ESCAPE TRIAL

Endovascular treatment for **S**mall **C**ore and **A**nterior circulation **P**roximal occlusion with **E**mphasis on minimizing CT to recanalization times

ESCAPE trial

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Signatures

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List Abbreviations

aPTT	Activated Prothrombin Time
AE	Adverse Event
ASA	Acetylsalicylic Acid
ASPECTS	Alberta Stroke Program Early CT Score
BI	Barthel Index
BP	Blood Pressure
CBC	Complete Blood Count
CBV	Cerebral Blood Volume
miFUNCTION	Comprehensive Hierarchical Evaluation of Disability based on Activity limitations
CRF	Case Report Form
CRU	Clinical Research Unit
CSC	Comprehensive Stroke Centre
CT	Computed Tomography
CTA	Computerized Tomographic Angiography
CTP	Computerized Tomographic Perfusion
DBP	Diastolic Blood Pressure
DSMB	Data and Safety Monitoring Board
DWI	Diffusion Weighted Imaging'
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
eCRF	Electronic Case Report form
ED	Emergency Department
EDC	Electronic Data Capture
EMEA	European Medicines Agency
EQ-5D	A standardized assessment instrument (developed by the EuroQol Group) that provides a simple descriptive measure of health outcome
FDA	Food and Drug Administration
FLAIR	Fluid Attenuated Inversion Recovery
g/L	Grams per Litre
GRE	Gradient Echo MRI
HIPAA	Health Insurance Portability and Accountability Act
IA	Intra-arterial
ICH	Intracranial Hemorrhage
ICH-GCP	International Conference on Harmonization Good Clinical Practice
INR	International Normalized Ratio
IRB	Institutional Review Board
IA	Intra-arterial
ICA	Internal Carotid Artery
ICH	Intracerebral Hemorrhage
IOML	Inferior Orbitomeatal Line

IVH	Intraventricular Hemorrhage
IV	Intravenous
MCA	Middle Cerebral Artery
MI	Myocardial Infarction
MIPS	Maximum Intensity Projections
MoCA	Montreal Cognitive Assessment
MOP	Manual of Procedures
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
mSv	Millisievert
MOP	Manual of Procedures
mRS	Modified Rankin Scale
NG	Nasogastric
NCCT	Noncontrast Head CT Scan
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
PI	Principal Investigator
PE	Pulmonary Embolus
PIPED	Personal Information and Portable Electronic Documents Act
PT	Prothrombin time
RCT	Randomised Controlled Trial
REB	Research Ethics Board
SAE	Serious Adverse Event
SAH	Subarachnoid Hemorrhage
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SDH	Subdural Hematoma
TICI	Thrombolysis in Cerebral Infarction Score
TIMI	Thrombolysis in Myocardial Infarction
tPA	Tissue Plasminogen Activator

Endovascular treatment for **S**mall **C**ore and **A**nterior circulation **P**roximal occlusion with **E**mphasis on minimizing CT to recanalization times (ESCAPE) trial

Protocol synopsis

Objectives	The primary objectives of this study are to show that rapid endovascular revascularization amongst radiologically selected (small core/proximal occlusion) patients with ischemic stroke results in improved outcome compared to patients treated in clinical routine. The secondary objectives of this study are to demonstrate the safety and feasibility of achieving rapid endovascular revascularization in this population of patients (<60 min CT-groin puncture ('Picture-to-puncture time'); <90 min CT-recanalization).
Experimental Design	A Phase 3, randomized, open-label with blinded outcome evaluation, controlled, parallel group design.
Population	500 male and female patients; additional subjects may be recruited until 200 subjects randomized to endovascular arm achieve CT-to-recanalization <90 minutes. Inclusion Criteria 1. Acute ischemic stroke 2. Age 18 or greater 3. Onset (last-seen-well) time to randomization time < 12 hours. 4. Disabling stroke defined as a baseline NIHSS > 5 at the time of randomization. 5. Pre-stroke (24 hours prior to stroke onset) independent functional status in activities of daily living with modified Barthel Index > 90. Patient must be living in their own home, apartment or seniors lodge where no nursing care is required. 6. Confirmed symptomatic intracranial occlusion, based on single phase, multiphase or dynamic CTA, at one or more of the following locations: Carotid T/L, M1 MCA, or M1-MCA equivalent (2 or more M2-MCAs). Anterior temporal artery is not considered an M2. 7. Non-contrast CT/CTA for trial eligibility performed or repeated at ESCAPE stroke center with endovascular suite on-site. 8. Endovascular treatment intended to be initiated (groin puncture) within 60 minutes of baseline non-contrast CT with target CT to first recanalization of 90 minutes.

	9. Signed informed consent or appropriate signed deferral of consent where approved. <u>Exclusion Criteria</u> 1. Baseline non-contrast CT reveals a moderate/large core defined as extensive early ischemic changes of ASPECTS 0-5 in the territory of symptomatic intracranial occlusion. 2. Other confirmation of a moderate to large core defined one of three ways: a. *On a single phase, multiphase or dynamic CTA*: no or minimal collaterals in a region greater than 50% of the MCA territory when compared to pial filling on the contralateral side (multiphase/dynamic CTA preferred) OR b. *On CT perfusion* (≥8 cm coverage): a low CBV and very low CBF ASPECTS <6 in the symptomatic MCA territory OR c. *On CT perfusion*(<8 cm coverage): a region of low CBV and very low CBF >1/3 of the CTP imaged symptomatic MCA territory. 3. Groin puncture is not possible within 60 minutes of the end of non-contrast CT acquisition (please note that if CTP is performed it should be done after CTA). 4. No femoral pulses or very difficult endovascular access will result in a CT-to-recanalization time that is longer than 90 minutes, or will result in an inability to deliver endovascular therapy. 5. Pregnancy; if a woman is of child-bearing potential a urine or serum beta HCG test is positive. 6. Severe contrast allergy or absolute contraindication to iodinated contrast. 7. Suspected intracranial dissection as a cause of stroke. 8. Clinical history, past imaging or clinical judgment suggests that the intracranial occlusion is chronic. 9. Patient has a severe or fatal comorbid illness that will prevent improvement or follow-up or that will render the procedure unlikely to benefit the patient. 10. Patient cannot complete follow-up treatment due to co-morbid non-fatal illness. *This population is expected to consist of patients:* *1. with unknown time of stroke onset but less than 12 hour time of last known normal.*

