b) coronary artery bypass surgery, (c) angina, (d) ischemic stroke, (e) transient ischemic attack, (f) carotid endarterectomy, (g) cerebral bypass surgery, (h) deep venous thrombosis, (i) pulmonary embolism, (j) any vascular angioplasty, stenting (coronary, peripheral vascular or cerebrovascular) or filter (e.g. vena cava filter); and/or known history of a high-risk thrombophilia (e.g. antithrombin III deficiency, antiphospholipid antibody syndrome, protein C deficiency, etc.)
4. Known hereditary (e.g. hemophilia) or acquired hemorrhagic diathesis or coagulation factor deficiency.
5. Any condition known that the investigator feels would pose a significant hazard if rFVIIa were administered.
6. Planned surgery for ICH within 24 hours (placement of intraventricular catheter is not an exclusion).
7. Known terminal illness or planned withdrawal of care or comfort care measures.
8. Known participation in another therapeutic trial.
9. Known allergy or other contraindication to iodinated contrast dye.
10. Known or suspected hypersensitivity to the trial product.

Medication Exclusions

1. Known unfractionated heparin use – must check PTT and exclude if elevated above upper limit of local lab's reference range.
2. Known low-molecular weight heparin, heparinoid, factor X inhibitor, or direct thrombin inhibitor use within previous 24 hours.
3. Known GPIIb/IIIa antagonist use in previous 2 weeks.
4. Known warfarin (or other anticoagulant) therapy with INR >1.40. Note: if the patient is suspected to have cirrhosis, study staff are to wait for the INR value prior to dosing, and ensure not to enroll the patient if the INR value is >1.40. Otherwise the physician should use their discretion if they believe the patient is not at risk for elevated INR.
5. Concurrent or planned treatment with prothrombin complex concentrate, vitamin K, fresh frozen plasma, or platelet transfusion.

Clinical/Laboratory Exclusions

1. Pregnancy or lactation. Women of childbearing potential must have a negative pregnancy test prior to randomization.
2. Current clinical symptoms suggestive of acute coronary ischemia (e.g. chest pain).
3. Baseline ECG evidence of acute coronary ischemia (e.g. ST elevation in 2 contiguous leads, new LBBB, ST depression).
4. Baseline troponin T or troponin I >0.1 ng/ml (>0.1 µg/L).
5. Baseline platelet count <50,000 or INR >1.40 or elevated PTT [Note: participants can be enrolled without awaiting these results unless a bleeding abnormality or thrombocytopenia is suspected, the participant is known to have been taking warfarin, heparin, or other anticoagulant, or anticoagulation use is uncertain.].

Justification of Eligibility Criteria

This study is targeting primary spontaneous, non-traumatic, non-anticoagulant-related ICH. The eligibility criteria reflect important refinements to previous rFVIIa trials intended to maximize efficacy

and minimize harm. Unlike previous trials that allowed enrollment of patients who already had massive ICH at baseline (>100 ml) or were comatose (GCS 5-7), this trial restricts entry to ICH volumes <70 ml, since >70 ml is usually fatal. Similarly, this study excludes patients who are already comatose as they have a dismal prognosis and are unlikely to benefit from a treatment that aims to prevent further bleeding. We have set a minimum ICH volume as very tiny ICH (<3 ml) tend to be benign. [31,32] For maximum safety, the study is excluding the very elderly because of a higher prevalence of comorbidities, post-stroke mortality, and thrombotic risk with rFVIIa [33] (previous trials did not set an upper age limit). To further minimize risk, the study is excluding patients with known thromboembolic events or vascular procedures within the past 6 months (the previous phase III trial only excluded patients with thromboembolic events within 30 days prior to enrollment). With these criteria, a lower incidence of SAEs is expected compared prior trials. This study is focusing on supratentorial bleeds, which account for the majority of ICH; brainstem/cerebellar bleeds have a different natural history and their inclusion would add too much heterogeneity. Cerebellar hemorrhages often require emergent surgery, which would also disqualify such patients.

Regarding baseline blood work, a normal troponin level is required prior to enrollment. However, because time is critical, enrollment should not be delayed while waiting for the results of INR, PTT, or platelet count unless a coagulopathy is suspected, the patient is known to have been taking warfarin or heparin, or anticoagulation use is uncertain. Baseline blood work must be checked for eligibility prior to enrollment for any patient being considered for enrollment with a waiver of consent. A serum creatinine value should ideally be obtained prior to CTA. However, because time is critical, CTA should not be delayed while waiting for the creatinine unless renal dysfunction is suspected (see Section 10.2 for further details).

Quick Screening Checklist for Potential Eligibility

A screening checklist has been developed to rapidly identify potential study candidates for whom the study team should come in to assess. This can be done by telephone, ideally between ED triage nurse and the on-call study nurse/coordinator/investigator. It lists automatic exclusions to study enrollment that can often be determined on admission/registration at ED triage desk (or from paramedic pre-notification available at some sites). Patients who fail this screening checklist need not undergo CTA if that is not standard clinical practice at some sites.

Automatic exclusions to study enrollment, assessed upon arrival to ED and prior to CT scanning:

- Patient cannot be scanned, randomized and treated within 6 hours after stroke symptom onset or "last seen normal time" (ED arrival >5 hours after onset is usually exclusionary).
- Age <18 years or >85 years
- Moderate or severe pre-existing disability or dependence, requiring assistance in ADLs
- Severe dementia
- Living in a nursing home
- Palliative or terminal illness with pre-stroke life expectancy <6 months
- Currently on IV heparin or receiving low molecular weight heparin injections
- Comatose (Glasgow Coma Scale score 3-7)
- Known renal failure or known allergy to iodinated contrast dye

3.2.3 Concomitant Medications / Prohibited Medications and Procedures

As stated in the above eligibility criteria, the following are exclusions to enrollment:

- warfarin (or other anticoagulant) with INR >1.40
- unfractionated heparin use with abnormal PTT

- low-molecular weight heparin, heparinoid, factor X inhibitor, or direct thrombin inhibitor use within previous 24 hours (e.g. dabigatran, rivaroxaban, apixiban, enoxaparin, dalteparin). A complete list of prohibited medications will be provided to sites.
- GPIIb/IIIa antagonist use in previous 2 weeks
- Concurrent or planned treatment with prothrombin complex concentrate (e.g. Octaplex), vitamin K, fresh frozen plasma, or platelet transfusion

Metformin should be stopped at the time of CTA and should not be restarted for at least 48 hours and only then if renal function remains stable (<25% increase compared to baseline creatinine).[38] There are no restrictions placed on other medication use or procedures in this study. All medications, including OTC medications and herbal/natural remedies, taken by the subject are to be recorded on the concomitant medication form in the CRF at specified visits.

Concomitant medications will be captured for the duration of patient participation in the trial.

3.2.4 Imaging Procedures

Brain imaging with a non-contrast head CT scan is performed at baseline and will be repeated as soon after dosing as possible (+ 15 min) and at 24 hours +/- 3 hours post-dosing to assess the rate and degree of ICH growth. The baseline and 24-hour CT scans are standard clinical care for ICH. Patients transferred from outlying hospitals will have the baseline CT repeated with the CT angiogram. The local study investigator will use the baseline CT as part of the screening process for eligibility and will estimate ICH volume using the simple "abc/2" formula, which takes seconds to calculate and is familiar to stroke clinicians.[48] If there is a delay of more than 20 minutes between the baseline CT and the CT angiogram, then a plain head CT must be repeated at the time of the CT angiogram and this will be considered the baseline CT for study purposes.

The local investigator will determine the presence or absence of a spot sign by reviewing the CTA source images obtained immediately following the non-contrast CT scan. Rigorous pre-study training and certification, and recertification, of study investigators on spot sign interpretation is required and is an essential part of our study plan. Dr. Aviv has developed a web-based training module for certification of investigators. CTA is performed only once at baseline. A post-contrast head CT scan will be performed as part of the CTA protocol to assess for additional contrast leakage.[19] CT angiograms will be reported by the local radiologists and results will be available to the local clinicians because of the possibility of detecting pathology.

While planned surgical hematoma evacuation within 24 hours of enrollment is an exclusion criterion, some patients may experience clinical deterioration and be taken for emergent surgery at the discretion of treating clinicians. If this occurs before a 24-hour CT is obtained, a pre-operative CT should be requested and will be used as the study's outcome CT to assess ICH growth. Similarly, for any study patient who is not expected to survive long enough to be rescanned at the planned 24 hour CT scan time (e.g. due to significant early neurological deterioration or if a medical decision for withdrawal of care is made), then a plain head CT should be obtained earlier than 24 hours to ensure the patient has a follow-up outcome scan for study purposes.

3.2.5 Imaging Safety

CTA is widely available and routinely performed as standard care in the emergency evaluation of ischemic stroke and subarachnoid hemorrhage in many centres. For ICH, it is used to exclude secondary causes of ICH and many Canadian stroke centres use CTA in the acute phase of ICH as part of clinical

routine. The potential risks of CTA are very small, well established, easily minimized, and virtually always treatable if they occur.

CTA involves a small amount of ionizing radiation. The radiation dose from a plain head CT is approximately 1.7 mSv, which is comparable to natural background whole-body radiation we are all exposed to over 8 months. The lifetime attributable risk of death from cancer from exposure to a head CT scan is less than 0.01% for patients aged 40-80 years.[51] The radiation dose delivered by CTA is slightly more than a non-contrast CT when centered on the intracranial vessels (1.9 mSv).[49] The CTA protocol for this study includes a CT angiogram and a post-contrast head CT scan for a radiation dose of 1.9 mSV + 1.7 mSv = 3.6 mSv). For comparison, the radiation dose from screening mammography is 3 mSv, chest CT 8 mSv, barium enema 15 mSv, abdomen and pelvis CT 15 mSv without contrast (31 mSv with contrast), coronary angiography 22 mSv.[51][52] Overall, then, the amount of radiation exposure for participants in this study is not excessive compared to other routine procedures and is considered to represent inconsequential risk relative to the information gained that may aid in the management of a life-threatening condition.

Radiographic iodinated contrast agents are used extensively in health care. Mild allergic reactions (hives, itching) occur in 2% with intravenous contrast dye; severe reactions occur in ≈0.1%. Contrast extravasation into a limb due to failure of intravenous access occurs in 0.25-0.6% of contrast-enhanced studies[50] and may result in local tissue damage.[53] Reported deaths from iodinated contrast agents range from 6.6 per million to 1 in 10,000.[45] The risk of contrast-induced nephropathy, (>25% increase in serum creatinine within 3 days of contrast administration),[38] is proportional to the amount of agent administered.[38] Only a single dose of contrast (75-100 ml) is required for this study. Chronic renal impairment is the main risk factor.[38] Patients with normal glomerular filtration rate (GFR) are at very low risk; with GFR 30-60, there is a low to moderate risk.[38] Guidelines recommend that patients be screened for risk factors associated with acute or chronic renal impairment, but acknowledge that this may not be possible in the acute setting.[38,54] The absence of risk factors effectively eliminates the probability of a given patient having renal impairment.[54] We and others have studied the renal safety of contrast CT studies in acute stroke patients. Our Calgary study found a low incidence of nephropathy (7/224; 3%) and no patients required dialysis.[34] Of patients who underwent CTA without knowledge of their creatinine, 2% developed nephropathy. Similarly, our Toronto study found elevated creatinine consistent with contrast-induced nephropathy in 5/175 (2.9%), and 1.8% of patients who were scanned before creatinine values were available; none required dialysis or had permanent renal sequelae.[35] A Boston study further supported the safety of emergency contrast CT studies before availability of renal function tests in code stroke patients who did not have a known history of renal disease.[56] A controlled study *(n=539)* reassuringly showed *no increase in risk of acute nephropathy in ICH patients who underwent CTA* (6%) vs. a control group who did not have CTA (10%).[57] Another controlled study showed *no increase in incidence of acute nephropathy in acute ischemic stroke patients who underwent a contrast-enhanced CT protocol (5%) vs. stroke patients who did not receive contrast studies (10%).*[55]

3.2.6 Randomization and Allocation Concealment

A computer-generated randomization schedule will be created for the trial by the study statistician such that there will be an equal number of patients assigned to each treatment. Randomization will be stratified by site using a variable block randomization scheme. Each site will identify an appropriate unblinded dispensing team (local Blood Bank, research pharmacy, or other appropriate team) who will hold the randomization list for that site, prepare the study drug in an unblinded manner, and dispense the blinded study drug to the investigator. The study statistician will provide the site dispensing team with the site randomization schedule, which includes the randomization numbers and the corresponding study drug assigned. The dispensing team will not be involved in any other aspect of the trial.

At the time that the informed consent form (or waiver of consent) is signed, a patient is considered to be enrolled in the study and will be assigned a patient number. Randomization should occur as quickly as possible after enrollment. The investigator will request the study drug STAT from the dispensing team. Upon request for study drug, the dispensing team will assign the patient a randomization number based on the next sequential randomization number on the site randomization list. The time of randomization is defined as the time that the study drug (NiaStase RT or saline) is allocated to the patient by the dispensing team from the site randomization list. The unblinded dispensing team will prepare the corresponding product (NiaStase RT or saline) in a blinded syringe ready for dosing (out of sight of the patient, investigator, and any other members of the blinded study team). Each site will use its own local supply of NiaStase RT and saline. In this trial, site standard sterile saline solution will be used for placebo (any brand is acceptable). Both saline and reconstituted Niastase RT are clear, colorless solutions identical in appearance and texture. The blinded syringe will be labeled according to Health Canada requirements including the randomization number, and provided to the site investigator for injection. Patients who are enrolled but not randomized are considered a screen failure. Once a patient has been randomized, study drug should be administered, and dosing should occur as soon as possible after randomization. Every effort should be made to minimize any delays from enrollment to randomization, and from randomization to dosing.

3.3 Blinding and Unblinding

This is a double-blind study in which the identity of a patient's treatment will be unknown to the patient and the study personnel involved in the administration of study drug, evaluation of AEs and all other study outcomes.

There are no expected clinical situations in which unblinding of treatment allocation is anticipated to become necessary. The active drug, Factor VIIa, has a short half-life of approximately 2 hours. Any major complications are thought to be due to the active mechanism of the drug as a procoagulant molecule. Treatment of any subsequent arterial or venous thrombosis will follow the clinical standard of care. The ability to provide aggressive treatment (i.e. thrombolytic or antiocoagulant therapy) will be substantially attenuated by the underlying disease under consideration in this trial, i.e. intracerebral hemorrhage.

As unexpected events occur, the following unblinding policy has been established:

Unblinding will be possible for all participants in the trial. If a site requires unblinding, the site PI or local treating physician will call the study's Medical Monitor. Discussion of the case will ensue during which time the medical monitor will ascertain if there are any reasons to unblind. If it is agreed that unblinding is necessary, the local site PI will request that the local dispensing team provides the information. Date, time, reasons for unblinding and signature will be documented every time a blind is broken.

4. STUDY TREATMENT

4.1 Description of Investigational Product

NiaStase RT® (Recombinant activated coagulation factor VIIa - room temperature formulation) is the active comparator in this trial. Recombinant activated coagulation factor VII, rFVIIa, (NiaStase®, NovoSeven®; Novo Nordisk, Denmark) has been used worldwide for years as a treatment for life-

threatening hemorrhage, and is approved in Canada and U.S. for the treatment of spontaneous and surgical bleeding in patients with hemophilia A or B and inhibitors to factors VIII or IX.[39] Coagulation factor VII is a naturally occurring initiator of hemostasis. Recombinant (r)FVIIa is functionally identical to naturally occurring FVIIa, binding to the surface of activated platelets where it generates activated Factor X allowing partial restoration of platelet surface thrombin generation.[40] Through its action of enhancing local hemostasis after binding to exposed tissue factors, rFVIIa is an effective initiator and amplifier of hemostasis in patients with normal coagulation.[37-41] It promotes hemostasis in central nervous system bleeding in patients with hemophilia.[42] With a relatively low frequency of systemic activation of coagulation, *rapid action at the site of bleeding, and a short half-life of 2.5 hours*, rFVIIa is an ideal agent for acute ICH.[43]

4.2 Dosage and Administration

The 80 μg/kg dose of rFVIIa chosen for this study is justified based on extensive preclinical testing, testing for non-stroke medical indications, dose-escalation ICH trials, and phase II and phase III RCTs in ICH.[10,11,14,44] There is consensus among the Steering Committee that 80 μg/kg is the most appropriate dose, providing the best balance of efficacy and safety according to previous studies. Consultation with other experts concludes that this dose carries an acceptable safety profile as a therapy for ICH, especially for patients with a spot sign. A lower dose arm was considered but rejected because it offers less chance of efficacy and inclusion of a third randomization arm would not be feasible based on patient recruitment projections and budgetary considerations. The maximum dose per patient to be used in this study is 10 mg (corresponding to a maximum patient weight of 125 kg or 275 lbs). Sites will use locally available product. Reconstitution and administration should be performed using the following procedures (as per the NiaStase RT® Product Monograph dated March 18, 2010). Always use aseptic technique.

Reconstitution

For detailed instructions on how to reconstitute NiaStase RT® refer to PART III of the Product Monograph. NiaStase RT® powder and histidine solvent vials should be at room temperature at reconstitution. If not at room temperature, hold vials to bring contents to room temperature. The specified volume of diluents corresponding to the amount of NiaStase RT® is as follows:

Vial Size (mg)	Volume of Histidine Diluent to be Added to Vial (mL)	Concentration of rFVIIa After reconstitution (mg per mL)
1.0	1.1	1.0
2.0	2.1	1.0
5.0	5.2	1.0

Administration

Administration should take place immediately. If not used immediately after reconstitution, the vial may be stored at room temperature (below 30°C) or refrigerated for up to 3 hours. Any unused solution should be discarded. Do not freeze reconstituted NiaStase RT® or store in syringes. NiaStase RT® is intended for intravenous bolus injection only and should not be mixed with infusion solutions or be given in a drip. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever the solution and container permit. Do not use if particulate matter or discolouration is observed. Remove and discard the transfer needle from the syringe; attach a suitable intravenous injection needle and administer over 2 minutes. For detailed instructions on how to administer NiaStase RT® refer to PART III of the Product Monograph.

Storage
Prior to reconstitution, keep NiaStase RT® powder and the histidine solvent refrigerated or store between 2° to 30°C. Do not freeze. Protect powder and solvent from light. Do not use past the expiration date.

4.3 Drug Safety

Over 800 ICH patients have received rFVIIa in RCTs. The main safety concern is its prothrombotic potential, i.e., arterial (myocardial infarction, ischemic stroke) or venous (deep venous thrombosis, pulmonary embolism) thrombotic events. In the published phase IIb trial there was no difference in the overall rate of thromboembolic events between groups (7% in the rFVIIa groups vs. 2% in the placebo group, p=0.12) but there was an excess of arterial thrombotic events with rFVIIa vs. placebo (5% vs. 0%, p=0.01).[10] These included 7 myocardial ischemic events and 9 cerebral infarctions within 4 days of dosing. In the phase III trial, 293 patients were in the 80 µg/kg rFVIIa group. Safety data are available from the published paper of investigator-reported events[11] and a retrospective blinded DSMB review of all ECGs and centrally-measured troponin levels.[33] There was no difference in the rates of venous thromboembolic events between rFVIIa and placebo. There was an increased incidence of arterial thromboembolic events in patients receiving 80 µg/kg rFVIIa vs. placebo. The frequency of myocardial infarction was 12.1% (rFVIIa) vs. 6.4% (placebo), p=0.015. These consisted of ST-elevation myocardial infarctions (2.0% rFVIIa vs. 1.5% placebo) and non-ST-elevation myocardial infarctions (10.1% rFVIIa vs. 4.9% placebo). The rate of "biochemical events" (isolated troponin leak) was 9.4% (rFVIIa) vs. 8.6% (placebo). Most cardiac events were considered to have "minor clinical impact". The rate of ischemic stroke was 6% (rFVIIa) vs. 3% (placebo), although there was no difference in the rate of ischemic stroke events considered possibly related to study drug (2.7% vs. 2.6%). Other thromboembolic events occurred in 2.0% (rFVIIa) vs. 1.8% (placebo) and included renal artery thrombosis, intracardiac thrombus, retinal artery embolism, and thrombophlebitis. Risk factors for thromboembolic events identified in the phase III trial included advanced age, preadmission antiplatelet therapy, and signs of acute ischemia on baseline ECG or head CT. *Overall, the potential risks of rFVIIa are relatively small when compared to the much greater risks of death and disability due to (untreated) ICH itself.* Nevertheless, the potential risks further underscore the need for conducting a much more focused trial like the present proposal with stricter selection criteria than previous studies to maximize the benefit/risk ratio (see Section 5.13 for safety monitoring details).

4.4 Standardized Blood Pressure Protocol

Blood pressure (BP) control in acute ICH is highly variable in practice and may influence ICH outcomes. Previous rFVIIa trials did not standardize BP. In this study, a standardized BP protocol is to be followed (see Appendix B) to minimize confounding influences of hypertension and antihypertensive drug use. An intuitive potential benefit of BP reduction is attenuation of ICH growth, and a pilot study suggested a clinical benefit of BP reduction in acute ICH.[48]. The protocol aims to achieve a target systolic BP <180 mmHg using bolus doses of IV enalapril, labetalol and/or hydralazine, which are familiar to stroke clinicians and have been used safely in acute ICH.[31] BP and heart rate will be closely monitored, and drugs/dosages will be recorded.

Elevated BP is common in acute ICH and patients with higher BP at presentation have elevated early mortality rates. Some multivariate analyses indicate a strong correlation between elevated systolic BP and subsequent ICH expansion, and acute BP reduction has been associated with a decreased incidence of expansion in some studies.[49] An MRI study provides evidence that edema in acute ICH is plasma-derived.[50] It has been hypothesized that reduction of BP, and subsequently of capillary hydrostatic pressures, may decrease edema formation as a result of altered Starling forces around the hematoma. Some physicians are reluctant to aggressively reduce BP in the acute phase predicated on a belief that

there is a zone of ischemia surrounding the acute hematoma, despite a lack of evidence of for this in many MRI and CT perfusion studies. In the absence of evidence favouring either treatment strategy, physicians have been forced to make empirical decisions, and clinical practice reflects this uncertainty. Therefore, based on current guidelines, this study specifies a conservative systolic BP target of <180 mmHg for this study. Although any BP treatment target will be associated with controversy, the potential interaction with ICH expansion necessitates a standardized management protocol be included in the study design.

5. ASSESSMENTS

The schedule of assessments is provided in Appendix A. The anticipated duration of patient participation is 1 year. The primary study endpoint is ICH volume on the 24 hour CT scan. The primary clinical endpoint is measured at the 90 day follow-up. All assessments are performed in-person, except the 30-day follow-up is allowed to be done by telephone. The investigator should delegate neither the dosing nor the assessments which affect the inclusion/exclusion criteria to other study staff.

5.1 Baseline Assessment

At the baseline (pre-treatment) assessment, patients will be assessed for eligibility and the following information will be collected in the CRF: patient demographics, medical history, pre-admission and concomitant medications, neurological examination, physical examination, GCS score, pre-stroke mRS score, ECG, blood work (creatinine, CBC, INR, PTT, troponin, CK, CK-MB, BUN), vital signs, CT scan, CTA scan, ICH volume calculation, spot sign characteristics, intraventricular hemorrhage rating, stroke onset time, hospital arrival time, scan times. Women of childbearing potential will have a pregnancy test performed. Women of childbearing potential and males must confirm double barrier contraception for the first 90 days after dosing]. Concomitant medications and adverse event information will be collected and documented throughout the visit.

5.2 Randomization/Dosing

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized and will receive a bolus injection of the study drug over a 2 minute period. Within 5 minutes before dosing, the NIHSS will be scored. Vital signs will be recorded at the time of dosing or within 5 minutes before dosing. The time of dosing will trigger the blood pressure protocol to begin (see Appendix B).

5.3 Immediate Post-Dose Follow Up

Immediately (+ 15 minutes) after study drug administration, a repeat CT head scan will be obtained to assess for early ICH expansion. GCS and NIHSS assessments will be done within 15 minutes following this CT scan.

5.4 24 Hour Follow Up

At 24 hours (+/- 3 hours) post-dosing, a repeat plain CT head scan, vital signs, ECG, bloodwork (creatinine, BUN, troponin, CK, CK-MB) will be obtained. The following clinical assessments will be obtained within a target of +/- 2 hours of the CT scan: GCS, NIHSS, and AE assessment. A brief questionnaire will be administered to the participant or LAR (approximately 15-30 minutes in duration) about the consent process used in this trial (see section 5.12) within 4 days, and again at approximately 90 days.

5.5 Day 2, 3, 4 Follow Up

On days 2 (48 hours +/- 6 hours post-dose), 3 (72 hours +/- 6 hours post-dose) and 4 (96 hours +/- 6 hours post-dose), the following assessments will be made: vital signs, creatinine, BUN, troponin, CK, CK-MB, ECG, updated concomitant medications, and AE assessment. Also on day 4, the GCS, NIHSS and mRS will be assessed.

5.6 Day of Discharge Follow Up

If the day of discharge is on a day other than day 4, a separate AE assessment will be made. Also on the day of discharge, information will be documented regarding patient disposition and interventions such as the hospital stay, ICU admissions, rehabilitation services, any neurosurgical interventions, intubation and ventilator use. Concomitant medications will be updated.

5.7 Day 30 Follow Up (may be in person or by telephone)

On day 30 (+/- 7 days) days post-dosing, the following assessments will be made: mRS, Barthel Index and AE assessment. Updates to patient disposition, interventions and concomitant medications will be documented. The day 30 visit may be done by telephone or in-person.

5.8 Day 90 Follow Up

At 90 days (+/- 7 days) post-dosing, the following assessments will be made: NIHSS, mRS, Barthel Index, MoCA, Stroke Impact Scale, EQ-5D, consent questionnaire, CES-D depression scale, clinical brain MRI scan, AE assessment, and updates to patient disposition, concomitant medications and interventions will be documented. To facilitate scheduling the 90 day clinical brain MRI scan may be scheduled on a different day +/- 30 days of the 90 day follow up visit date. Subjects who had a 25% or more increase in baseline creatinine within 72 hours of the baseline imaging will have their creatinine and BUN measured. The day 90 follow up visit should be done in-person.

5.9 1 Year Follow Up

At 1 year (+/- 14 days) post-dosing, the following assessments will be made: NIHSS, mRS, Barthel Index, MoCA, Stroke Impact Scale, EQ-5D and CES-D depression scale. Updates to patient disposition, concomitant medications and interventions will be documented

The 1 year follow up visit should be done in person.

5.10 Clinical Scales (Neurological Impairment, Disability and Quality of Life)

a) Modified Rankin Scale (mRS)
The modified Rankin scale (see Appendix C) a clinician-reported measure of global disability, is a standard disability outcome in stroke trials. It is predominantly a physical disability, mobility and ambulation index ranging from 0 (no symptoms) to 1 (symptoms; no disability), 2 (mild disability), 3 (moderate disability; independent), 4 (dependent), 5 (severe disability, bedridden, incontinent), 6 (death). Certification for the mRS will be required every 2 years.

b) Glasgow Coma Scale (GCS)
The Glasgow Coma Scale (see Appendix D) is a neurological scale to assess the level of consciousness.

c) NIH Stroke Scale (NIHSS)
The NIH Stroke Scale (see Appendix E) is a standard neurological deficit rating scale for acute stroke. It will document impairments (e.g. hemiparesis, aphasia, neglect) and overall stroke severity and facilitate comparison with other trials. Certification for the NIHSS will be required every 2 years.

d) Barthel Index
The Barthel Index (see Appendix F) is a widely used 100-point scale assessing level of assistance stroke patients require in activities of daily living.

e) Montreal Cognitive Assessment (MoCA)
The Montreal Cognitive Assessment (see Appendix G) is a bedside cognitive test battery developed in Canada and available in 26 languages.[58].The NINDS-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards recommends MoCA as the test of choice for brief assessments.[59] It is preferred over others (e.g. Folstein MMSE) that are less sensitive to executive dysfunction and mild memory impairment. It takes about 10 minutes to administer. The maximum score is 30 points. Given that ICH is a major cause of cognitive impairment and dementia (and previous rFVIIa trials did not measure cognition), it is important to assess cognition as an outcome in this study.

f) Stroke Impact Scale (SIS)
The Stroke Impact Scale (see Appendix H) is a stroke-specific assessment that evaluates quality of life dimensions (emotion, communication, memory, social participation).[60,61]

g) European Quality of Life Scale EQ-5D
The EQ-5D (see Appendix I) is a standardized instrument for use as a measure of health outcomes. It includes measures of mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

h) Center for Epidemiologic Studies Depression Scale (CES-D)
The CES-D (see Appendix J) is a 20-item instrument developed by NIMH to detect major or clinical depression, and is recommended by the NINDS-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards. [59]

5.11 Laboratory Evaluations / Specimen Collection

Standard Laboratory tests will be obtained. At the baseline visit the following will be measured: CBC, INR, PTT, serum creatinine, BUN, troponin, CK, CK-MB. At the 24 hour and days 2, 3 and 4 follow up visits the following will be measured: troponin, CK, CK-MB, creatinine, BUN. Patients who had a 25% or more increase in baseline creatinine within 72 hours of baseline imaging will have their creatinine and BUN measured again at day 90.

5.12 Waiver of Consent Evaluation

A structured consent questionnaire will probe patient and family attitudes regarding consent and acceptability regarding the use of a waiver of consent for study randomization and treatment. This will be offered to patients or LAR of patients who are enrolled in SPOTLIGHT, and also to patients or LAR of patients who qualify for SPOTLIGHT but do not consent to participate.

The questionnaire will be administered within approximately 4 days. The duration will be approximately 15-30 minutes. The questionnaire will be administered again after approximately 90 days of the original visit.

5.13 Safety Assessments

Safety assessments consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs). In developing this protocol, we have consulted with cardiologists and other expert clinicians and have been extra-cautious in addressing the safety aspects. Our strict eligibility criteria aim to exclude patients at elevated risk for cardiac or other thromboembolic complications. Clinical safety assessments, ECG, troponin, CK and CK-MB will be obtained daily for 4 days post-treatment to monitor for adverse events possibly related to study drug. Four days is an appropriate timeframe given the very short duration of study drug exposure (single dose, short half-life) and ongoing or long-term risks beyond 4 days are not expected. Serum creatinine on days 1, 2, 3, 4 and 90 will monitor for nephropathy following contrast CTA. Each site is advised to appoint a local emergency room physician as a sub-investigator to facilitate smooth implementation of the protocol including arrangements for enrolling physicians to obtain real-time consultation on baseline ECG interpretation from a staff emergency physician prior to subject randomization. If there is any suspicion of a cardiac AE/SAE, the site investigator is encouraged to obtain a clinical cardiology consultation and 2D echocardiogram.

The relationship of adverse events to study drug will be defined as probable, possible, or unlikely. Options for "definite" and "unrelated" will not be available to the investigator on the CRF, as the investigator will be blinded. Because there is only a single dose, there is a short half-life of approximately 2 hours, and there will be no difference in treatment for adverse events between arms, it is expected that the investigator will not require unblinding. See section 3.3. Outcomes will be rated as: recovered, recovering, recovered with sequelae, or fatal. The clinical importance of events will be rated. Detailed AE/SAE reporting procedures will be outlined in the study's procedure manual and a summary is provided in section 7. Sites will be required to report all fatal events, unanticipated problems and other SAEs to the Coordinating Centre within 24 hours and reportable AEs within 5 days. Site PIs are responsible for promptly informing their local REB of SAEs. All events will be independently reviewed by an Adjudication Committee (see Section 9.1.6).

6 SAFETY OUTCOMES

Primary

- Composite endpoint: Rate of myocardial infarction within 4 days post-dose, ischemic stroke within 4 days post-dose, or pulmonary embolism within 4 days post-dose

Secondary

- Unstable angina within 4 days
- Troponin rise above upper limit of normal within 4 days (without clinical symptoms or ECG evidence of acute coronary syndrome)
- Transient ischemic attack within 4 days
- Deep venous thrombosis (DVT) within 4 days
- Pulmonary embolism (PE) within 30 days
- Any other arterial or venous thromboembolic SAEs within 4 days (detailed in the operations manual)
- 90-day mortality
- Acute nephropathy, defined as a 25% or more increase in baseline creatinine within 72 hours of contrast administration [38]

7 ADVERSE EVENTS

7.1 Adverse Events and Adverse Drug Reactions

An adverse event is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. AEs include those reported spontaneously by the subject and those noted incidentally or as observed by the investigator or study personnel.