	2. stroke-on-awakening but less than 12 hours from going to bed. *3. stroke with time of onset <4.5h but stroke patients with an elevated INR > 1.7 precluding routine thrombolysis* *4. stroke with time of onset <4.5h but taking anticoagulants (dabigatran, apixaban, rivaroxaban, LMWH, vitamin K antagonists and others),* *5. stroke with time of onset <4.5h but recent MI, surgery, or bleeding prohibiting standard of care thrombolysis* *6. stroke patients who have received intravenous tPA in a drip-and-ship paradigm and fulfill inclusion/exclusion criteria after repeat clinical and imaging evaluation at the ESCAPE site* *7. stroke patients who have received intravenous tPA at the ESCAPE site <4.5h and can be rapidly moved to the neuro-angiography suite in a direct IV-IA approach. In this case, the patient meets all the ESCAPE inclusion/criteria and is additionally treated with IV tPA.* 8. *In-hospital stroke patients who meet all other criteria, and in particular that they had a functional status (Barthel Index > 90) immediately prior to the stroke. [For example: severely ill hospitalized patients are not candidates for the study; patients with stroke due to elective coronary angiography are potentially eligible for inclusion.]* *The study population will be clinically heterogenous, but will be highly homogenous as defined by imaging. Thus the selection of patients will have a clinical component to define the sample frame and a second imaging component to refine the population.*
Countries	Canada (Calgary, Vancouver, Edmonton, Winnipeg, Toronto, Montreal, Ottawa), US, European, Asian sites.
Treatments	All patients will receive the best standard of medical care according to modern acute stroke care guidelines. Control arm subjects will receive best medical care. In the intervention/experimental arm, subjects will be treated with endovascular thrombectomy or thrombolysis using currently available technology for use in the ESCAPE site for thrombectomy/thrombolysis.
Duration of Treatment	This study consists of one 90-day study period for each subject. Subjects will be hospitalized for care after their acute stroke

	according to the current standard of care. Subjects are required to return to clinic on Days 30 & 90 for end-of-study procedures.
Evaluation Criteria	Safety Analysis: *incidence of serious adverse events associated with the treatment protocol. These include:* a. vessel perforation b. symptomatic ICH c. iatrogenic vessel dissection d. retroperitoneal hematoma e. femoral neuropathy at the groin puncture site f. major extracranial bleeding Primary Efficacy Outcome: A shift or one or more categories (proportional odds analysis) on the modified Rankin scale. Key Secondary Outcomes: NIHSS 0-2 mRS 0-2 Mortality at 90 days EQ-5D (EuroQoL)Cognitive outcomes (Trailmaking A, B; MoCA; Boston Naming test; Sunnybrook hemi-spatial neglect battery) Barthel Index > 90 (≥95) Barthel Index shift analysis (ordinal logistic regression) miFUNCTION score Economic (cost-effectiveness) analysis Qualitative evaluation of the waiver/deferral of consent process
Training Considerations	1. Optimisation of NCCT scanning protocols and training of CT scanner technicians at each site will be undertaken by the study personnel. 2. Training of investigators on the 'tips and tricks' of endovascular thrombectomy. Training of the endovascular team (angio suite nurses and technologists) to reduce CT-to-recanalization times. 3. Study discipline and rigour on randomization of all patients who might fit these criteria. Given the possibility of the "loss of equipoise" in an active procedural trial, it is critical to get recruitment completed fast and to maintain

	study-wide discipline in subject enrolment. Patients must not cross over.
Sample Size Considerations	The study will test the hypothesis that patients undergoing endovascular revascularization will show shift in the distribution of scores on the mRS scale at 90 days, assuming that categories 5 and 6 (bedbound with severe disability, and death) are collapsed, and the effect leads to an assumed common odds ratio of 1.8. The predicted sample size is 500 patients, allowing for potential cross-over and drop-outs.
Randomization	Randomization will use a minimal sufficient balance algorithm to ensure balance within groups on important predictors of outcome including age, baseline stroke severity, initial arterial lesion location, ASPECTS score and site. We will have suggested time quotas for treatment: CT-to-randomization: 15 minutes; Randomization-to-puncture: 30 minutes; Puncture-to-recanalization: 30 minutes; we will aim to meet this time quotas by ongoing training of the sites and by choosing sites a priori that can meet these targets.
Analysis	The primary analysis will be an intention to treat analysis. It will use an ordinal logistic regression model to derive the common odds of improvement ("shift") along the mRS scale. The proportional odds assumption will be testing using a Brant test. The analysis will be adjusted for the 6 variables used for minimization (age, sex, NIHSS score, ASPECTS score, occlusion location, intravenous tPA use).
Consent	Waiver/deferral of consent when necessary and where possible according to local IRB approval. Assent or informed consent at other sites. Consent must be obtained within the proposed time targets.

Trial Organization

The trial will be organized by an executive committee principally centred in Calgary at the Calgary Stroke Program (Hotchkiss Brain Institute, University of Calgary and Department of Clinical Neurosciences, Department of Radiology, Department of Community Health Sciences). The overall PI for the trial will be Michael D. Hill. The Interventional Neuro-radiology PI will be Mayank Goyal. The Neurology PI will be Andrew Demchuk. The overall project nursing coordinator will be Karla Ryckborst. The financial and contracts manager will be Michelle Wright. The safety of the trial will be overseen by an independent DSMB. An international advisory committee will provide intellectual input into trial design and management. A steering committee will manage the day-to-day activities of the trial. Data will be managed by the Hotchkiss Brain Institute CRU. Project management will be overseen by the Stroke Clinical Trials office.

The trial will be advised by an International advisory committee – to be named – and a DSMB – to be named.

Study Objectives

The principal objectives of the study are to show that acute, rapid, revascularization in the setting of a small established infarct core with good collateral circulation, among a population of patients not currently routinely eligible for this therapy results in better clinical outcomes compared to conservative care. The biological hypotheses to be proven are that time from symptom onset is simply a surrogate for the degree of core infarction and salvageable brain tissue, and therefore recanalization improves outcome.

Background

The rationale for this study is the following –

1) There is no convincing, randomized trial evidence that modern endovascular therapy is better than routine care, including routine intravenous thrombolysis, for acute ischemic stroke. There is nevertheless, strong evidence that endovascular therapy can result in faster, more complete recanalization and that this should result in better stroke outcomes.
2) Modern acute endovascular therapy has advanced to a stage where testing is now possible because complication rates are very low and technology is both increasingly operator independent and expertise is widespread.
3) The mismatch hypothesis (MR perfusion-diffusion or CT perfusion-CBV) has not been shown to be useful for making treatment decisions in large part because of

the time-trade off between the time required to gather information and the imperative to treat quickly.