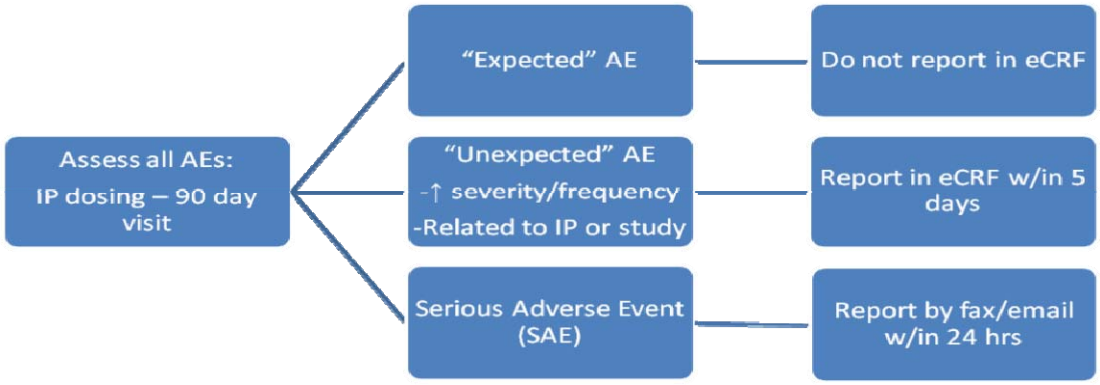
Study staff will assess all adverse events that occur during the period from dosing up to and including the day 90 follow up visit and document these in the source. Investigators will evaluate any changes in laboratory values and physical symptoms/signs and will determine if the change is clinically important and different from what is expected in the course of treatment for patients being treated for ICH. If clinically important and unexpected adverse experiences occur, they will be recorded in the CRF.

Expected Adverse Events
Expected adverse events are untoward clinical occurrences that are perceived by the investigator to occur with reasonable frequency in the day to day care of patients being treated for ICH. Adverse events that are expected in the course of this study may include (but are not limited to) headache, vomiting, seizure, cerebral edema, hydrocephalus, impaired consciousness, pneumonia, and urinary tract infection. These events will not be considered reportable adverse events unless the event is considered by the investigator to be associated with the study drug or procedures, or unexpectedly severe or frequent for an individual patient being treated for ICH or are of a Grade 3, 4 or 5 as defined by the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

Reportable Adverse Events
Reportable adverse events will be those AEs which are considered by the Investigator to be unexpected or of greater severity than expected or of greater frequency than usually found in the day to day care of patients being treated for ICH. Additionally, any AE that in the opinion of the Investigator is probably or possibly related to the investigational product or study procedures will be reported. As well, AEs of a grade 3, 4 or 5 severity as defined by the CTCAE version 4.0 are considered reportable.

Reportable AEs must be reported to the coordinating centre (i.e. entered into the eCRF) within 5 days of becoming aware of the event.

Figure 1. Schematic of AE Reporting Procedures



7.2 Serious Adverse Events (SAEs) and Serious Adverse Drug Reactions (SADRs)

A Serious Adverse Event is defined as any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or prolongation of an existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Medical and scientific judgment should be exercised in deciding whether other conditions should also be considered serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above. These should also be considered serious. Follow up information regarding SAEs will be pursued until the event has resolved (with or without sequelae), until death, or until 30 days after the 90 day visit (whichever comes first.), as drug related events are not expected to occur after this period of time given the short half-life of the rFVIIa. For any deaths where there is uncertainty about the cause of death, site investigators may request an autopsy if appropriate.

7.2.1 Reporting Serious Adverse Events (SAE)

Any SAE, including death due to any cause, which occurs between dosing and the 90 day follow up visit whether or not related to the study drug, must be reported immediately (within 24 hours of the study site's knowledge of the event) by email or fax to the SPOTLIGHT Coordinating Centre. The report will contain as much available information concerning the SAE to enable the Coordinating Centre to file a report that satisfies regulatory reporting requirements. Criteria for documenting the relationship to study drug as well as severity and outcome will be the same as those previously described. Additionally**,** any arterial or venous thromboembolic event and/or death occurring within 30 days of dosing will be reported as an SAE.

Definitions of Thromboembolic Serious Adverse Events (SAE) of Special Interest

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 embolism (PE)
   Clinically suspected and confirmed by contrast-enhanced CT (CTPA) as a constant intraluminal filling defect in one or segmental or larger pulmonary arteries or by high probability ventilation/perfusion (V/Q) lung scan (defined as one or more segmental mismatched defect). If the largest filling defect on CTPA is at the subsegmental level or if a V/Q scan is abnormal but not high probability, these results are considered nondiagnostic. Proven fatal pulmonary embolism: death with autopsy proven major PE that was the likely direct or indirect cause of death. Possible fatal pulmonary embolism: sudden death in a patient with no autopsy in whom there is no more likely alternate diagnosis.

4. Deep venous thrombosis (DVT)
   Clinically suspected and confirmed by positive result on Doppler ultrasound in a proximal deep leg vein (popliteal, femoral or iliac) [symptomatic proximal DVT] or clinically suspected and confirmed by positive result on Doppler ultrasound in a deep leg vein (posterior tibial, peroneal, popliteal, femoral, or iliac) [symptomatic calf DVT]

5. Myocardial damage with enzyme leak, defined as a troponin rise without ECG changes from baseline or clinical evidence to suggest myocardial dysfunction.

6. Other arterial or venous thromboembolic SAEs (please refer to the study's operations manual for a complete list).

7.2.2 Recording of AEs and SAEs

Reportable AEs and SAEs will be recorded in the electronic case report form (eCRF) and in the source documents. To avoid vague, ambiguous, or colloquial expressions, the AE should be recorded using standard medical terminology that is as specific as possible, rather than the subject's own words. Whenever the investigator is confident in making a unifying diagnosis, all related signs, symptoms, and abnormal test results should be grouped together and recorded as a single AE (e.g. cough and rhinitis may be reported as an "upper respiratory tract infection"). Each AE is to be evaluated for duration, severity, seriousness and causal relationship to the investigational drug and the outcome of the AE will be assessed.

Severity

The severity of the AE will be graded according to the CTCAE Version 4.0 guidelines:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

Drug-Event Relationship

The causal relationship between the study drug and the AE should be characterized according to the following:

– Unlikely – suggests that only a remote connection exists between the study drug and the event. Other conditions, including concurrent illness, progression or expression of the disease state or reaction to concomitant medication, appear to explain the AE.

- Possible – suggests that the association of the AE with the study drug is unknown, however the event is not reasonably supported by other conditions.
- Probable – suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator's clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and other conditions (concurrent illness, progression or expression of the disease state, or concomitant medication reactions) do not appear to explain the AE.

Outcome

The outcome of the adverse event should be classified according to the following definitions:

- Recovered / resolved: the event has resolved (no further symptoms are present and no treatment is being received by the subject)
- Recovered / resolved with sequelae: the event has resolved but there may be lingering effects present (e.g., a scar following a cut or abrasion).
- Recovering: the event may have resolved, the patient is returning to health
- Fatal: the subject died as a result of the event. This code should only be used for the event that caused the death, not any event that was present at the time of the subject's death. Fatal events require immediate reporting to the Sponsor (or an authorized representative).
- Unknown: may only be used in the event that the subject is lost to follow-up and no reliable data can be obtained.

All efforts should be made to classify the AE according to the above categories.

7.2.3 Follow-up of AEs and SAEs

All AEs and SAEs occurring during the study are to be followed up in accordance with good medical practice until resolved, judged no longer clinically significant, study completion, or if a chronic condition, until fully characterized. All follow-up results are to be recorded in the CRF as necessary. The outcome of any pregnancies occurring during the first 90 days of the study will be followed until the birth of the child and the child will be followed until one month of life.

7.2.4 Reporting of Serious Unexpected Adverse Drug Reactions (SUADRs)

The PI (or an authorized representative) is responsible for submitting reports of SUADRs to Health Canada within the required reporting period. All investigators participating in ongoing clinical studies with the study drug will be notified by the Coordinating Centre (or an authorized representative) of all SUADRs that require prompt submission to the REB/IRB. Investigators are responsible for notifying the REB/IRBs in writing of the SUADRs within the required reporting timelines. Copies of the notification will be maintained by the investigator in the study documentation files. Sites will receive detailed reporting guidelines for the SAE reporting process.

8. STATISTICAL METHODS

8.1 Sample Size

Sample size calculations are based on data from the ongoing PREDICT study regarding the expected baseline and 24-hour ICH volumes in spot-sign positive patients. The standard deviation of ICH volume at 24 hours is about 41 ml. Since all data to date indicate that rFVIIa reduces bleeding and does not increase bleeding, calculations are based on a one-sided Type I error chance of 5%. We believe a 20 ml

difference in final ICH volume between groups would be highly clinically significant based on the literature, and we wish to have 80% power to detect this difference. With a 1:1 allocation ratio, a sample size of 53 rFVIIa and 53 placebo patients is required.

8.2 Details of Statistical Analysis

Baseline characteristics will be summarized by descriptive statistics as appropriate (mean and SD for continuous variables; frequencies and percentages for categorical variables).

The primary outcome of ICH growth within 24 hours will be compared between the 2 treatment groups by analyzing the final ICH volume on CT scan at 24 hours, adjusting for baseline ICH volume, by means of linear regression. The 24 hour ICH volume will be summarized for each group by descriptive statistics and the adjusted treatment effect and 95% confidence interval will be obtained from the regression model. Although absolute change or percent change in ICH volume between baseline and 24 hours has been the traditional method of analysis in prior studies, the proposed approach is more methodologically sound.[62] However, change and percent change will be summarized with descriptive statistics to allow comparison with other studies. Similar analyses will be performed for intraventricular hemorrhage volume and total volume (ICH plus intraventricular hemorrhage). We will calculate the minimum clinically important difference for ICH growth, adjusted for baseline ICH volume and anatomical location.

The feasibility parameters will be analyzed using descriptive statistics with the aim of determining if the spot sign can be assessed and treatment begun within an acceptable time period to conduct a larger trial of clinical outcomes. We expect the trained enrolling physicians will accurately interpret the presence of a spot sign in this trial, and we will carefully assess any spot signs that were over-called (i.e. false positives) compared to blinded over-read by the "gold standard" study neuroradiologist. Qualitative analysis of the waiver of consent questionnaire will examine feasibility and acceptability of a consent waiver for future trials. We will describe the characteristics of patients enrolled with a waiver and compare their median treatment times (and ICH volumes) with those enrolled with standard consent.

The frequency of adverse events will be compared between the treatment groups. Since the sample is small and adverse events are not expected to be common, expected frequencies (under the assumption of no difference) may be too low for chi-square tests, so Fisher's exact test will be employed. For safety, stopping rules have been developed based on data from the phase III trial demonstrating a 12% rate of myocardial infarction associated with 80 μg/kg rFVIIa (see below).

8.3 Imaging Analyses

De-identified CT and CTA images will be transferred to the Imaging Core Labs for central blinded interpretation. ICH size will be calculated by volumetric analysis. We will assess ICH location, intraventricular hemorrhage volume, edema volume, presence of hydrocephalus, mass effect, spot sign patterns (number, morphology) and score. Segmented volumes are obtained 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. The operator places seed-points within the volume of interest and adjusts lower and upper intensity HU thresholds until the entire volume is correctly selected. Where ICH volume cannot be differentiated from intraventricular hemorrhage volume, the operator uses freehand drawing tools to remove intraventricular hemorrhage. In this situation, intraventricular hemorrhage volume will be determined using the original over-segmented volume that includes the combined ICH and intraventricular hemorrhage volumes, V_{total}, as intraventricular hemorrhage volume =

V_{total} - ICH. This limitation is unavoidable as intraventricular hemorrhage has the same density as ICH and the 2 volumes are often contiguous. The volume (ml), mean (HU), standard deviation (HU) and the affected part(s) of the brain will be measured from the segmented volume. CT data will be transferred to a research PACS system and analyzed on a personal workstation using Quantomo software developed at University of Calgary. User-selected parameters used to segment the volumes (i.e., seed-points, HU intensity thresholds) 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 be saved in XML files. Statistical analysis will be performed off-line using the data collected in XML files. We will also collect MRI scans for blinded centralized volumetric analysis at the Sunnybrook Brain Imaging Analysis Laboratory.[63-64] As our sites typically obtain MRI as part of clinical routine for ICH survivors, we will not mandate MRI as a study-related investigation (to minimize budget), but will acquire these scans by a standardized protocol at day 90 to allow tissue segmentation. MRI analysis will yield regional tissue compartment volumes, including white matter disease (which may affect outcomes), residual lesion volumes and microhemorrhages [63-64]

8.4 Frequency of Statistical Analysis and Stopping Rules

Myocardial infarction, ischemic stroke, pulmonary embolism and all thromboembolic SAEs will be monitored on a continuous basis by the DSMB, which includes an unblinded statistician.

The medical monitor will review all SAEs and provide adjudicated reports to the DSMB. The DSMB will review and assess each SAE against the suggested stopping rules that are detailed in the DSMB charter.

8.5 Planned Subgroup Analyses

We will assess treatment in subgroups based on onset-to-treatment time (<3 vs. >3 hours); baseline ICH volume (<30 vs. >30 ml); anatomical location (deep vs. lobar); intraventricular hemorrhage (present vs. absent, and by Graeb score); spot sign score (1-2 vs. 3-4)[27] and morphological pattern,[13] and presence or absence of contrast leakage on post-contrast head CT performed as part of the baseline CT angiogram.[65]

8.6 Planned Pooled Analysis

A pooled analysis is planned with other similar trials, including the STOP-IT study based at the University of Cincinnati that received NIH (NINDS) funding and FDA approval and plans to begin recruitment in 2010, and STOP-AUST, an Australian trial that is proposed. SPOTLIGHT and these other studies will run independently as separate trials. The Executive Steering Committees of these studies have collaborated on a harmonized core study protocol to enable a future pooled analysis after completion of each study. The benefits of pooling individual patient data from small RCTs have been exemplified by other key stroke trials (e.g. hemicraniectomy, carotid endarterectomy). A pooled analysis will enable analyses of clinical efficacy. The proportion of patients in each group achieving a 90-day modified Rankin score 5-6 (death or severe disability) will be compared in an adjusted analysis. A generalized linear mixed model with log-link will assess the relative risk of poor outcome in the two groups, adjusting for site, age, baseline ICH volume, treatment times, intraventricular hemorrhage, Glasgow Coma score, and pre-stroke Rankin score. Similar analyses will be performed for mortality and the other clinical scales. A shift analysis across the full range of mRS scores will be performed using the methodology of

Saver to estimate the number of patients needed to treat for 1 additional patient to improve by 1 or more levels of disability on the mRS.[66]

9. TRIAL MANAGEMENT

9.1 Study Group Members

A list of study group members will be maintained and stored at the Coordinating Centre.

9.1.1 Coordinating Centre

The Study Headquarters is Sunnybrook Health Sciences Centre, University of Toronto. The SPOTLIGHT Coordinating and Data Management Centre is located in the Applied Health Research Centre (AHRC), Li Ka Shing Knowledge Institute of St. Michael's Hospital (www.stmichaelshospital.com/research), University of Toronto. This comprehensive clinical trials unit employs expert project management staff and uses state of the art, secure, encrypted, web-based data management software (Medidata RAVE™) with sophisticated data validation rules. The Coordinating Centre will be responsible for developing and programming the electronic CRFs, trial procedure manual, data monitoring, regulatory documents, data management and analysis, and providing progress and data reports to the Executive Steering Committee, DSMB, Health Canada and participating sites.

9.1.2 DSMB

The DSMB will provide oversight and monitoring of the conduct of the trial to ensure safety of participants and validity and integrity of the data. A Charter will outline roles, responsibilities and processes to be followed. The DSMB is an independent group not otherwise associated in any way with the trial, and will make ongoing recommendations concerning the continuation, modification and termination of the trial.

9.1.3 Executive Steering Committee

An advisory committee, has advised in the study planning and protocol development, and will provide ongoing direction during the course of the study.

9.1.4 Steering Committee

The Steering Committee consists of members of the Executive Committee and the Coordinating Centre, plus site PIs from each participating centre, and expert external advisors.

9.1.5 Imaging Core Labs

The Imaging Core Lab for all the CT analyses is at the Seaman Family MR Research Centre, University of Calgary, under the direction of Dr. Andrew Demchuk. All CTA spot sign analyses will be performed by Dr. Richard Aviv at Sunnybrook Health Sciences Centre in Toronto. MRI scans will be analyzed at Sunnybrook Health Sciences Centre under the direction of Dr. Sandra Black.

9.1.6 Adjudication Committee

A Medical Monitor will independently review all SAEs in real time and submit opinions to the PIs and DSMB regarding the relationship of events to study drug. A blinded Neuroradiologist will independently adjudicate the imaging aspects of suspected cerebrovascular SAEs.

9.1.7 Ethics Committee

The Ethics Committee will review the enrolment of every incapacitated patient for whom a waiver of consent has been used, and report to the DSMB, Steering Committee, and local REBs. The committee will be chaired by the trial ethicist, Dr. Julie Spence, an emergency physician at the University of Toronto, and a former Chair of the St. Michael's Hospital Research Ethics Board.

9.2 Research Ethics Board/Institutional Review Board

A copy of the protocol (including protocol amendments), all versions of informed consent forms, other information to be completed by participants such as survey instruments or questionnaires, and any proposed advertising/ recruitment materials must be reviewed and approved by the REB/IRB of each participating centre prior to implementation of the trial. The investigator will be responsible for obtaining REB/IRB approval and annual Continuing Review throughout the duration of the study.

9.3 Early Termination

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified, and without penalty or loss of benefits to which the subject is otherwise entitled. Study patients will be informed of the possibility to withdraw consent without giving any reason. Subjects may be withdrawn for specific reasons during the study, which include: ineligibility, non-compliance or for administrative reasons (including study closure). Before a subject is declared lost to follow-up, all efforts should have been made to contact the patient for a final assessment.

9.4 Monitoring

Annual monitoring visits will be conducted at each site by a member(s) of the SPOTLIGHT Coordinating Centre to inspect all study related documentation and records, including, but not limited to, study data, patient medical records, and source documents.

9.5 Source Documents and Access to Source Data/Documents

Each participating site must maintain appropriate medical and research records for this trial and regulatory/institutional requirements for the protection of confidentiality of study subjects. Source documentation should support the data collected on the CRF. The Principal Investigator is responsible for assuring that the data collected are complete, accurate, and recorded in a timely manner. Access to the source documentation will be as per regulatory/institutional guidelines.

9.6 Data Management

Electronic data capture (Medidata RAVE™) will be used for this trial, meaning that all study data will be entered in electronic forms (eCRF) at the investigational site. Data collection will be completed by authorized study site personnel designated by the Investigator. Appropriate training and security measures

will be completed with the Investigator and all authorized study site personnel prior to the study being initiated and any data being entered into the system for any study subjects.

The study data will be housed on a secure in-house server at St. Michael's Hospital in Toronto throughout the duration of study, and up to 10 years after the study is complete. A copy of the tabulated raw study data will be stored at Sunnybrook Health Sciences Centre for 25 years after completion of the study.

9.7 Participant Confidentiality

All subject related information including Case Report Forms, evaluation forms, reports, etc. will be kept strictly confidential. All records will be kept in a secure, locked location and only research staff will have access to the records. Subjects will be identified only by means of a coded number specific to each subject. All computerized databases will identify subjects by numeric codes only, and will be password protected.

9.8 Disclosure and Publication Policy

The study will be registered on clinicaltrials.gov after REB approval is obtained from at least one site. Study results will be published upon completion of the study, and authorship will be in line with ICMJE guidelines.

10 INFORMED CONSENT PROCESS

This study is predicated on the ability to provide ultra-rapid study drug administration, as rFVIIa is a highly time-sensitive treatment. Given the time constraints necessary for this emergency treatment protocol and the nature of ICH (many potential participants are expected to be incapacitated during the hyperacute phase of a spot-sign positive ICH), obtaining timely prospective fully informed consent prior to enrolment is not feasible. Family members or representatives may or may not be present at the moment the CT scan diagnosis of ICH is made. Even if present, they may have difficulty understanding and appreciating the full Informed Consent Form. Thus, this study is designed to streamline consent procedures to allow eligible participants the opportunity to be treated as quickly as possible to maximize the benefit/risk ratio of this study protocol. Any delay to study drug administration is expected to significantly diminish, or even negate, the potential benefits of rFVIIa.

Therefore, a two-phase consent process is proposed. A short summary form has been developed and will be used to seek *assent* for randomization and study drug administration from a patient with capacity to consent and/or the patient's legally authorized representative (LAR). The full consent document will subsequently be reviewed with either the patient or the patient's LAR at the earliest possible time, to ensure that all research-related questions are addressed. Both the assent and consent documents are signed and copies are provided to the patient or LAR.

However, because ICH patients are frequently incapacitated and LAR consent may not be possible to obtain immediately, a waiver of informed consent option has been developed for this study to enable enrolment of eligible patients without delay. In Canada, there is REB allowance to approve a consent waiver in emergency situations when patient consent is not possible and a LAR is not immediately available. Ethical justification to waive informed consent prior to study-related procedures is provided below in accordance with the criteria of the Tri-Council Policy Statement for ethical conduct of research in emergency health situations (Article 2.8). [67] These criteria are similar to U.S. federal regulations that

allow emergency consent to be conducted without informed consent; in contrast to U.S. regulations, community consultation is not mandated in Canada.

10.1 Justification for the Use of a Waiver of Consent in the Emergency Health Situation (Tri-Council Policy Statement Article 2.8)

1. A serious threat to the prospective subject requires immediate intervention.

As outlined in the protocol, acute ICH is a life-threatening emergency that requires immediate management (40% 30-day mortality; half of deaths occurring within 48 hours). Bleeding may increase minute by minute, and the majority of ICH expansion occurs very early. [1] Therefore, treatment to stop active bleeding must be applied as soon as possible. Delaying study drug administration to obtain consent is expected to significantly diminish, or even negate, the potential benefits of rFVIIa, and may potentially expose patients to unnecessary harm if patients are treated late (after intracerebral bleeding has stopped). Indeed, the failure of other acute stroke trials to demonstrate efficacy may in some cases relate directly to the fact that study drug was administered too late. [68]

2. Either no standard efficacious care exists, or the research offers a real possibility of direct benefit to the subject in comparison with standard care.

At present, there are no specific acute medical or surgical treatments for ICH that are approved or have proven efficacious in a randomized trial. The published phase IIb and phase III rFVIIa trials suggest the first real possibility of direct benefit to patients compared to standard care alone. According to post-hoc analysis of the phase III trial, a subgroup that derived significant clinical benefit from rFVIIa consisted of patients who could be treated very quickly (within 2.5 hours of stroke onset), aged ≤70 years, with baseline ICH size ≤60 ml and intraventricular hemorrhage volume ≤5 ml.[11] While encouraging, we estimate that such results would only apply to a minority (<7%) of ICH patients who meet these criteria (data on file, Registry of the Canadian Stroke Network, May 2008). Our approach (using image-guided patient selection with the CTA spot sign) offers a way to potentially help many more patients.

3. Either the risk of harm is not greater than that involved in standard efficacious care, or it is clearly justified by the direct benefits to the subject.

rFVIIa in the ICH population is associated with an increased incidence of arterial thromboembolic complications (the major risks are myocardial infarction and ischemic stroke). With the 80 μg/kg dose, the potential risks are offset by a realistic chance of benefit for patients who otherwise have very high morbidity and mortality (i.e. spot sign positive patients). Our trial design and strict eligibility criteria aim to minimize harm by excluding patients at elevated risk for adverse events and those unlikely to respond to hemostatic therapy (i.e. spot sign negative patients). Careful clinical and laboratory monitoring for potential thromboembolic adverse events is an essential component of this study. Indeed, we expect that using a waiver of consent to expedite treatment may maximize the benefit/risk ratio of rFVIIa. In some centres, rFVIIa is already being used "off-label" for ICH, which may expose some patients to potential risk without expected benefit if active bleeding has already stopped. In this study, hemostatic therapy is being tailored to individual patients in a rational way. By stratifying patients according to CTA findings, spot-sign negative patients in this study (who are not at high risk for ICH expansion) would not be enrolled. With respect to CT angiography, this is already a widely used diagnostic test for patients with acute ICH because it provides information about treatable pathologies (e.g. aneurysm, arteriovenous malformation, etc.). Early identification of unsuspected secondary causes of ICH may have an important impact on subsequent patient care. Many ICH patients undergo CT angiography at some point during their hospitalization; in this study CT angiography is simply being performed as part of the initial assessment. Intravenous contrast may be associated with nephrotoxicity or allergic reaction, but these are uncommon; patients with known renal disease are excluded and we will monitor for renal toxicity.

4. The prospective subject is unconscious or lacks capacity to understand risks, methods, and purposes of the research.

In all but those with the smallest hemorrhages, ICH patients are rendered incapable of making informed decisions in the acute stage due to altered level of consciousness or cognitive impairment (e.g., aphasia, anosognosia). Because most stroke patients are rendered acutely incompetent to make personal medical decisions by their stroke (ischemic or ICH), restricting enrolment only to patients who are fully alert, cooperative, and capable to provide consent is not feasible. Without a waiver option, there will be an obvious selection bias (according to who is able to provide consent), which undermines the study's external validity, i.e. skewed toward patients with milder ICH and failing to represent those with moderate and severe ICH. For our study results to have true generaliazability, we must enroll a representative sample of patients. The ethical principle of justice may be considered to be violated if experimental therapies can only be offered to selected patients. Waiver of consent suspends the principle of autonomy in favour of the principle of justice: unless such patients can be studied, effective treatments for future similar patients will never be advanced.

5. Third-party authorization cannot be secured in sufficient time, despite diligent and documented efforts to do so.

In the emergency setting associated with ultra-early treatment of ICH, LARs may not be immediately available at the time of the baseline imaging. Without a waiver of consent option, these patients would be excluded from the study or included after significant delay.. Based on experience from another emergency stroke trial (IMS study), we estimate a LAR may not be present in about 20-25% of eligible candidates.

6. No relevant prior directive by the subject is known to exist.

If advance directives are available, either in writing or from a LAR, the treating physician will be responsible for informing the study team of only those patients who are potentially eligible for study enrolment.

10.2 Description of Proposed Consent Procedures

There are 3 versions of the consent form:

- Document A: Brief Study Summary/Informed Consent Form for participants and/or LAR from whom two-staged *assent-consent* will be sought prior to enrolment
- Document B: Long version of the Information Sheet/Informed Consent Form to be used after enrolment as a follow-up to Document A
- Document C: Letter of Information/Informed Consent Form for continued participation in the study for participants who are enrolled with a waiver of consent.

There are two possible routes for study enrolment:

- *Assent-Consent*

  For eligible patients who have capacity to consent or for eligible incapacitated patients with a Legally Authorized Representative (LAR) present, a short study summary (Document A) will be presented in addition to the full consent form. A consent discussion based on the study summary will take place and *assent* for randomization and study drug administration will be sought. If the LAR is not present but can be reached by telephone, then telephone assent-consent from the LAR will be permitted to enable enrolment without delay. After study drug administration, full informed consent will then be sought from the patient or LAR using the more detailed, longer version information sheet and consent form (Document B).
- *Waiver of Consent*

In the event that assent-consent cannot be obtained (i.e. for eligible patients who are incapacitated and for whom a LAR is not immediately available), a waiver of consent will be invoked to enable randomization and study drug administration without delay. An additional screening form for potential contraindications to rFVIIa must be completed for those who are considered for enrolment with waived consent. After study drug administration, every effort must be made by the investigator to promptly identify and contact the LAR to provide full explanation of the study and seek informed consent for continued study participation using Document C.

Additional Eligibility Screening Requirement for Incapacitated Patients with No LAR

If an incapacitated participant appears to be a good study candidate and there is no LAR available in person or by telephone, then a waiver of consent option may be invoked by the investigator. In this situation, the investigator must first determine eligibility by obtaining information about the participant's past medical history from all available sources, i.e. medical information should be sought from the patient, paramedics, electronic medical records, medic alert card/bracelet, primary care physician or other physicians, etc., and inferred from the patient's medication list, physical examination findings, and laboratory tests, with particular emphasis on identifying any exclusions to study participation. A second physician will confirm subject incapacity.

If any of the following additional features are present, in addition to the exclusion criteria listed above, the patient is not eligible for enrolment using a waiver of consent.

- Preadmission medications: ASA plus clopidogrel
- Preadmission medication: warfarin
- Known hospital admission or emergency department visit (for any reason) within past 3 months
- Physical examination findings to suggest previous stroke (chronic neurological deficits), cardiac surgery (sternotomy scar), carotid endarterectomy (neck incision), recent stenting/catherization procedure (femoral or radial artery puncture)

Procedures for Obtaining Patient Consent After Enrolment

In all cases, informed consent from the patient must be actively pursued by the investigator after daily assessments to determine if the previously incapacitated patient has regained capacity. If the patient is discharged or leaves the hospital prior to patient or LAR contact, attempts will be made using registered letter and documented phone calls weekly for a minimum of 28 days post-discharge. When the patient regains capacity, the investigator will inform him/her about enrolment in the study and will seek consent for continued participation. Despite LAR consent, the investigator must continue to seek informed consent from the patient for continuation in the study. In the event that capacity is regained, patient consent supersedes the authority of the consent provided by the LAR.

Investigators are advised to use the CURVES method of Chow et al. to assess and document capacity (see Appendix K).[67]

All processes for obtaining consent must be in compliance with local sites' REB guidelines. All participants or LAR will be given detailed oral and written information about the trial. Consent forms describing in detail the study intervention, study procedures and risks will be given to each participant or LAR. All participants or LAR must sign informed consent document B or C that have been approved by a participating centre's REB. Participants or LAR may withdraw consent at any time during the course of the trial. The informed consent form will be signed and dated by the participant or LAR and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the participant's study files and a copy of the signed form will be provided to the participant or LAR.

Please see Figure 2 for a schematic of the consent procedures.

Waived Consent for CT Angiography

CTA is a widely used diagnostic test for patients with ICH because it provides information about treatable pathologies (e.g. aneurysm, arteriovenous malformation, etc.). Early identification of unsuspected secondary causes of ICH may have an important impact on subsequent patient care. As such, many ICH patients undergo CTA at some point during their hospitalization. In this study CTA is being performed as part of the initial assessment, ideally within the first half-hour of arrival at the emergency department. When performed acutely, CTA also provides important prognostic information for patient care based on the presence and characteristics of a spot sign(s).[12,28] The 2010 American Heart Association Guideline on Management of Intracerebral Hemorrhage recommends CTA: "CT angiography and contrast-enhanced CT may be considered to help identify patients at risk for hematoma expansion (Class IIb; Level of Evidence: B), and CT angiography,…contrast-enhanced CT,…can be useful to evaluate for underlying structural lesions, including vascular malformations and tumors when there is clinical or radiological suspicion (Class IIa; Level of Evidence: B)".[30]

All of the stroke centres selected as participating sites in this trial already perform CTA as part of standard clinical care for many patients with ICH. The emergency use of CTA for acute ICH assessment is becoming a leading practice at designated stroke centres. Many, but not all, of the participating Canadian sites in this trial already routinely obtain CTA acutely as part of standard clinical care for "code stroke" cases in the emergency department, including acute ICH and acute ischemic stroke.

Therefore, for sites that are already performing CTA acutely as part of their standard clinical care acute stroke imaging protocols, consent for participation in this trial will be sought following CTA. For sites that are not already routinely performing acute CTA as standard clinical care for ICH, site REB approval for a waiver of consent policy for CTA is requested to enable CTA to be performed without delay for ICH patients who are potential study candidates after passing the Quick Screening Checklist for Eligibility. Consent for study enrollment for eligible patients will then be sought after CTA has been completed.

Local radiology protocols at each site are to be followed for excluding patients with known contraindications to CTA, i.e. known allergy to iodinated contrast dye, known renal insufficiency or creatinine clearance <30 ml/min), and administration of a low-osmolar or iso-osmolar contrast agent (e.g. Visipaque) for patients whose serum creatinine is not known prior to scanning or creatinine clearance is 30-60 ml/min.[34,35,38] Site PIs will be responsible for preparing a written standard operating procedure specific to their site in conjunction with their local site neuroradiologist co-investigator to describe the local criteria/contraindications for CTA.