4) Substantial variation in subject susceptibility to infarction makes average time limits for thrombolysis, derived from clinical trials, less relevant to individual patients.
5) Patients with a small core of infarct but a significant clinical deficit benefit from reperfusion even at late time windows after treatment.
6) Up to 25% of ischemic stroke patients awake with stroke symptoms, have an unwitnessed time of onset, have an ischemic stroke as a complication of a surgical procedure, have an ischemic stroke despite treatment with anticoagulants and are therefore not eligible for routine chemical thrombolysis with IV tPA.
7) Patients with large vessel occlusions frequently do not recanalize fast enough with intravenous chemical thrombolysis (eg. tPA).
8) Endovascular thrombectomy results in very high recanalization rates of about 80%.
9) There is a compelling need to evaluate patients who are not currently treated with thrombolytic therapy (chemical or mechanical) and to use these groups to demonstrate that endovascular therapy is an effective treatment modality for acute ischemic stroke.

Two key concepts will be evaluated in this trial:

(i) Revascularization of patients with large vessel occlusion and small core, good collaterals will result in a greater proportion of patients with a good outcome
(ii) Endovascular revascularization can be done with a CT to TICI3 flow in < 90 minutes.

Endovascular device therapy

The only randomized trial of endovascular therapy compared to medical therapy was published in 1999. The PROACT-2 trial used an unlicensed thrombolytic agent – recombinant pro-urokinase (r-proUK)- infused directly at the face of a MCA thrombus.[1] No mechanical thrombus disruption was permitted. The control arm received low-dose (400 U per hour) intravenous heparin. A positive result was shown with a 15% absolute increase in the proportion of patients who achieved an independent outcome defined as a mRS 0-2. The result has been criticized because the control arm used a treatment, which is now known to be, on average, harmful for acute ischemic stroke. The drug, r-proUK, was never brought to market.

Since then, endovascular therapy has made rapid and significant technological gains. The dominant modality 13 years later is mechanical thrombectomy. Beginning with the MERCI Concentric Retriever, which was approved by the FDA under the 510(k) clearance mechanism for thrombus retrieval, the evolution progressed to the use of the Penumbra Stroke System micro-aspiration. Currently the retractable stent (stentriever) has developed to become the most successful device in achieving safe and rapid recanalization. The recent publication of the SWIFT and TREVO-2 studies

have demonstrated improved recanalization with the stentriever devices over the MERCI retriever.[2,3]

Politically and administratively, the FDA and the EMEA play dominant roles in the global regulation of new devices. Device regulation and approval has been historically different from drugs. Thus, devices are approved based upon demonstrated engineering and efficacy of technical application and not because the procedures in which they are used make patients better. Clinical outcomes have not been used as the gold standard for approval. Thus, devices are approved currently in Europe and North America without randomized trial proof of clinically efficacy.[4] Fundamentally, this is the basis and thinking behind the need for this trial. We require proof of clinical efficacy.

Key cohort studies have shown that mechanical thrombectomy is feasible, safe include the MultiMERCI study, PENUMBRA pivotal stroke study, are summarized below.[5,6]

Study	N	Intervention	Artery	Time	bNIHSS	% mRS <=2	% mortality	% recanalization intervention group	sICH
PROACT-2	180	IA pro-UK vs. heparin control	MCA (M1, M2)	6 h	17	40	25	66	10
IMS-1	80	IV + IA tPA	MCA, (M1, M2) ICA, VB	7 h	18	42	16	56	6.3
IMS-2	81	IV + IA tPA +/- EKOS US catheter	MCA, (M1, M2) ICA, VB	7 h	19	46	16	58	9.9
MERCI	141	MERCI retriever	MCA, (M1, M2) ICA, VB	8 h	20	27.7	43.5	60.3	7.8
Multi-MERCI	164	MERCI retriever	MCA, (M1, M2) ICA, VB	8 h	19	36	34	68	9.8
Penumbra Pivotal Stroke Trial	125	Penumbra aspiration device	MCA, (M1, M2) ICA, VB	8 h	17	25	32.8	81.6	11.2
SWIFT	144	Solitaire vs MERCI clot retriever	MCA, (M1, M2) ICA, VB	8h	18	36.3 vs 29.1	18.2 vs 43.8	68.5 vs 30.2	1.7 vs 10.9

Adapted from: Ellis et al.[7]

The SWIFT study compared the use of the MERCI concentric retriever to the use of the SOLITAIRE retrievable stent. The TREVO study demonstrated the use of the

CONCENTRIC TREVO retractable stent. In both studies complication rates were low and recanalization was achieved in 80% or more of cases.[2,3]

Key outcomes of recent studies have been the safety of device use. Whereas, technically, the MERCI retriever resulted in significant torque applied to the intracranial vasculature and an increased risk of vessel perforation and sub-arachnoid hemorrhage, this is not true for the novel retractable stents. The SWIFT study demonstrated a major complication rate of 1.7% in the Solitaire arm.