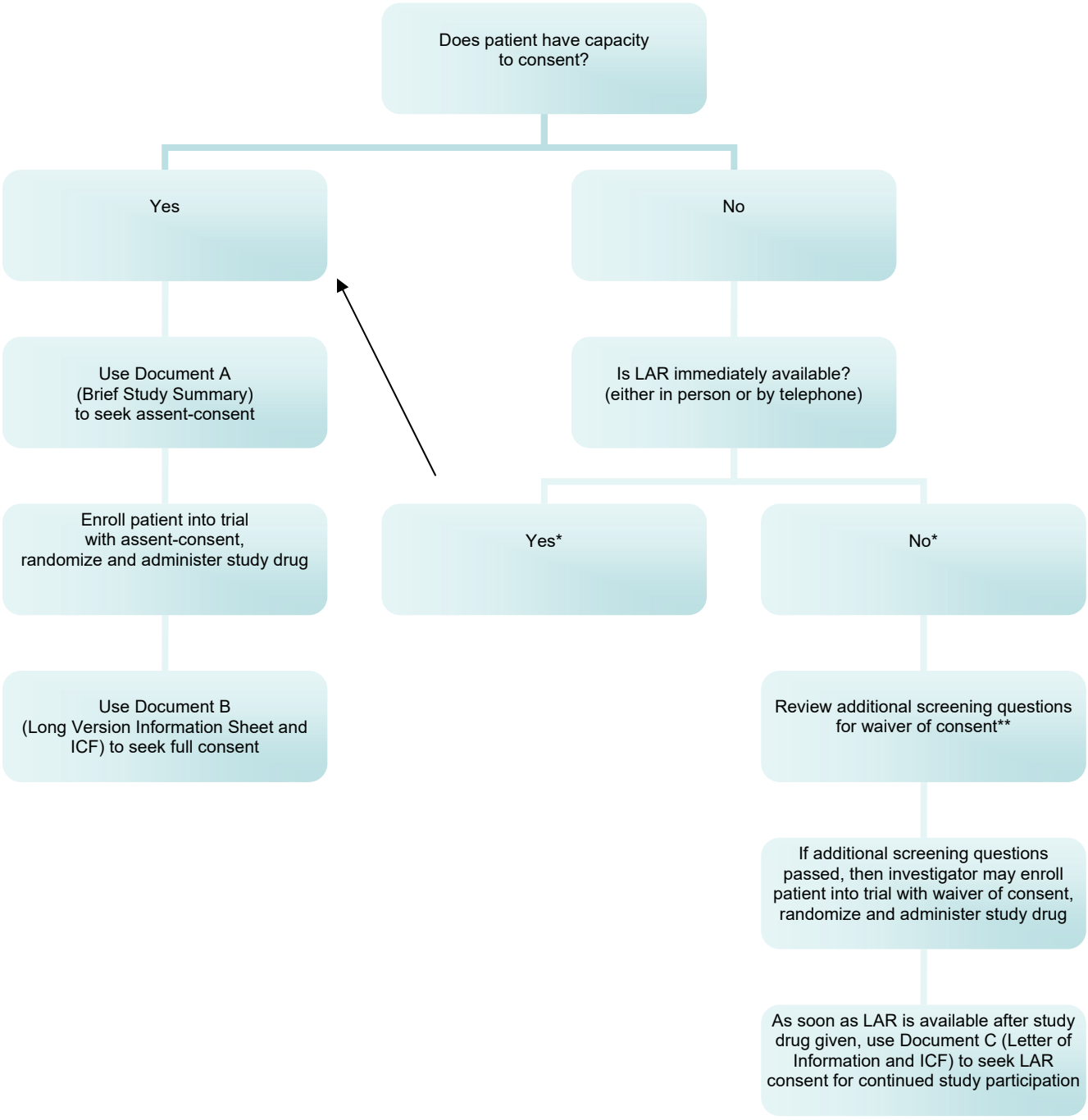
A serum creatinine value should ideally be obtained prior to CTA. However, turnaround time for stat blood work at sites is variable and serum creatinine measurement is frequently waived in the emergency situation. The European Society of Urogenital Radiology guideline states that "in emergency situations serum creatinine measurement can be waived". [36] If a baseline serum creatinine result is not available at the time of the proposed CTA, the investigator should check for any available previous creatinine levels or documentation of renal insufficiency in the patient's electronic medical record, and assess for risk factors for renal failure (see the list below). In the absence of a recent creatinine value, it will be up to the investigator's judgment to proceed with CTA or not based on the individual patient profile and situation. According to the Canadian Association of Radiologists, "the absence of risk factors [see below] for renal disease effectively eliminates the likelihood of a patient having renal impairment" and states that "delays whilst awaiting serum creatinine results may adversely affect patient care".[38] They recommend the use of iso-osmolar or low-osmolar agents rather than high osmolar agents, plus fluid administration, e.g. intravenous normal saline (0.9% NaCl) 1 ml/kg/h for 12 hours post-CTA.[38]

Screening for Contraindications to CT Angiography

According to the Canadian Association of Radiologists Consensus Guidelines for the Prevention of Contrast Induced Nephropathy, patients should be screened for the following risk factors for renal impairment or development of contrast-induced nephropathy:

- Diabetes mellitus
- Renal disease or solitary kidney
- Sepsis or acute hypotension
- Dehydration or volume contraction
- Age >70 years
- Previous chemotherapy
- Organ transplant
- Cardiovascular disease (hypertension, congestive heart disease, cardiac or peripheral vascular disease)
- Nephrotoxic drugs (loop diuretics, amphotericin B, aminoglycosides, vancomycin, non-steroidal anti-inflammatory drugs, cancer and immune suppressant chemotherapy)
- HIV or AIDS

Figure 2. Schematic of Consent Procedures



* For all incapacitated patients who are enrolled, the investigator must do daily reassessments of patient capacity, and seek patient consent with Document C if/when patient regains capacity
** See protocol

References

1. 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):1-5.
2. Leira R, Davalos A, Silva Y, Gil-Peralta A, Tejada J, Garcia M, Castillo J. Early neurologic deterioration in intracerebral hemorrhage: predictors and associated factors. *Neurology* 2004 August 10;63(3):461-7
3. Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, Begtrup K, Steiner T. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology* 2006 April 25;66(8):1175-81.
4. Flaherty ML, Haverbusch M, Sekar P, Kissela B, Kleindorfer D, Moomaw CJ, Sauerbeck L, Schneider A, Broderick JP, Woo D. Long-term mortality after intracerebral hemorrhage. *Neurology* 2006 April 25;66(8):1182-6
5. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage: incidence and time course. *Stroke* 1996;27(10):1783-7.
6. Fujii Y, Takeuchi S, Sasaki O, Minakawa T, Tanaka R. Multivariate analysis of predictors of hematoma enlargement in spontaneous intracerebral hemorrhage. *Stroke* 1998;29(6):1160-6.
7. Cheung RT. Predictors of hematoma growth? Stroke 29[11], 2442-2443. 1998.
8. Gladstone D, Rodan LH, Fang J, Linday P, Hill MD, Silver FL, Kapral MK. Incidence and outcomes of warfarin-associated intracerebral hemorrhage compared to spontaneous intracerebral hemorrhage in a prospective stroke registry. (submitted)
9. Kissela B, Schneider A, Kleindorfer D, Khoury J, Miller R, Alwell K, Woo D, Szaflarski J, Gebel J, Moomaw C, Pancioli A, Jauch E, Shukla R, Broderick J. Stroke in a biracial population: the excess burden of stroke among blacks. *Stroke* 2004 February;35(2):426-31.
10. 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. *New England Journal of Medicine* 2005;352:777-85.
11. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2008;358(20):2127-37.
12. 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 April;38(4):1257-62.
13. Thompson AL, Kosior JC, Gladstone DJ, Hopyan JJ, Symons SP, Romero F, Dzialowski I, Roy J, Demchuk AM, Aviv RI. Defining the CT angiography 'spot sign' in primary intracerebral hemorrhage. *Can J Neurol Sci* 2009 July;36(4):456-61.
14. Mayer SA, Brun NC, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T. Safety and feasibility of recombinant factor VIIa for acute intracerebral hemorrhage. *Stroke* 2005 January;36(1):74-9.
15. Yamaki T, Yoshino E, Higuchi T. Extravasation of contrast medium during both computed tomography and cerebral angiography. *Surg Neurol* 1983;19(3):247-50.
16. Yamamoto T, Muraki M, Oishi H, Uemura K. [Contrast-enhanced MRI of hypertensive intracerebral hemorrhage in the peracute stage--extravasation of contrast medium as detector of growing hematoma]. *Nippon Rinsho* 1993;51 Suppl:48-54.
17. Wolpert SM, Schatzki SC. Extravasation of contrast material in the intracerebral basal ganglia. *Radiology* 1972;102(1):83-5.
18. Huckman MS, Weinberg PE, Kim KS, Davis DO. Angiographic and clinico-pathologic correlates in basal ganglionic hemorrhage. *Radiology* 1970;95(1):79-92.

19. 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(10):2025-32.
20. Kowada M, Yamaguchi K, Matsuoka S, Ito Z. Extravasation of angiographic contrast material in hypertensive intracerebral hemorrhage. *J Neurosurg* 1972;36(4):471-3.
21. 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(4):650-5.
22. Yamaguchi K, Uemura K, Takahashi H, Kowada M, Kutsuzawa T. [Extravasation of contrast media in hypertensive cerebral hemorrhage]. *Rinsho Hoshasen* 1972;17(4):257-63.
23. Gazzola S, Aviv RI, Gladstone DJ, Mallia G, Li V, Fox AJ, Symons SP. Vascular and nonvascular mimics of the CT angiography "spot sign" in patients with secondary intracerebral hemorrhage. *Stroke* 2008 April;39(4):1177-83.
24. 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 March 20;68(12):889-94.
25. Aviv RI, Gladstone D, Goldstein J, Flaherty M, Broderick J, Demchuk A. Contrast extravasation predicts hematoma growth: where to now? *AJNR Am J Neuroradiol* 2008.
26. Kim J, Smith A, Hemphill JC, III, Smith WS, Lu Y, Dillon WP, Wintermark M. Contrast extravasation on CT predicts mortality in primary intracerebral hemorrhage. *AJNR Am J Neuroradiol* 2008 March;29(3):520-5.
27. Delgado Almandoz JE, Yoo AJ, Stone MJ, Schaefer PW, Goldstein JN, Rosand J, Oleinik A, Lev MH, Gonzalez RG, Romero JM. Systematic characterization of the computed tomography angiography spot sign in primary intracerebral hemorrhage identifies patients at highest risk for hematoma expansion: the spot sign score. *Stroke* 2009 September;40(9):2994-3000.
28. Delgado Almandoz JE, Yoo AJ, Stone MJ, Schaefer PW, Oleinik A, Brouwers HB, Goldstein JN, Rosand J, Lev MH, Gonzalez RG, Romero JM. The spot sign score in primary intracerebral hemorrhage identifies patients at highest risk of in-hospital mortality and poor outcome among survivors. *Stroke*. 2010 Jan;41(1):54-60. Epub 2009 Nov 12.
29. Yeung R, Ahmad T, Aviv RI, de Tilly LN, Fox AJ, Symons SP. Comparison of CTA to DSA in determining the etiology of spontaneous ICH. *Can J Neurol Sci* 2009 March;36(2):176-80.
30. Morgenstern LB, Hemphill JC 3rd, Anderson C, Becker K, Broderick JP, Connolly ES Jr, Greenberg SM, Huang JN, Macdonald RL, Messé SR, Mitchell PH, Selim M, Tamargo RJ; on behalf of the American Heart Association Stroke Council and Council on Cardiovascular Nursing. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage. A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2010 Jul 22. [Epub ahead of print]
31. Dowlatshahi D, Smith EE, Flaherty M, Ali M, Lyden P, Demchuk A, VISTA collaborators. Small intracerebral hemorrhages are associated with less hematoma expansion and better outcomes. (submitted)
32. Demchuk A, Kosior J, Tymchuk S, Molina C, Dzialowski I, Boulanger J-M. Multicentre prospective study demonstrates validity of CTA spot sign for hematoma expansion prediction in noncoagulopathic primary ICH patients. *Cerebrovasc Dis* 2008;25(Suppl 2):52.
33. Diringer MN, Skolnick BE, Mayer SA, Steiner T, Davis SM, Brun NC, Broderick JP. Thromboembolic events with rFVIIa in spontaenous ICH: results from the FAST trial. (manuscript under review)
34. 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 August;38(8):2364-6.
35. Hopyan JJ, Gladstone DJ, Mallia G, Schiff J, Fox AJ, Symons SP, Buck BH, Black SE, Aviv RI. Renal safety of CT angiography and perfusion imaging in the emergency evaluation of acute stroke. *AJNR Am J Neuroradiol* 2008 November;29(10):1826-30.

36. Tomsen HS, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR). In which patients should serum creatinine be measured before iodinated contrast medium administration? Eur Radiol 2005; 15: 749-754
37. American College of Radiology. Manual on Contrast Media. http://www.acr.org/secondarymainmenucategories/quality_safety/contrast_manual.aspx
38. Benko A, Fraser-Hill M, Magner P, Capusten B, Barrett B, Myers A, Owen RJ. Canadian Association of Radiologists: consensus guidelines for the prevention of contrast-induced nephropathy. *Can Assoc Radiol J* 2007 April;58(2):79-87.
39. Hedner U. Recombinant activated factor VII as a universal haemostatic agent. *Blood Coagul Fibrinolysis* 1998 March;9 Suppl 1:S147-S152.
40. Hedner U, Ingerslev J. Clinical use of recombinant FVIIa (rFVIIa). *Transfus Sci* 1998 June;19(2):163-76.
41. Friederich PW, Henny CP, Messelink EJ, Geerdink MG, Keller T, Kurth KH, 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 January 18;361(9353):201-5.
42. Rice KM, Savidge GF. NovoSeven (recombinant factor VIIa) in centeral nervous systems bleeds. *Haemostasis* 1996;26 Suppl 1:131-4.
43. Fewel ME, Park P. The emerging role of recombinant-activated factor VII in neurocritical care. *Neurocrit Care* 2004;1(1):19-29.
44. Roberts HR, Monroe DM, White GC. The use of recombinant factor VIIa in the treatment of bleeding disorders. *Blood* 2004 December 15;104(13):3858-64.
45. GE Healthcare Inc.Visipaque (iodixanol) injection package insert. 2006.
46. Kazuhiro Ohwaki, et al. Blood Pressure Management in Acute Intracerebral Hemorrhage: Relationship Between Elevated Blood Pressure and Hematoma Enlargement. Stroke. 2004;35:1364-1367
47. Ken S. Butcher, Tracey Baird, Lachlan MacGregor, Patricia Desmond, Brian Tress, and Stephen Davis. Perihematomal Edema in Primary Intracerebral Hemorrhage Is Plasma Derived. Stroke. 2004;35:1879-1885
48. Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, Khoury J. The ABCs of measuring intracerebral hemorrhage volumes. *Stroke* 1996 August;27(8):1304-5.
49. Cohnen M, Wittsack HJ, 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 September;27(8):1741-5.
50. Cochran ST, Bomyea K, Sayre JW. Trends in adverse events after IV administration of contrast media. *AJR Am J Roentgenol* 2001 June;176(6):1385-8.
51. Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. *NEJM* 2007 Nov 29;357(22):2277-84
52. Smith-Bindman R, Lipson J, Marcus R, et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. *Arch Intern Med* 2009;169:2078–86
53. Bellin MF, Jakobsen JA, Tomassin I, Thomsen HS, Morcos SK, Thomsen HS, Morcos SK, Almen T, Aspelin P, Bellin MF, Clauss W, Flaten H, Grenier N, Idee JM, Jakobsen JA, Krestin GP, Stacul F, Webb JA. Contrast medium extravasation injury: guidelines for prevention and management. *Eur Radiol* 2002 November;12(11):2807-12.
54. 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 January;47(1):254-61.
55. Lima FO, Lev MH, Levy RA, Silva GS, Ebril M, de Camargo EC, Pomerantz S, Singhal AB, Greer DM, Ay H, González RG, Koroshetz WJ, Smith WS, Furie KL. Functional contrast-

enhanced CT for evaluation of acute ischemic stroke does not increase the risk of contrast-induced nephropathy. *AJNR Am J Neuroradiol.* 2010 May;31(5):817-21. Epub 2009 Dec 31.
56. Mehdiratta M, Schlaug G, Kumar S, Caplan LR, Selim M. Reducing the delay in thrombolysis: is it necessary to await the results of renal function tests before computed tomography perfusion and angiography in patients with code stroke? *J Stroke Cerebrovasc Dis*. 2008 Sep;17(5):273-5.
57. Oleinik A, Romero JM, Schwab K, Lev MH, Jhawar N, gado Almandoz JE, Smith EE, Greenberg SM, Rosand J, Goldstein JN. CT angiography for intracerebral hemorrhage does not increase risk of acute nephropathy. *Stroke* 2009 July;40(7):2393-7.
58. www.mocatest.org. Accessed Sept. 1,2009.
59. Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, Powers WJ, DeCarli C, Merino JG, Kalaria RN, Vinters HV, Holtzman DM, Rosenberg GA, Wallin A,Dichgans M, Marler JR, Leblanc GG. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. *Stroke* 2006 September;37(9):2220-41.
60. Lai SM, Perera S, Duncan PW, Bode R. Physical and social functioning after stroke: comparison of the Stroke Impact Scale and Short Form-36. *Stroke* 2003 February;34(2):488-93.
61. Duncan PW, Wallace D, Lai SM, Johnson D, Embretson S, Laster LJ. The stroke impact scale version 2.0. Evaluation of reliability, validity, and sensitivity to change. *Stroke* 1999 October;30(10):2131-40.
62. Vickers AJ, Altman DG. Statistics notes: Analysing controlled trials with baseline and follow up measurements. *BMJ* 2001 November 10;323(7321):1123-4.
63. Pettersen JA, Sathiyamoorthy G, Gao FQ, Szilagyi G, Nadkarni NK, St George-Hyslop P, Rogaeva E, Black SE. Microbleed topography, leukoaraiosis, and cognition in probable Alzheimer disease from the Sunnybrook dementia study. *Arch Neurol* 2008 June;65(6):790-5.
64. Levy-Cooperman N, Ramirez J, Lobaugh NJ, Black SE. Misclassified tissue volumes in Alzheimer disease patients with white matter hyperintensities: importance of lesion segmentation procedures for volumetric analysis. *Stroke* 2008 April;39(4):1134-41.
65. Ederies A, Demchuk A, Chia T, Gladstone DJ, Dowlatshahi D, Bendavit G, Wong K, Symons SP, Aviv RI. Postcontrast CT extravasation is associated with hematoma expansion in CTA spot negative patients. *Stroke* 2009 May;40(5):1672-6.
66. Saver JL. Novel end point analytic techniques and interpreting shifts across the entire range of outcome scales in acute stroke trials. *Stroke* 2007;38(11):3055-62.
67. Canadian Institutes of Health Research NSaERCoC, Social Sciences and Humanities Research Council of Canada. Tri-Council Policy Statement (TCPS): Ethical conduct for research involving humans, Canadian Institutes of Health Research NSaERCoC, Social Sciences and Humanities Research Council of Canada. Tri-Council Policy Statement (TCPS): Ethical conduct for research involving humans, (1998).
68. Gladstone DJ, Black SE, Hakim, SE. Toward Wisdom From Failure: Lessons From Neuroprotective Stroke Trials and New Therapeutic Directions. *Stroke* 2002;33;2123-2136

Appendix A: Schedule of Events

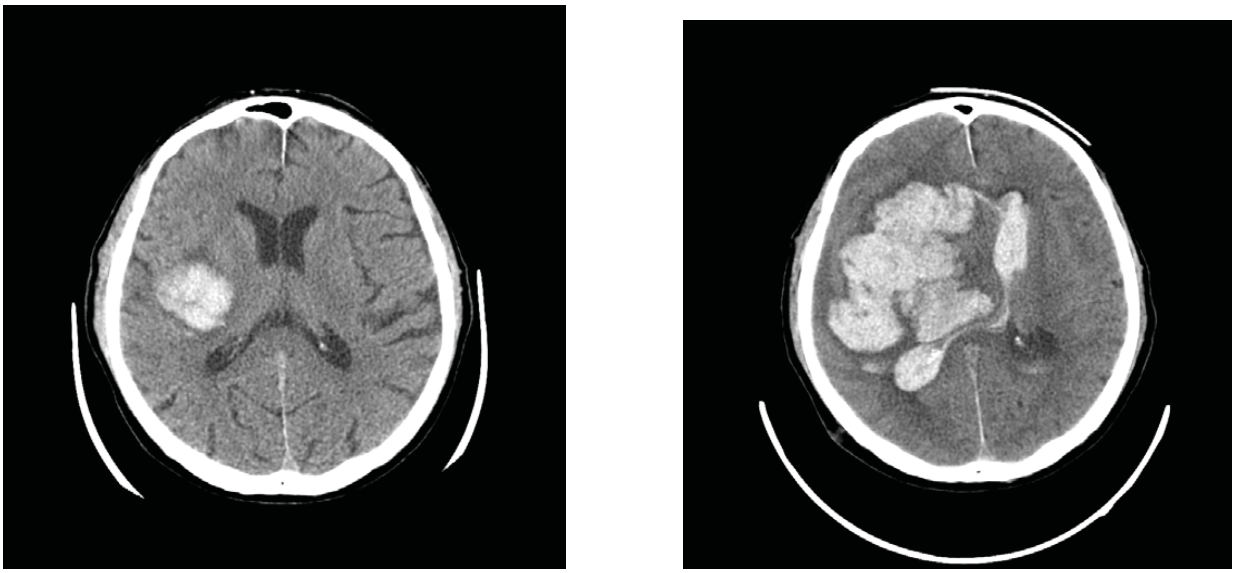
	Baseline	Immediate Post-Dose (+ 15 min)	24 hours (+/- 3 hrs)	Day 2 (48 +/- 6 hrs)	Day 3 (72 +/- 6 hrs)	Day 4 (96 +/- 6 hrs)	Day of Discharge	Day 30 (+/- 7 days)	Day 90 (+/- 7 days)	1 year (+/- 2 wks)
Consent	X									
Medical History	X									
Physical Exam	X									
Vital Signs	X	X***	X	X	X	X				
Demographic Information	X									
Creatinine	X		X	X	X	X			X**	
Pregnancy Test *	X									
CBC, INR, PTT	X									
Glasgow Coma Scale	X	X	X			X				
NIH Stroke Scale	X	X	X			X			X	X
Barthel Index								X	X	X
Modified Rankin Score	X					X		X	X	X
MoCA cognitive assessment									X	X
Stroke Impact Scale									X	X
EQ-5D									X	X
Consent Questionnaire			X						X	
CT head scan	X	X	X							
CT angiogram	X									
Clinical brain MRI									X	
Electrocardiogram	X		X	X	X	X				
Troponin, CK, CK-MB, BUN	X		X	X	X	X			X**	
Adverse Event Assessment		X	X	X	X	X	X	X	X	
Patient Disposition							X	X	X	X
Interventions							X	X	X	X
Preadmission/Concomitant Medications	X	X	X	X	X	X	X	X	X	X
CES-D									X	X

* Women of childbearing potential
** Subjects who had a 25% or more increase in baseline creatinine within 72 hours of baseline imaging will have their creatinine and BUN measured.
*** Follow blood pressure protocol per Appendix B
Note: All assessments are done in-person except the 30-day visit can be done in-person or by telephone

Appendix B: Standardized Blood Pressure Protocol to Achieve a Target Systolic BP <180 mmHg within One Hour of Randomization

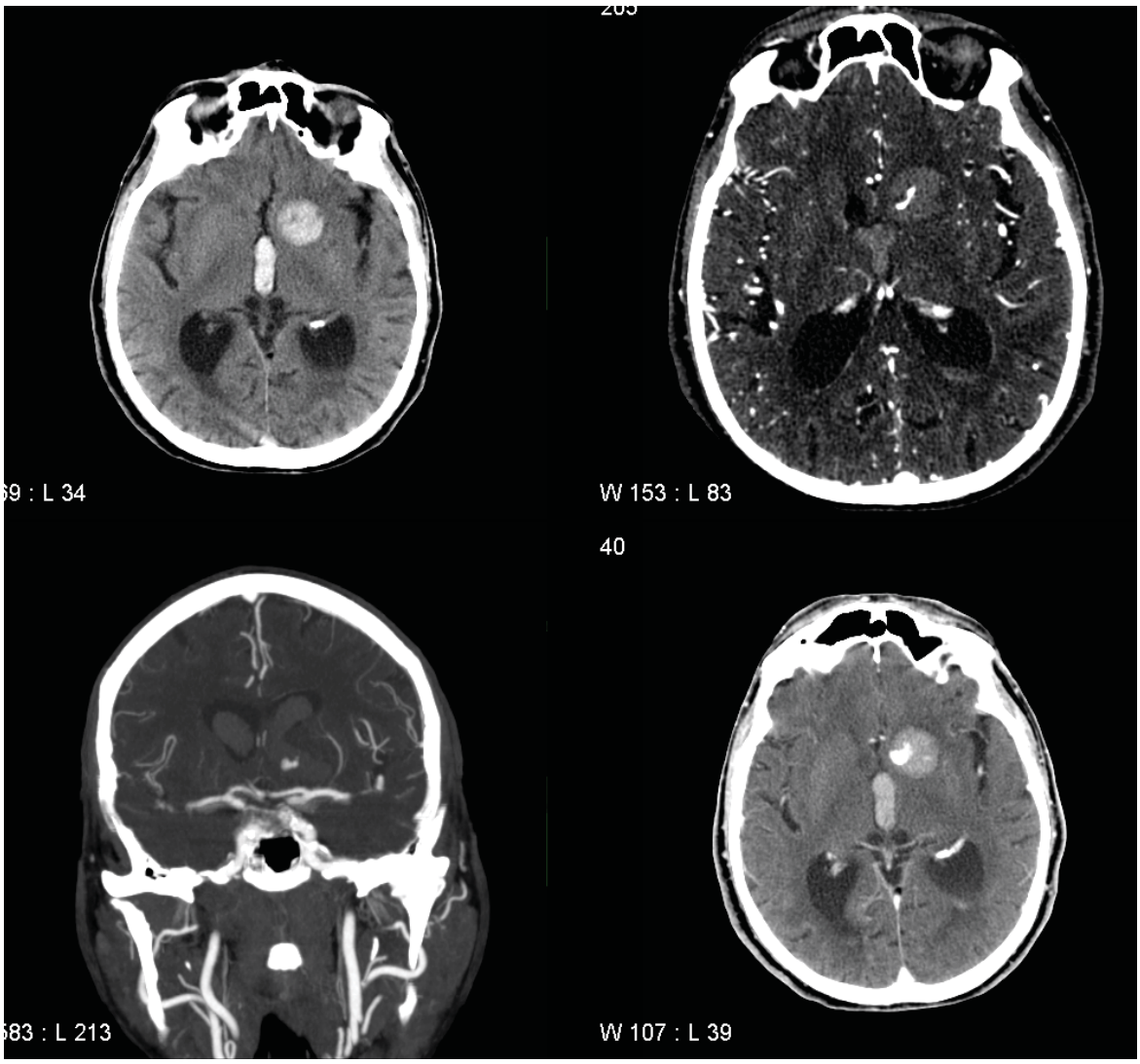
SPOTLIGHT Blood Pressure Protocol	
Target Systolic BP	Target SBP < 180 mmHg x 24 h minimum
Monitoring	● Continuous HR monitoring × 24 h minimum ● Record BP/HR q 15 min × 1 h, q 30 min × 5 h and q 1 h × 18 h
Initial Therapy	
Enalapril (IV; if available)	● Enalapril 1.25 mg bolus if initial SBP >180 mmHg
Labetalol (IV)	● Labetalol test dose: 10 mg bolus over 1 min ● If SBP ≥ 180 mmHg and HR > 55 BPM, repeat 10 mg bolus in 5 minutes. ● 10-20 mg IV push q 5 min until SBP < 180 mmHg or HR < 55 BPM ● Maximum labetalol dose: 300 mg / 24 h
Hydralazine (IV)	If BP persistently > 180 mmHg: ● Hydralazine test dose: 5 mg IV bolus over 1 min ● If SBP ≥ 180 mmHg, repeat 5 mg IV bolus in 5 min ● 10-20 mg IV bolus q 5 min until SBP < 180 mmHg ● Maximum hydralazine dose = 240 mg/24 h
Maintenance Therapy	
IV treatment prn	If SBP > 180 mmHg at any point: ● Labetalol (20 mg) / hydralazine (10–20 mg) boluses. BP and HR should then be recorded 5 and 15 minutes later ● Enalapril 1.25 mg may be repeated q 6 h if SBP >180 mmHg ● If SBP ≤ 180 mmHg or HR < 55 BPM, hold IV antihypertensives

Figure 2. Example of ICH Growth



This patient presented to the emergency department with an initially mild hemiparesis and the baseline CT scan performed at approximately 2 hours post-onset shows an acute ICH in the right basal ganglia region (left image). Within hours, the patient deteriorated neurologically, progressing to complete hemiplegia and coma requiring intubation. A repeat CT scan about 6 hours later showed massive expansion of the hematoma with intraventricular extension (right image). The patient died 48 hours later.

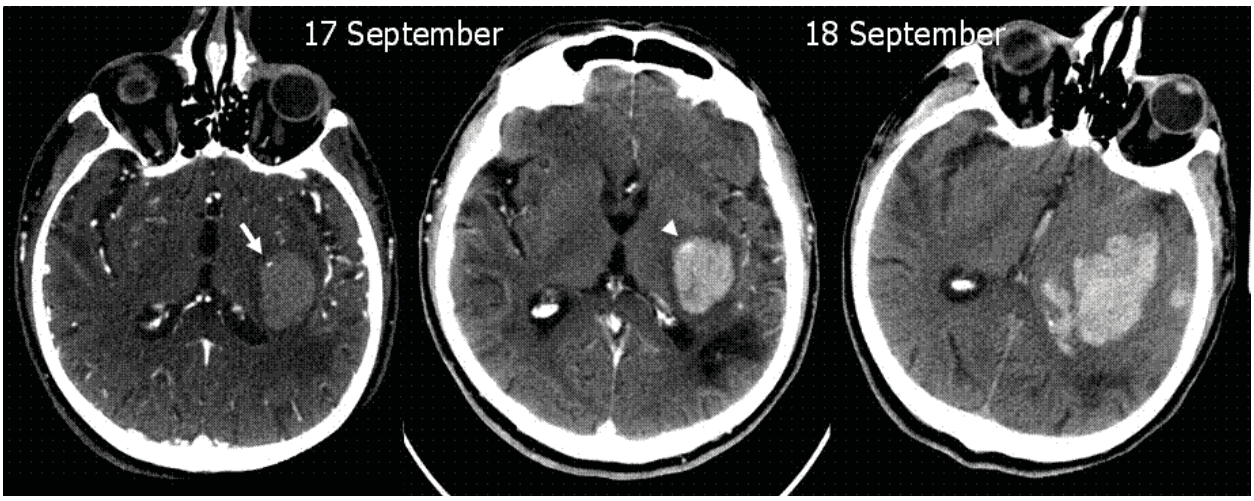
Figure 3. The CT Angiography Spot Sign



Axial non-contrast head CT scan (top left image) demonstrating a left putaminal hematoma and third ventricular hemorrhage. The axial CT angiography source images (top right image) and coronal maximum intensity projection (bottom left image) demonstrate a prominent spot sign (bright white density within the hematoma), which also shows active extravasation on post-contrast head CT scan (bright white density within the hematoma; bottom right image).

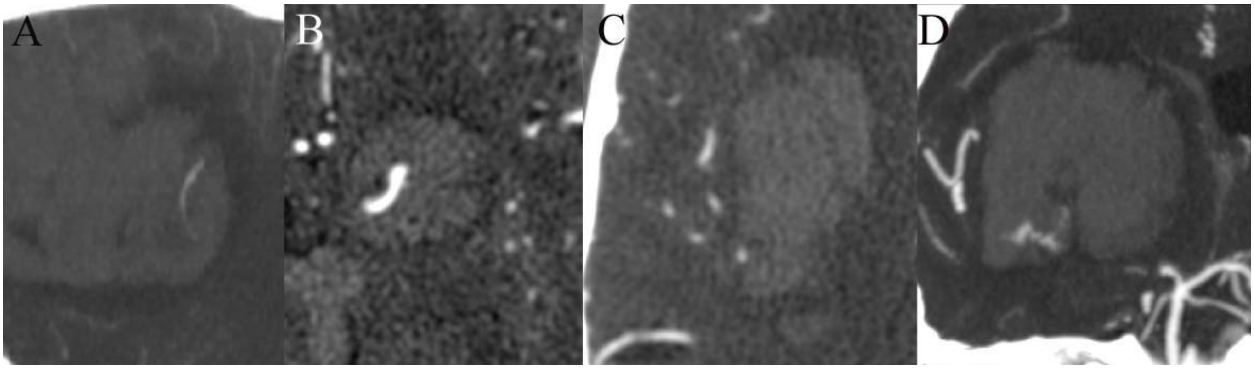
The defining criteria of a spot sign are: (1) shape: spot-like, serpiginous, or linear; (2) location: within the margin of a parenchymal hematoma without connection to an outside vessel; (3) size: >1.5 mm diameter in at least one dimension; (4) density: at least double the density (Hu) of the hematoma; (5) number: single or multiple; and (6) it is not caused by hyperdensity in same location on noncontrast CT.