Revascularization Rates

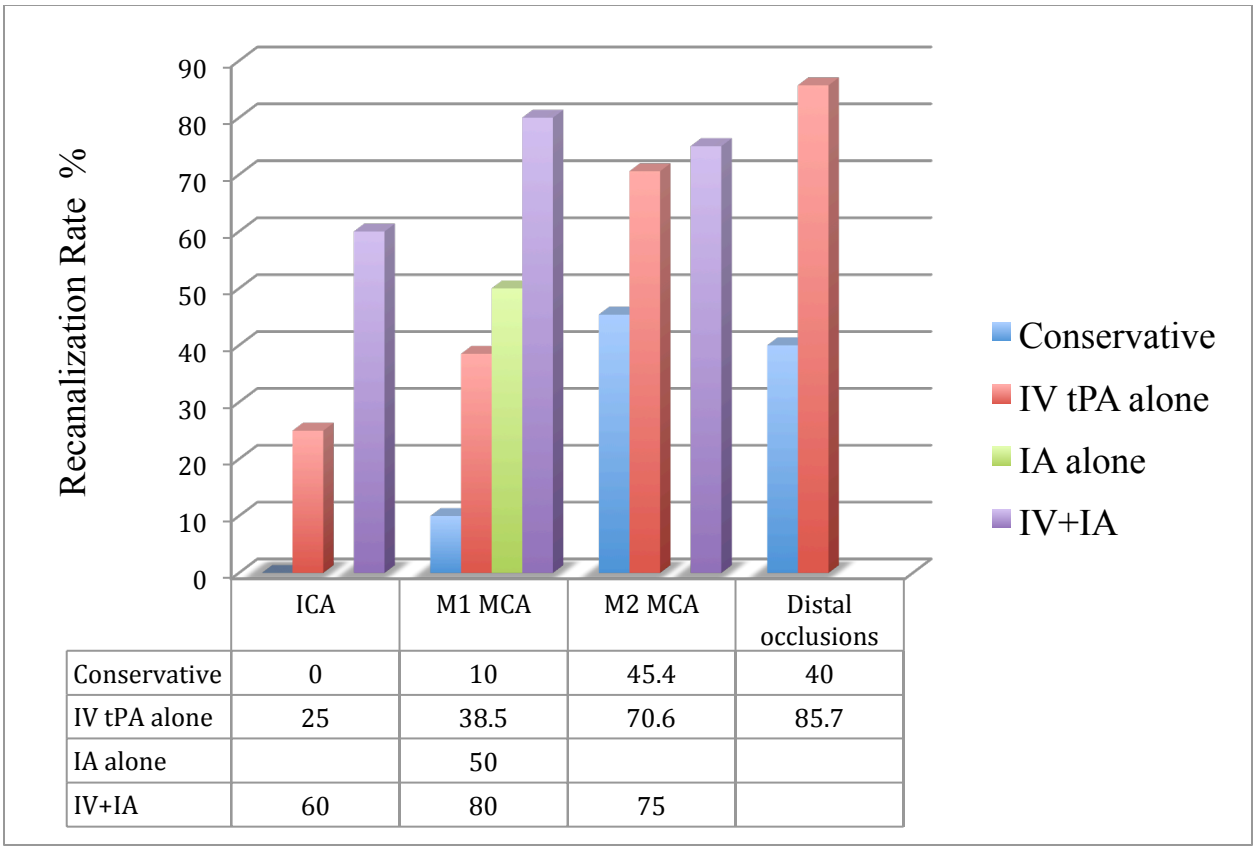
The use of IV tPA revolutionized stroke treatment.[8] However, early recanalization rates with IV tPA are not overwhelming. The only angiographically controlled study is now 20 years old. The del Zoppo study used intravenous duteplase, a double-stranded from to tPA and assessed it in a dose-finding study.[9] Recanalization rates at 1 hour post-treatment were as follows:

ICA (n=23)	M1 (n=34)	M2 (n=26)	M3 (n=44)	All MCA (n=104)
8.7%	35.3%	53.8%	65.9%	52.9%

We and others have found similar results.[10] We have recently conducted a prospective cohort study using CT angiography to determine recanalization rates at 4 hours post-treatment. Preliminary results are shown below [Personal communication, Menon B, Demchuk AM et al):

	ICA	M1 MCA	M2 MCA	Distal occlusions	Basilar
Conservative	0/1 (0%)	1/ 10 (10%)	5/11 (45.4%)	2/5 (40%)	---
IV tPA alone	2/8 (25%)	5/13 (38.5%)	12/17 (70.6%)	6/7 (85.7%)	---
IA alone	---	3/6 (50%)	---	---	---
IV+IA	3/5 (60%)	8/10 (80%)	3/4 (75%)	---	1/1 (100%)

Table: Recanalization rate (post IA or at 4 hr CTA) stratified by site of occlusion and type of treatment (n=98). Cells with no patients are coded ---.



	ICA	M1 MCA	M2 MCA	Distal occlusions
Conservative	0	10	45.4	40
IV tPA alone	25	38.5	70.6	85.7
IA alone		50		
IV+IA	60	80	75	

Figure: Recanalization rates (post IA or at 4 hr CTA) stratified by site of occlusion and type of treatment (n=98). Blanks in data cells are with no patients and not missing data.

We and others have concluded the following:

1) The effect of early recanalization is very large on clinical outcomes. We infer this to be true because there is a profound clinical average benefit with the use of IV tPA where recanalization rates are 50% at best. Similarly, among cohorts of patients treated with endovascular therapy, the dominant factor in predicting outcome is consistently recanalization.
2) The use of endovascular or combined IV tPA plus endovascular treatments is required for the treatment of proximal vessel occlusions. The corollary is that there is very little incremental benefit to endovascular treatment for distal occlusions when recanalization occurs in over 85% of cases.

Imaging as a biomarker for patients selection

Imaging using multi-modal MR or CT is the most likely biomarker for selection of patients for thrombolytic therapy. The theoretical construct of the penumbra defined by the difference between (a) tissue-at-risk or destined for infarction but not already infarcted and (b) tissue that is already irreversibly infarcted, is clear. There is consensus in the stroke community and little doubt that this is a correct conceptual way of thinking about the problem.

However, it is a simplification of reality because the line between (a) and (b) is not a straight black line border. It is gray. The operational definitions of what is irreversibly infarcted and what is potentially salvageable have proven to be very challenging to delineate. Thus, measurement errors using either multi-modal CT or multi-modal MRI have proven to be major barriers in using the mismatch hypothesis. In addition, acquisition and analysis of the data from the multi-modal imaging can be time consuming which itself can influence outcome. There is a great need to move very rapidly to get treatment started. Any trade-off of time to gather advanced information must be worth the expense in the treatment delay. Currently, it is our belief that this is not the case.

Two trials, assessing the novel thrombolytic agent desmoteplase, have failed to show that selecting patients using a mismatch paradigm is a useful technique for defining a thrombolysis eligible cohort.[11] However, much has been learned and cohort analysis of the EPITHET study[12] and the DEFUSE studies have shown that certain populations can be selected as ideal or non-ideal for treatment. For example, DEFUSE has further confirmed the CT literature, that patients with very large burdens of infarction (>100cc volume defined by DWI) do not benefit from recanalization therapy. [13]

The key imaging data that are needed to make a treatment decision then are as follows (framed as questions):

1) Is the inclusive diagnosis a moderate to severe ischemic stroke (defined as >5 on the NIHSS)? The corollary is that ischemic stroke is not a diagnosis of exclusion.
2) Is there extensive infarction defined as tissue hypodensity on non-contrast CT scan (defined on the basis of ASPECTS scoring system) or extensive ADC restriction/DWI lesion volume (>100cc) on MR?
3) Where is the location of the arterial occlusion defined by non-invasive imaging?
4) Is the arterial occlusion amenable to safe and fast recanalization using endovascular means or combined intravenous thrombolysis plus endovascular treatment?