Figure 4. Another Example of the CT Angiography Spot Sign



The spot sign appears as a tiny bright dot (arrow) within the larger parenchymal hematoma on the CT angiogram source image (left image). A repeat non-contrast head CT scan the next day reveals expansion of the hematoma (right) compared to the baseline volume (centre).

Figure 5. Four Different Spot Sign Patterns



CTA sagittal (a), axial (b, c) and coronal (d) images demonstrating 4 spot sign patterns. Pattern 1 – line only; pattern 2 - line and spot; pattern 3 - single spot; pattern IV -confluent branching spots and lines.

Appendix C. Modified Rankin Scale

Modified Rankin Scale[3]	Structured Interview for the Modified Rankin Scale
5=Severe disability: bedridden, incontinent, and requiring constant nursing care and attention.	5=Severe disability; someone needs to be available at all times; care may be provided by either a trained or an untrained caregiver. Question: Does the person require constant care?
4=Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance.	4=Moderately severe disability; need for assistance with some basic ADL, but not requiring constant care. Question: Is assistance essential for eating, using the toilet, daily hygiene, or walking?
3=Moderate disability; requiring some help, but able to walk without assistance.	3=Moderate disability; need for assistance with some instrumental ADL but not basic ADL. Question: Is assistance essential for preparing a simple meal, doing household chores, looking after money, shopping, or traveling locally?
2=Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance.	2=Slight disability; limitations in participation in usual social roles, but independent for ADL. Questions: Has there been a change in the person's ability to work or look after others if these were roles before stroke? Has there been a change in the person's ability to participate in previous social and leisure activities? Has the person had problems with relationships or become isolated?
1=No significant disability despite symptoms; able to carry out all usual duties and activities.	1=No significant disability; symptoms present but not other limitations. Question: Does the person have difficulty reading or writing, difficulty speaking or finding the right word, problems with balance or coordination, visual problems, numbness (face, arms, legs, hands, feet), loss of movement (face, arms, legs, hands, feet), difficulty with swallowing, or other symptom resulting from stroke?
0=No symptoms at all.	0=No symptoms at all; no limitations and no symptoms.

References

Wilson JTL, Hareendran A, Grant M, Baird T, Schulz UGR, Muir KW, Bone I "**Improving the Assessment of Outcomes in Stroke: Use of a Structured Interview to Assign Grades on the Modified Rankin Scale"** *Stroke* 2002;33;2243-2246

Appendix D. Glasgow Coma Scale

GLASGOW COMA SCALE

Patient Name: _____

Rater Name: _____

Date: _____

Activity		Score
EYE OPENING		
None	1 = Even to supra-orbital pressure	
To pain	2 = Pain from sternum/limb/supra-orbital pressure	
To speech	3 = Non-specific response, not necessarily to command	
Spontaneous	4 = Eyes open, not necessarily aware	_____
MOTOR RESPONSE		
None	1 = To any pain; limbs remain flaccid	
Extension	2 = Shoulder adducted and shoulder and forearm internally rotated	
Flexor response	3 = Withdrawal response or assumption of hemiplegic posture	
Withdrawal	4 = Arm withdraws to pain, shoulder abducts	
Localizes pain	5 = Arm attempts to remove supra-orbital/chest pressure	
Obeys commands	6 = Follows simple commands	_____
VERBAL RESPONSE		
None	1 = No verbalization of any type	
Incomprehensible	2 = Moans/groans, no speech	
Inappropriate	3 = Intelligible, no sustained sentences	
Confused	4 = Converses but confused, disoriented	
Oriented	5 = Converses and oriented	_____
		_____
	TOTAL (3–15):	

References

Teasdale G, Jennett B. "Assessment of coma and impaired consciousness. A practical scale." The Lancet 13:2(7872):81-4,1974

Appendix E. NIH Stroke Scale (NIHSS)

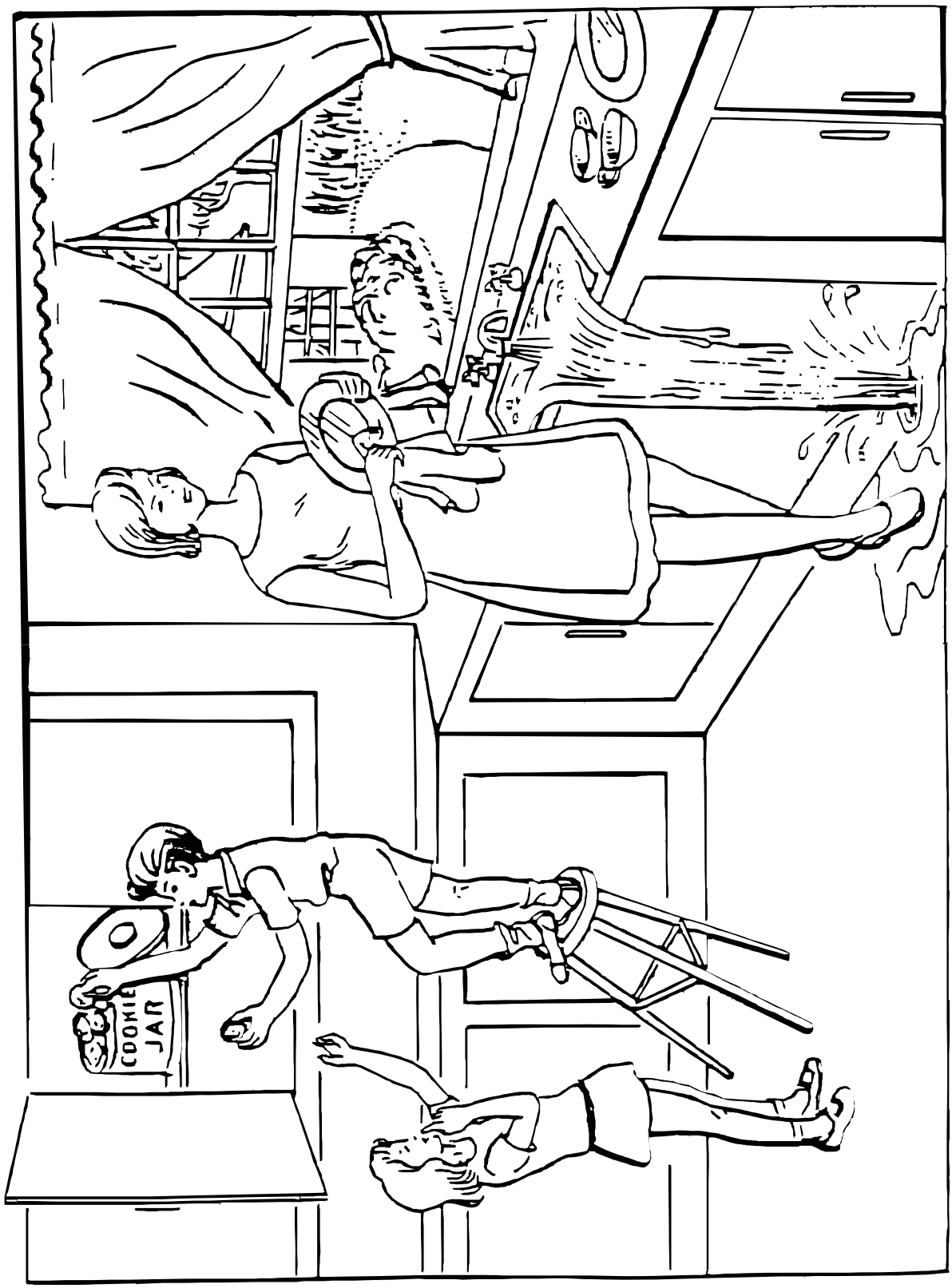
Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician 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.

NIH Stroke Scale			
NIH Stroke Scale Item	**Function**	**Scores**	**Exam**
1a. Level of Consciousness (Alert, drowsy, etc.)	Alert Drowsy Stuporous (requires repeated stimuli) Comatose (reflex responses only)	0 1 2 3	
1b. LOC Questions (Month, age)	Both Correct One correct Incorrect	0 1 2	
1c. LOC Commands (Open, close eyes, make fist, let go)	Obeys both correctly Obeys one correctly Incorrect	0 1 2	
2. Best Gaze (Eyes open – patient follow examiner's finger or face)	Normal Partial gaze palsy Forced deviation	0 1 2	
3. Visual (Introduce visual stimulus/threat to patient's visual field quadrants)	No loss Partial hemianopia Complete hemianopia Bilateral hemianopia	0 1 2 3	
4. Facial Palsy (show teeth, raise eyebrows and squeeze eyes shut)	Normal Minor asymmetry Partial (lower face paralysis) Complete	0 1 2 3	
5a. Motor Arm - Left (Elevate extremity 90° and score drift/movement)	No drift Drift Some effort against gravity No effort against gravity No movement Amputation, joint fusion	0 1 2 3 4 9	
5b. Motor Arm - Right (Elevate extremity 90° and score drift/movement)	No drift Drift Some effort against gravity No effort against gravity No movement Amputation, joint fusion	0 1 2 3 4 9	
6a. Motor Leg – Left (Elevate extremity 30° and score drift/movement)	No drift Drift Some effort against gravity No effort against gravity No movement Amputation, joint fusion	0 1 2 3 4 9	
6b. Motor Leg - Right (Elevate extremity 30° and score drift/movement)	No drift Drift Some effort against gravity No effort against gravity No movement Amputation, joint fusion	0 1 2 3 4 9	
7. Limb Ataxia (Finger-nose, heel down shin)	Absent Present in upper or lower Present in both	0 1 2	

8. Sensory (Pin prick to face, arm, trunk, and leg – compare side to side)	Normal Partial loss Dense loss	0 1 2	
9. Best Language (Name items, describe a picture and read sentences)	No aphasia Mild - moderate aphasia Severe aphasia Mute	0 1 2 3	
10. Dysarthria (Evaluate speech clarity by patient repeating listed words)	Normal articulation Mild - moderate slurring Severe, nearly unintelligible or worse	0 1 2	
11. Extinction and Inattention (Use information from prior testing to identify neglect or double simultaneous stimuli testing)	No neglect Partial neglect Profound neglect	0 1 2	
		NIH Stroke Scale TOTAL:	

The "Quick & Easy" NIHSS Authored by: Judith A. Spilker, RN, BSN, Dept. of Emergency Medicine & Laura R. Sauerbeck, RN, BSN, Dept. of Neurology University of Cincinnati


COOKIE
JAR

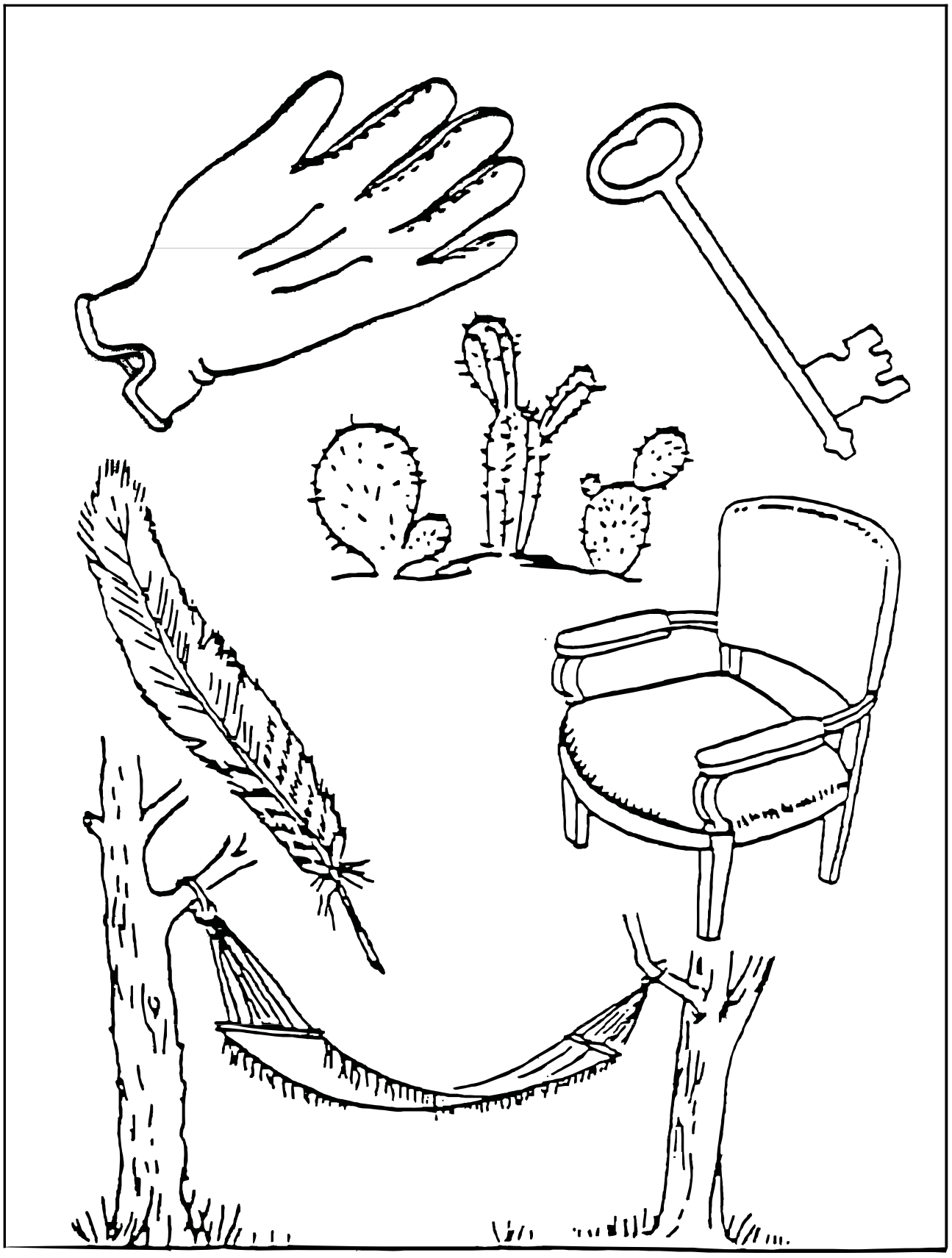
You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.



MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

Appendix F. Barthel Index

THE BARTHEL INDEX

Patient Name: _____
Rater Name: _____
Date: _____

Activity	Score
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	_____
BATHING 0 = dependent 5 = independent (or in shower)	_____
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	_____
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 = continent	_____
TOILET USE 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	_____
TRANSFERS (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	_____
MOBILITY (ON LEVEL SURFACES) 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 any aid; for example, stick) > 50 yards	_____
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	_____
TOTAL (0–100):	_____

Provided by the Internet Stroke Center — www.strokecenter.org

The Barthel ADL Index: Guidelines

1. The index should be used as a record of what a patient does, not as a record of what a patient could do.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. The need for supervision renders the patient not independent.
4. A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives and nurses are the usual sources, but direct observation and common sense are also important. However direct testing is not needed.
5. Usually the patient's performance over the preceding 24-48 hours is important, but occasionally longer periods will be relevant.
6. Middle categories imply that the patient supplies over 50 per cent of the effort.
7. Use of aids to be independent is allowed.

References

Mahoney FI, Barthel D. "Functional evaluation: the Barthel Index."
Maryland State Medical Journal 1965;14:56-61. Used with permission.

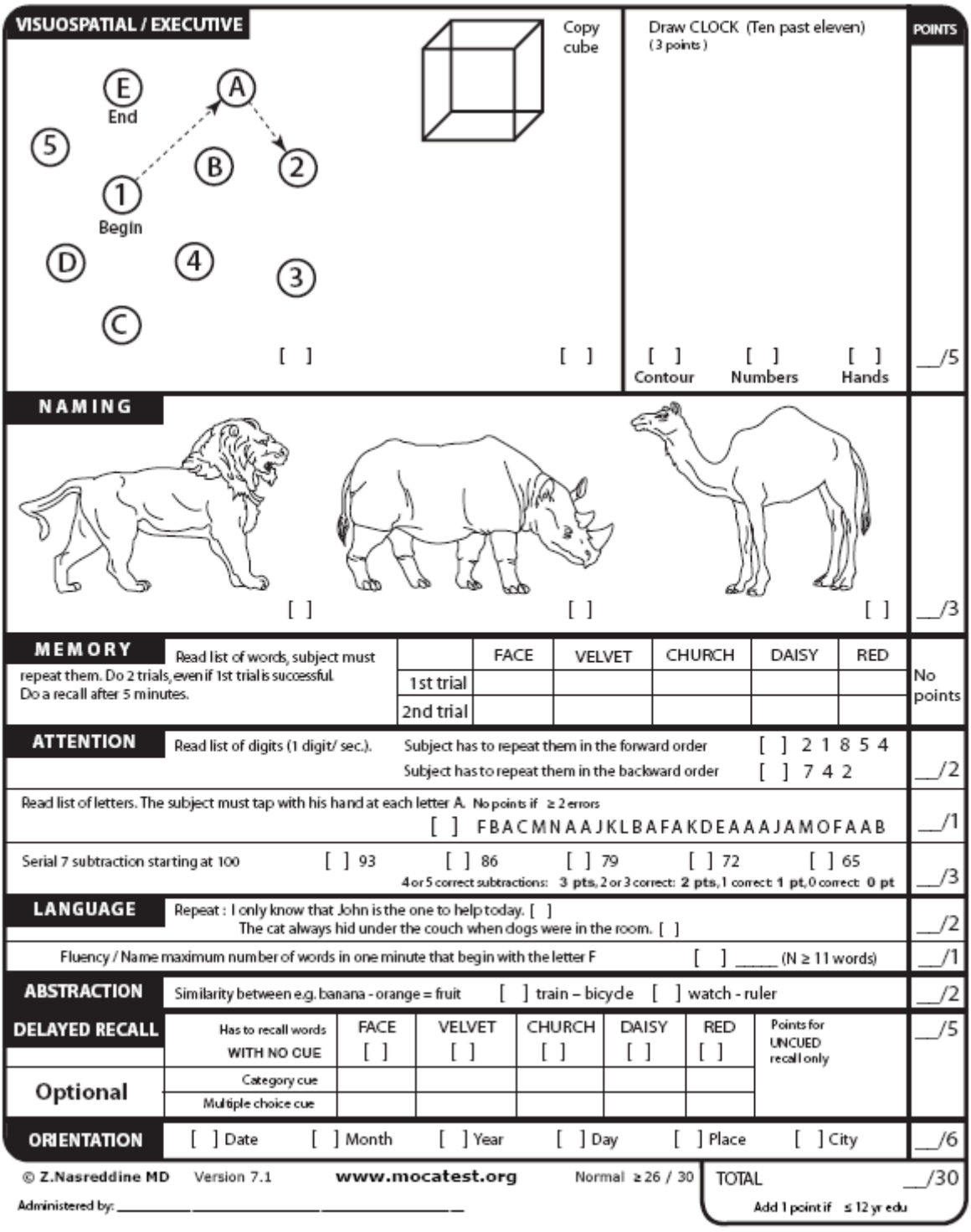
Loewen SC, Anderson BA. "Predictors of stroke outcome using objective measurement scales."
***Stroke.* 1990;21:78-81.**

Gresham GE, Phillips TF, Labi ML. "ADL status in stroke: relative merits of three standard indexes."
***Arch Phys Med Rehabil.* 1980;61:355-358.**

Collin C, Wade DT, Davies S, Horne V. "The Barthel ADL Index: a reliability study."
***Int Disability Study.*1988;10:61-63.**

Copyright Information

Appendix G. Montreal Cognitive Assessment (MoCA)



Appendix H. Stroke Impact Scale (SIS)

Stroke Impact Scale

VERSION 3.0

The purpose of this questionnaire is to evaluate how stroke has impacted your health and life. We want to know from **YOUR POINT OF VIEW** how stroke has affected you. We will ask you questions about impairments and disabilities caused by your stroke, as well as how stroke has affected your quality of life. Finally, we will ask you to rate how much you think you have recovered from your stroke.

Stroke Impact Scale

These questions are about the physical problems which may have occurred as a result of your stroke.

1. In the past week, how would you rate the strength of your....	A lot of strength	Quite a bit of strength	Some strength	A little strength	No strength at all
a. Arm that was most affected by your stroke?	5	4	3	2	1
b. Grip of your hand that was most affected by your stroke?	5	4	3	2	1
c. Leg that was most affected by your stroke?	5	4	3	2	1
d. Foot/ankle that was most affected by your stroke?	5	4	3	2	1

These questions are about your memory and thinking.

2. In the past week, how difficult was it for you to...	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Extremely difficult
a. Remember things that people just told you?	5	4	3	2	1
b. Remember things that happened the day before?	5	4	3	2	1
c. Remember to do things (e.g. keep scheduled appointments or take medication)?	5	4	3	2	1
d. Remember the day of the week?	5	4	3	2	1
e. Concentrate?	5	4	3	2	1
f. Think quickly?	5	4	3	2	1
g. Solve everyday problems?	5	4	3	2	1

These questions are about how you feel, about changes in your mood and about your ability to control your emotions since your stroke.

3. In the past week, how often did you...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Feel sad?	5	4	3	2	1
b. Feel that there is nobody you are close to?	5	4	3	2	1
c. Feel that you are a burden to others?	5	4	3	2	1
d. Feel that you have nothing to look forward to?	5	4	3	2	1
e. Blame yourself for mistakes that you made?	5	4	3	2	1
f. Enjoy things as much as ever?	5	4	3	2	1
g. Feel quite nervous?	5	4	3	2	1
h. Feel that life is worth living?	5	4	3	2	1
i. Smile and laugh at least once a day?	5	4	3	2	1

The following questions are about your ability to communicate with other people, as well as your ability to understand what you read and what you hear in a conversation.

4. In the past week, how difficult was it to...	**Not difficult at all**	**A little difficult**	**Somewhat difficult**	**Very difficult**	**Extremely difficult**
a. Say the name of someone who was in front of you?	5	4	3	2	1
b. Understand what was being said to you in a conversation?	5	4	3	2	1
c. Reply to questions?	5	4	3	2	1
d. Correctly name objects?	5	4	3	2	1
e. Participate in a conversation with a group of people?	5	4	3	2	1
f. Have a conversation on the telephone?	5	4	3	2	1
g. Call another person on the telephone, including selecting the correct phone number and dialing?	5	4	3	2	1

The following questions ask about activities you might do during a typical day.

5. In the past 2 weeks, how difficult was it to...	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Could not do at all
a. Cut your food with a knife and fork?	5	4	3	2	1
b. Dress the top part of your body?	5	4	3	2	1
c. Bathe yourself?	5	4	3	2	1
d. Clip your toenails?	5	4	3	2	1
e. Get to the toilet on time?	5	4	3	2	1
f. Control your bladder (not have an accident)?	5	4	3	2	1
g. Control your bowels (not have an accident)?	5	4	3	2	1
h. Do light household tasks/chores (e.g. dust, make a bed, take out garbage, do the dishes)?	5	4	3	2	1
i. Go shopping?	5	4	3	2	1
j. Do heavy household chores (e.g. vacuum, laundry or yard work)?	5	4	3	2	1

The following questions are about your ability to be mobile, at home and in the community.

6. In the past 2 weeks, how difficult was it to...	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Could not do at all
a. Stay sitting without losing your balance?	5	4	3	2	1
b. Stay standing without losing your balance?	5	4	3	2	1
c. Walk without losing your balance?	5	4	3	2	1
d. Move from a bed to a chair?	5	4	3	2	1
e. Walk one block?	5	4	3	2	1
f. Walk fast?	5	4	3	2	1
g. Climb one flight of stairs?	5	4	3	2	1
h. Climb several flights of stairs?	5	4	3	2	1
i. Get in and out of a car?	5	4	3	2	1

The following questions are about your ability to use your hand that was MOST AFFECTED by your stroke.

7. In the past 2 weeks, how difficult was it to use your hand that was most affected by your stroke to...	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Could not do at all
a. Carry heavy objects (e.g. bag of groceries)?	5	4	3	2	1
b. Turn a doorknob?	5	4	3	2	1
c. Open a can or jar?	5	4	3	2	1
d. Tie a shoe lace?	5	4	3	2	1
e. Pick up a dime?	5	4	3	2	1

The following questions are about how stroke has affected your ability to participate in the activities that you usually do, things that are meaningful to you and help you to find purpose in life.

8. During the past 4 weeks, how much of the time have you been limited in...	**None of the time**	**A little of the time**	**Some of the time**	**Most of the time**	**All of the time**
a. Your work (paid, voluntary or other)	5	4	3	2	1
b. Your social activities?	5	4	3	2	1
c. Quiet recreation (crafts, reading)?	5	4	3	2	1
d. Active recreation (sports, outings, travel)?	5	4	3	2	1
e. Your role as a family member and/or friend?	5	4	3	2	1
f. Your participation in spiritual or religious activities?	5	4	3	2	1
g. Your ability to control your life as you wish?	5	4	3	2	1
h. Your ability to help others?	5	4	3	2	1

9. Stroke Recovery

On a scale of 0 to 100, with 100 representing full recovery and 0 representing no recovery, how much have you recovered from your stroke?

_____ 100 Full Recovery

_____ 90

_____ 80

_____ 70

_____ 60

_____ 50

_____ 40

_____ 30

_____ 20

_____ 10

_____ 0 No Recovery

Item Clarifications

1. If patient says "I don't have an affected side", then instruct them to score using their perceived weaker side. If they still insist there is no affected, or weaker, side instruct them to score using their dominant side.

4. If patient says s/he does not do any or all of the items listed, code item(s) as *Extremely Difficult.*
   (Item f) If patient does not call but is handed the phone this is OK.
   (Item g) If patient cannot hold a phone book, if they can read it this is OK. This item addresses whether the patient is able to initiate a phone call, look up the number, and dial this number correctly.

5. If patient says s/he does not do any or all of the items listed, code item(s) as *Cannot do at all.*
   (Item a) If person is on pureed food, even if they feel they could cut the food, code as *Cannot do at All* (1/5/98)
   (Item c) Bathing oneself does not include getting into the tub.
   (Item e) This question is associated with movement. Does the person have the physical ability to get to the bathroom quickly enough?
   (Item f) Losing a little urine/dribbling is considered an accident.
      If person has intermittent catheter and is having no leaking problems code them as per report. (1/5/98)
      If person has an in-dwelling Foley catheter, code as *Cannot do at all.* (1/5/98)
   (Item g) Constipation is not counted here, person has to have an accident.
   (Item i) "Shopping" means any type of shopping and does not include driving.

6. If patient hasn't done any of the items in the past two weeks code as *Cannot do at all.*
   (Item h) If patient hasn't "climbed several flights of stairs" in two weeks, they may be prompted by saying "have you gone up and down one flight of stairs a couple of times in a row." If they still say they have not done it then they must be coded as *Cannot do at all.*
   (Item i) If the patient wants to know what kind of car say "your car" or "the car you ride in most."

7. If patient says "I don't have an affected side", then instruct them to score using their perceived weaker side. If they still insist there is no affected, or weaker, side instruct them to score using their dominant side.
   (Item a) If the patient says s/he has not been to the grocery store say "have you carried anything heavy with that hand."
   (Item d) This item is to tie a shoelace/bow using both hands.

8. If patient does not do any of the specific items (and has never done), code interference as *None of the time.*

Appendix I. EQ-5D

By placing a check-mark in one box in each group below, please indicate which statements best describe your own state of health today.

Mobility

I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-Care

I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

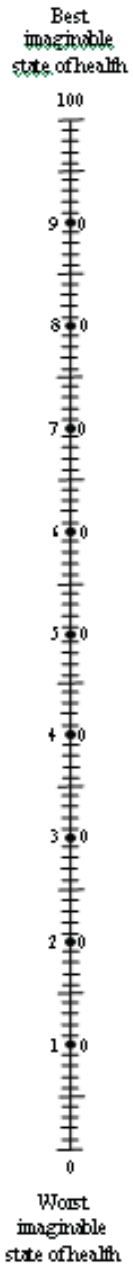
Anxiety/Depression

I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

To help people say how good or bad their state of health is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your state of health is today.

Your own state of health today



Appendix J: CES-D

CENTER FOR EPIDEMIOLOGIC STUDIES—DEPRESSION SCALE				
Circle the number of each statement which best describes how often you felt or behaved this way – DURING THE PAST WEEK.				
	Rarely or none of the time (less than 1 day)	**Some or a little of the time (1-2 days)**	**Occasionally or a moderate amount of the time (3-4 days)**	**Most or all of the time (5-7 days)**
During the past week:	0	1	2	3
1) I was bothered by things that usually don't bother me	0	1	2	3
2) I did not feel like eating; my appetite was poor	0	1	2	3
3) I felt that I could not shake off the blues even with help from my family and friends	0	1	2	3
4) I felt that I was just as good as other people	0	1	2	3
5) I had trouble keeping my mind on what I was doing	0	1	2	3
6) I felt depressed	0	1	2	3
7) I felt that everything I did was an effort	0	1	2	3
8) I felt hopeful about the future	0	1	2	3
9) I thought my life had been a failure	0	1	2	3
10) I felt fearful	0	1	2	3
11) My sleep was restless	0	1	2	3
12) I was happy	0	1	2	3
13) I talked less than usual	0	1	2	3
14) I felt lonely	0	1	2	3
15) People were unfriendly	0	1	2	3
16) I enjoyed life	0	1	2	3
17) I had crying spells	0	1	2	3
18) I felt sad	0	1	2	3
19) I felt that people disliked me	0	1	2	3
20) I could not get "going"	0	1	2	3

Appendix K: Suggested Framework for evaluating capacity for consent in an emergency setting

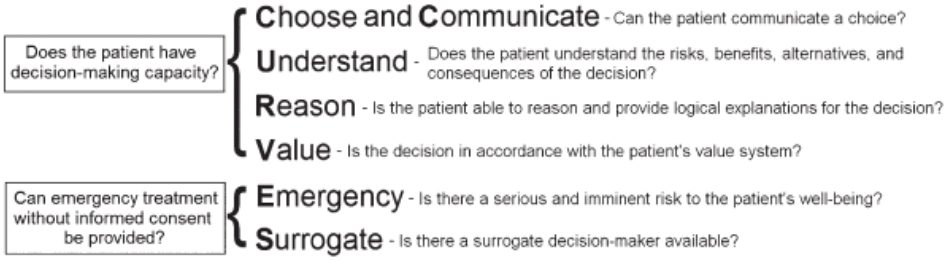


FIGURE 1. Mnemonic for the assessment of decision-making capacity and provision of emergency treatment. A patient lacks capacity if any of the prerequisite abilities (to choose and communicate, understand, reason, or value a decision) are absent. If a patient lacks capacity in an emergent situation and no surrogate decision maker is available, then emergency treatment without informed consent may be provided for a medically warranted course of action.

- **C** – Choose and Communicate. Patients must be able to choose from among the options before them. Furthermore, their choice must be made without coercion or manipulation, although appropriate persuasion is permitted.[1] Each patient must be able to communicate his or her preferences, whether verbally, in writing, or through the use of signals.
- **U** – Understand. The patient must understand the relevant risks, benefits, alternatives, and consequences of any planned intervention or course of action.
- **R** – Reason. The patient must be able to reason and provide adequate explanations for accepting or declining each intervention.
- **V** – Value. The patient's decision should be consistent with his or her value system. Physicians should strive to be aware of and understand the patient's values, and they must also be aware that patient values and goals may change with time.

- **E** – Emergency. A true emergency exists, meaning that there is serious and imminent risk to life or limb.
- **S** – Surrogate. No surrogate decision maker or legal document detailing the patient's desires is immediately available, and there is no time to obtain an ethics consultation.

Chow et al. Curves: A Mnemonic for Determining Medical Decision-Making Capacity and Providing Emergency Treatment in the Acute Setting. Chest 2010; 137; 421-427.