We have solved these questions using CT scanning and can gather and interpret these data in <10 minutes. Using the ASPECTS score, we can exclude extensive infarction. Using CT angiography, we can gain detailed information on the location of occlusion and the burden of thrombus. Further the CTA (from arch to vertex) can aid the interventionist in pre-planning navigation from the aortic arch to the thrombus. The pattern of collaterals is also discernible from CTA; patients with absent or very poor collaterals do not benefit from therapy, simply because it cannot be brought to bear in a timely enough fashion to prevent significant infarction.

Thus, we adopt a fast image acquisition "good scan (small core), occlusion" model of patients selection and believe that this group of patients are the best ones to show a large magnitude of effect and provide the proof that endovascular therapy is the right treatment for patients with stroke. A future trial might examine expanding this population of patients.

Study Design

This will be a Phase 3 randomized, open-label with blinded outcome evaluation, parallel group design study with blinded outcome evaluation.

Outcomes

Primary Outcome

A shift or one or more categories (proportional odds analysis) on the modified Rankin scale at 90 d.

Secondary Outcome

The following outcomes will be assessed as the proportion of patients who achieve each score. We will also examine each score as raw score comparisons. Where appropriate, we will examine the scores as continuous measures or binned at logical groupings (eg. quartiles).

(i) NIHSS score of 0-2 at 30 days and 90 days
(ii) mRS score of 0-2 at 30 days and 90 days
(iii) NIHSS score at 90 days
(iv) mRS score at 90 days
(v) BI score at 90 days
(vi) BI shift at 90 days
(vii) Health Utilities index at 90 days
(viii) EQ-5D (EuroQoL) at 90 days
(ix) Fast cognitive battery using the following subscales at 90 days
    a. Trail-making A & B
    b. MoCA
    c. Boston Naming test
    d. Sunnybrook hemi-neglect battery
(x) NIHSS score at 24 hours
(xi) NIHSS score at 48 hours
(xii) NIHSS score at discharge
(xiii) Recanalization of the target arterial occlusive lesion (TICI 3 flow) at the end of the procedure
(xiv) TICI 3 score at the end of the procedure
(xv) miFUNCTION scale
(xvi) Economic analysis – cost effectiveness.

(xvii) Deferral of consent survey

Safety Outcomes

(i) symptomatic intracranial hemorrhage
(ii) major bleeding due to femoral artery access complications including groin hematoma, retroperitoneal hematoma [definition]
(iii) contrast nephropathy
(iv) total radiation dose (CT, CTA, angiography)
(v) malignant MCA infarction
(vi) hemicraniectomy

Process and Quality Outcomes

(i) CT-to-groin puncture time ("Picture-to-puncture")
(ii) CT-to-recanalization time
(iii) Aspiration pneumonia
(iv) Rate of use of general anesthesia
(v) Rate of symptomatic deep venous thrombosis / pulmonary embolism
(vi) Proportion of patients with any SAE per site
(vii) Qualitative Interview to assess the process of waiver/deferral of consent.

Symptomatic intracranial hemorrhage defined as new intracranial hemorrhage (ICH, SAH, IVH, SDH) associated with clinical evidence of neurological worsening, in which, the hemorrhage is judged to be the most important cause of the neurological worsening. Clinical worsening will be guided by the NIHSS score of a minimum of 2 or more points different from baseline.

Major extracranial hemorrhage defined as life threatening, resulting in hemodynamic compromise or hypovolemic shock, requiring inotropic support or other means to maintain cardiac output, requiring blood transfusion of more than 2 units of packed red blood cells, or associated with a fall in hemoglobin greater than or equal to 5 g/L.

Contrast nephropathy will be defined as any rise of the serum creatinine by 50% of more between the baseline pre-treatment level and that measured at 24h post-treatment.

Total radiation dose will be measured in mSv and recorded directly from the CT scanner. Dose-length product will be recorded directly from the CT scanner.

Malignant MCA infarction will be defined as any large infarction with mass effect observed on imaging where treatment (medical or surgical) is required for the treatment of mass effect.

Hemicraniectomy will be defined as that surgical procedure used to decompress the swollen hemisphere.

Selection and Enrolment of Subjects

Inclusion Criteria

Clinical (Heterogeneous sampling frame)

1. Acute ischemic stroke
2. Age 18 or greater
3. Onset (last-seen-well) time to randomization time < 12 hours.
4. Disabling stroke defined as a baseline NIHSS > 5 at the time of randomization.
5. Pre-stroke (24 hours prior to stroke onset) independent functional status in activities of daily living with modified Barthel Index > 90. Patient must be living in their own home, apartment or seniors lodge where no nursing care is required.

Imaging (Homogeneous target population)

6. Confirmed symptomatic intracranial occlusion, based on single phase, multiphase or dynamic CTA, at one or more of the following locations: Carotid T/L, M1 MCA, or M1-MCA equivalent (2 or more M2-MCAs). Anterior temporal artery is not considered an M2.
7. Non-contrast CT and CTA for trial eligibility performed or repeated at ESCAPE stroke center with endovascular suite on-site.
8. Endovascular treatment intended to be initiated (groin puncture) within 60 minutes of baseline non-contrast CT with target baseline non-contrast CT to first recanalization of 90 minutes.
9. Signed informed consent or appropriate signed deferral of consent where approved.

Exclusion Criteria

1. Baseline non-contrast CT reveals a moderate/large core defined as extensive early ischemic changes of ASPECTS 0-5 in the territory of symptomatic intracranial occlusion.
2. Other confirmation of a moderate to large core defined one of three ways:
    a. *On a single phase, multiphase or dynamic CTA*: no or minimal collaterals in a region greater than 50% of the MCA territory when compared to pial filling on the contralateral side (multiphase/dynamic CTA preferred)
    OR
    b. *On CT perfusion* (≥8 cm coverage): a low CBV and very low CBF ASPECTS <6 AND in the symptomatic MCA territory
    OR

   c. *On CT perfusion*(<8 cm coverage): a region of low CBV and very low CBF >1/3 of the CTP imaged symptomatic MCA territory.
3. Groin puncture is not possible within 60 minutes of the first slice of non-contrast CT acquisition (please note that if CTP is performed it should be done after CTA).
4. No femoral pulses or very difficult endovascular access that will result in a non-contrast CT-to-recanalization time that is longer than 90 minutes, or will result in an inability to deliver endovascular therapy.
5. Pregnancy; if a woman is of child-bearing potential a urine or serum beta HCG test is positive.
6. Severe contrast allergy or absolute contraindication to iodinated contrast.
7. Suspected intracranial dissection as a cause of stroke.
8. Clinical history, past imaging or clinical judgment suggests that the intracranial occlusion is chronic.
9. Patient has a severe or fatal comorbid illness that will prevent improvement or follow-up or that will render the procedure unlikely to benefit the patient.

This population is expected to consist of patients:

1. *with unknown time of stroke onset but less than 12 hour time of last known normal.*
2. *stroke-on-awakening but less than 12 hours from going to bed.*
3. *stroke with time of onset <4.5h but stroke patients with an elevated INR > 1.7 precluding routine thrombolysis*
4. *stroke with time of onset <4.5h but taking anticoagulants (dabigatran, apixaban, rivaroxaban, LMWH, vitamin K antagonists and others),*
5. *stroke with time of onset <4.5h but recent MI, surgery, or bleeding prohibiting standard of care thrombolysis*
6. *stroke patients who have received intravenous tPA in a drip-and-ship paradigm and fulfill inclusion/exclusion criteria after repeat clinical and imaging evaluation at the ESCAPE site*
7. *stroke patients who have received intravenous tPA at the ESCAPE site <4.5h and can be rapidly moved to the neuro-angiography suite in a direct IV-IA approach. In this case, the patient meets all the ESCAPE inclusion/criteria and is additionally treated with IV tPA.*
8. *In-hospital stroke patients who meet all other criteria, and in particular that they had a functional status (Barthel Index > 90) immediately prior to the stroke. [For example: severely ill hospitalized patients are not candidates for the study; patients with stroke due to elective coronary angiography are potentially eligible for inclusion.]*

The study population will be clinically heterogeneous, but will be highly homogenous as defined by imaging. Thus the selection of patients will have a clinical component to define the sample frame and a second imaging component to refine the population.

Study Enrolment Process

Patients will be identified using usual standard of care screening methods at the acute stroke hospital. This will include screening by neurology residents, fellows, nurse practitioners, physician assistants or faculty physicians. Sites will only be selected to participate in the study if they have intact mechanisms for screening this population of patients. This includes standard of care use of CT angiography among stroke patients. All patients will undergo an acute clinical assessment, blood laboratory assessment and baseline brain imaging with acute CT and CTA. CT perfusion or MR imaging are not mandated in the study, but not prohibited. However from the perspective of imaging to recanalization time, the first slice of the baseline non-contrast CT is when the clock starts. It is mandated that a CT perfusion cannot be performed before the CTA.

If the patient remains eligible after completion of routine screening, the patient will be consented (as required) and enrolled into the study. The patient is considered enrolled into the study once the randomization assignment has been received (eg. study number assigned over the internet). A patient who consents but is not randomized will be considered a screen failure.

Treatment will be assigned using 1:1 randomization. Randomization will be conducted using a web-based algorithm with treatment assignment allocated by web-based real-time interaction with the site. The initial randomization of the first 40 patients will be completed using randomly ordered permuted blocks of 4 or 6 and assigned by site. Thereafter randomization, subject data will be entered into an on-line database within 6 hours of patient enrolment. A minimal sufficient balance method[15] will be used to ensure that the patients entered into the trial will be matched between control and active treatment arms on the key variables of site, age, sex, baseline NIHSS score, baseline NCCT ASPECTS score, and location of the symptomatic target arterial occlusive lesion. This method will ensure that by the end of the trial, the patients are well matched for important prognostic variables and therefore that by chance, the groups are not unbalanced on one particular variable.

Study Interventions

Patients will be randomized to routine stroke care governed by current guidelines (control group) or to emergency endovascular revascularization. Endovascular mechanical revascularization may be undertaken with any currently available and approved device or paradigm and used according to the manufacturers specifications for use.

Endovascular Intervention

Regulatory agency approved devices may be used (stentriever, aspiration devices). Endovascular intervention may include the administration of intra-arterial thrombolytic (eg. tPA) and the use of balloon angioplasty or guidewire manipulation of thrombus. Endovascular intervention may include direct aspiration of the thrombus through a large bore access catheter. It is not recommended that permanent stents be left in the intracranial circulation or in the internal carotid artery. Guidelines for recommended approaches to endovascular revascularization are reported in Appendix 1.

Guidelines-based Care – the Control Group

Acute stroke patients should receive the best standard of care according to national guidelines. The model will be the Canadian best practices guidelines for acute stroke care. These are very similar to the guidelines of the American Stroke Association and the European Stroke Organization.

In brief, we expect –

A. Patients who are appropriate candidates for intravenous thrombolytic therapy within 4.5hours of defined stroke onset to get rapidly administered IV therapy.
B. All patients to be managed urgently with attention to physiology. Airway, breathing and circulation first. Fluids – usually normal saline - should be administered as most patients are slightly hypovolemic. Blood pressure should not be aggressively treated other than to guidelines to allow thrombolytic therapy.
C. All patients should be managed on a stroke unit which should include early mobilization, early rehabilitation, DVT prophylaxis, swallowing assessment and prevention of aspiration pneumonia, NG feeding as appropriate and delayed (up to 4 weeks) placement of PEG tubes in the uncommon instance that these are needed.
D. All patients should receive ASA therapy (minimally) within the first 48h of stroke but after a day +1 brain image shows no evidence of hemorrhage.
E. Patients should not receive intravenous unfractionated heparin.
F. All patients should be thoroughly investigated to sort out the mechanism of stroke and appropriate stroke prevention strategies implemented. There is little use in working very hard on a technical and aggressive approach to acute stroke if it is to be undone on day +10 with a recurrent embolus because a patient has not been effectively treated for a preventable cause of stroke.
G. All patients should have relevant and appropriate stroke rehabilitation therapy.

In summary, we expect that all patients should have excellent, guideline based stroke care through the full 90 days. These are outlined in our Guidance Document for Best Medical Care.

Speed of Intervention

A key principle of the endovascular intervention is that it must be both fast and safe. The target non-contrast CT to revascularization time is 90 minutes or less. This will be measured from the time of the first slice of the baseline non-contrast CT head done at the ESCAPE centre. The target complication rate is less than 1%. The quality of intervention will be ensured by hand-selection of sites and only be approved by the executive committee after a site visit. All sites must submit evidence within the 2 years prior to commencement of the trial that they can meet the 90-minute target of CT-to-recanalization time.

A key and critical component of the trial will be an ongoing quality assurance program to ensure that sites can meet these targets for endovascular intervention. Training will be undertaken at the sites and continued on a quarterly basis. Monitoring of interval times will be collated and provided to sites on a quarterly basis so that regular feedback might induce appropriately fast treatment processes. Sites that fail to meet these objectives in the trial will be dropped from the trial.

We will help, aid, abet and work with sites to achieve these targets. It is our strong conviction that in order for the intervention to work well enough to show the sought after effect size, it must be executed with military precision. This will require tremendous teamwork within the trial and within each site.

Consent Process

In order to achieve the rapid treatment process we are seeking, one option will be to utilize the deferral of consent process for research. The emergency nature of the treatment paradigm means that obtaining a standard research consent from a surrogate (eg. spouse or family member) will result in an unacceptable time delay that would:
(a) exclude a large proportion of patients because a surrogate consent giver is not available
(b) nullify the potential treatment effect because of the time delay. A 30-minute time delay will result in approximately an average 10% absolute risk difference on the primary outcome. It routinely takes 30-45 minutes to obtain a proper informed consent.

This is a novel aspect of this stroke trial. Further details are provided below.

Baseline Clinical and Laboratory Evaluations

All patients will undergo a routine neurological and clinical assessment at baseline including the NIHSS, pre-stroke Barthel Index. Routine emergency blood work will be evaluated including: CBC, PT, aPTT, serum creatinine and serum glucose. The results of this bloodwork are <u>not</u> required prior to randomization. If the patient is female and is of childbearing potential a pregnancy test (urine point-of-care

pregnancy test) must be completed and the result must be negative; this is the only mandatory laboratory test prior to randomization. Other laboratory or point-of-care testing may be performed at the discretion of the attending physicians and team. The study will use and collect local laboratory results and will not use a central lab. An ECG will be completed at baseline but may be completed in the first 6 hours of hospitalization; it is not required prior to randomization because it may slow down rapid treatment.

All patients will undergo rapid CT and CTA imaging. The target door-to-imaging time should be 25 minutes or less and target door-to-needle time for IV tPA treated patients should be less than 45 minutes . Routine CT and CTA imaging guidance are provided in the standard operating procedures manual.

CT quality is a critical component of the study. Each site will undergo a site visit in which the study neuroradiologist will review and discuss the CT imaging paradigm at the site. The site must agree to maximize their CT quality. This will be done on a site-by-site basis since it will be dependent upon the technical factors associated with the existing imaging infrastructure at the site.

CT angiography is mandatory for assessment of the inclusion criteria in the study. We are strongly recommending the use of a 3-phase CTA data acquisition paradigm. This will be detailed in the MOP.

CT perfusion and/or MR are not required. These imaging techniques are not prohibited by protocol; however, the stringent time requirements for initiating treatment mean that it would be very difficult to complete CTP and/or MR stroke imaging as part of the imaging work-up of these patients.

Schedule of Assessments

	Baseline	2-8 h	Day 1 (24 ±6 h from randomization)	Day 2 (48 ±6 h from randomization)	Day 5 or discharge (±1 d)	Day 30 (±5 d)	Day 90 (±7 d)§
Informed consent or documented deferral of consent	X					X	X
History and examination	X						
NIHSS	X	X	X	X	X	X	X
mRS			X¶			X	X
Barthel	X					X	X
miFUNCTION			X¶			X	X
Trailmaking A, B							X
MoCA							X
Boston Naming test							X
Sunnybrook Neglect Assessment Procedure (SNAP)							X
EQ-5D						X	X
NCCT head	X		X*				
CTA COW	X	X**					
Full emergency stroke labs	X‡						
Creatinine and CBC only			X				
ECG	X‡		X				
Adverse event assessment		X	X	X	X	X	X
Prior medications	X‡						
Concomitant medications	X	X	X	X	X	X	
Consent process survey			X				X

*Day +1 NCCT head may be supplanted by an MR head at the discretion of the local site. We encourage this.

**2-8 hours CTA COW – Control group only. We encourage early CTA within this time window. If there is a situation that arises where a subject randomized to the endovascular group does not have a final cerebral angiogram performed, that patient should have a 2-8h CTA to evaluate recanalization.

¶ The mRS and miFUNCTION scores at 24 hours are captured as estimates of historical (pre-stroke) scores

‡ These tests are required at baseline. Blood should be drawn at baseline, but results are not required prior to randomization. ECG should be done within 6 hours of hospital admission, but is not required prior to randomization. Prior medications should be collected but are not required prior to randomization.

§ At minimum 90d evaluations of mRS, NIHSS, BI should be performed by an evaluator blinded to the acute intervention. It is preferred if all 90d evaluation are done by a blinded evaluator.
d = days; h = hours

Clinical Management of the Patient

It is expected that subjects will receive the best usual standard of stroke unit care. All subjects are expected to be admitted to hospital as part of routine standard of care.

It is expected that all subjects will undergo a routine work-up for the mechanism of their stroke and be treated appropriately and definitively. This is critically important because subjects who have an excellent early recovery are at the highest risk of early recurrent stroke.[16] We wish to prevent recurrent stroke from confounding the 30-day and 90-day clinical outcome such that patients who are well at discharge remain that way for the duration of the 90-day follow-up period.

We expect the following preventive care. Relevant patients with atrial fibrillation should be anti-coagulated. Patients with symptomatic carotid artery stenosis should undergo carotid revascularization early and definitely within 2 weeks of stroke onset.[17] Risk factors, including hypertension, elevated cholesterol, diabetes mellitus, tobacco smoking, should be treated appropriately and aggressively according to current standards of care.

We expect patients to receive adequate hydration to prevent renal complications. Patients will receive intravenous radio-contrast media for CT angiography and in half the study population for endovascular intervention. While this medication is generally extremely safe in stroke patients,[18] simple hydration can prevent renal complications, particularly among patients with baseline borderline renal function and among those with diabetes mellitus. Further, patients with ischemic stroke are generally slightly hypovolemic at baseline. We recommend use of intravenous normal saline (0.9% saline) infusion at 1.5 – 2.0 cc/kg/h until the subject is eating and drinking safely and well. Therefore, for the typical subject this will mean IV NS at 75-125 cc/h overnight only. We do not recommend the use of bicarbonate solutions or N-acetyl-cysteine solutions for renal protection.[19,20]

For patients that are disabled from their stroke and require a longer in-patient stay and/or rehabilitation, it is expected that they will receive standard stroke unit care to prevent complications. These include:

- DVT prophylaxis for patients who are bed-bound or primarily bed-bound
- Swallowing assessments and prevention of aspiration pneumonia
- Early mobilization and physiotherapy to prevent skin breakdown, pneumonia, DVT/PE
- Early diagnosis and treatment of fever

All patients are expected to receive expert stroke unit care and then rehabilitation according to their clinical need.

Evaluations Following Randomization

Creatinine and CBC are collected at 24 (± 6 hours). An ECG will be completed at 24 (± 6 hours). Subjects randomized to the control arm (best medical management) will have a CTA COW completed at 2-8 hours following randomization. If there is a situation that arises where a subject randomized to the endovascular group does not have a final cerebral angiogram performed, that patient should have a 2-8h CTA to evaluate recanalization. All subjects will undergo a follow-up NCCT scan or brain MRI (including a minimum of diffusion-weighted imaging [DWI], gradient-echo [GRE], FLAIR, and intracranial MR angiography [MRA]) at 24 hours (± 6 hours) from the time of randomization. All subjects will have an historical mRS and miFUNCTION scale scores evaluated at 24 hours, 30 days (± 7 days) and 90 days (± 7 days). All subjects also undergo a NIHSS assessment at 2-8h (at the time of CTA), 24 hours (± 6 hours), 48 hours (± 6 hours), and 5 days or discharge, whichever comes first, 30 days (± 5 days) and 90 days (± 7 days). Where the deferral of consent process is approved and in use, all subjects who are enrolled using this process should have the deferral of consent survey completed in the 1-5d window and at 90 days. A mRS will be completed at 30 days (± 5 days) and 90 days (± 7 days). The Barthel Index will be completed at 30 days (± 5 days) and 90 days (± 7 days). The EQ-5D will be completed at 30 days (± 5 days) and 90 days (± 7 days). A cognitive battery using the following subscales will be completed at 90 days (± 7 days): Trailmaking A & B, MoCA, Boston Naming test and Sunnybrook hemi-neglect battery. At minimum 90-day outcomes assessments on the mRS, NIHSS and BI should be conducted by an evaluator blind to the acute treatment. It is preferred if all 90-day outcome assessments are conducted by a blinded evaluator.

Imaging

All imaging completed of the brain, NCCT, CTA, Angiogram and MRI will be rendered anonymous and sent to the ESCAPE core lab (Calgary) for central adjudication. Minimally the baseline, 2-8h CTA /Angiogram and the 24-hour imaging should be included. In addition, safety brain scans or other brain imaging within the first 48 hours should be sent to the core imaging lab. Core imaging lab will review all imaging for the acute stroke intervention period. Core imaging requirements are discussed in the MOP. We strongly encourage the use of MR (rather than CT) for the 24-hour brain assessment.

Clinical Management of Adverse Experiences

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Adverse events can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom,

or disease temporarily associated with the use of a drug, without any judgment about causality. Adverse events occur after randomization and are defined as not being present prior to enrolment. For example, a subject with known episodic gouty arthritis of the great toe, who develops an attack of gout is not considered to have suffered an adverse event; the event was known prior to enrolment. A subject who develops a new diagnosis of gout during the study period is judged to have suffered an adverse event. This is reportable as an adverse event even though it is most likely entirely unrelated causally to the study drug, but is instead only associated with study drug use temporally. Adverse events should be managed according to the best current standard of care.

Serious adverse events (SAEs) are those adverse events that are life threatening, require a surgical or medical procedure to prevent disability or death, result in admission to hospital, prolongation of hospitalization or transfer to an ICU, or result in death. A SAE can also be an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. For example, any new diagnosis of cancer (made after study enrollment) is considered an important medical event. A SAE is also an event that results in a congenital anomaly or birth defect, but this is an unlikely consideration for this trial since all or nearly all participants will not be of reproductive potential. Because our primary safety outcomes for the trial are also serious adverse events by definition, they will be reported dually as SAEs and as outcomes. Serious adverse should be managed according to the best current standard of care.

Adverse Event Reporting and Review

Adverse events should be reported as they occur on the eCRF. There are no timelines for reporting simple adverse events. Documentation must be supported by an entry in the subject's file. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product as judged by the Investigator, action taken and outcome.

Serious adverse events (SAEs) must be reported within 1 business day of the local investigator's first awareness of its occurrence. SAEs will be reviewed by the trial medical monitor. Because the ESCAPE trial is not a regulatory trial, SAEs do not require reporting to Health Canada, EMEA or other regulatory authorities. Because the adverse event profile of mechanical thrombectomy is well known due to the experience of its use, we do not predict that there will be unexpected adverse events.

Pregnancies occurring in study subjects will be treated procedurally as SAEs.

All safety outcomes and serious adverse events will be adjudicated by a designated safety committee comprising a stroke neurologist, and an independent neuro-

radiologist with experience in clinical trials. This adjudication process will determine the classification of the event.

At the end of the study, assuming the study proceeds to completion, the DSMB will be asked again to review the safety profile of the complete study data set and provide an opinion for the record.

Members of the DSMB will be acknowledged publically but will not be considered authors for any manuscripts that arise from this trial. The DSMB members may be involved in academic publications that describe or involve the actions of the DSMB in relation to the trial process. If relevant, this should occur in parallel with or after the publication of the primary manuscript describing the trial. Such a publication should not precede publication of the primary manuscript.

List of Expected Adverse Events

Expected serious adverse outcome events are the same as the safety outcomes.

Criteria for Intervention Discontinuation

The intervention is endovascular mechanical thrombolysis/thrombectomy. This procedure will be discontinued if there is an intra-procedural event that warrants stopping. This could include, but is not limited to, intracranial vessel rupture, iatrogenic arterial dissection, failure of the endovascular equipment with breakage of a stent or stent tine, groin or retroperitoneal hematoma, or other acute medical illness that precludes ongoing treatment of the stroke. As a guideline, we strongly recommend stopping the procedure if the time from baseline non-contrast CT is 180 minutes or greater.

Since the intervention is hyperacute only without repetition, it is inferred that the vast majority, if not all patients will have a completed intervention and therefore that the risk of cross-over from the surgical to the medical arm is quite low. We anticipate this could occur due to failure of vascular access, technical failure of angiography equipment, a completely uncooperative subject.

Statistical Considerations

The primary outcome will be a shift or one or more categories (proportional odds analysis) on the modified Rankin scale determined at 90 days from randomization.

The primary hypothesis is:

H_A: Subjects in the intervention arm will have a 1.8-fold greater odds of showing improvement on the mRS at 90 days.

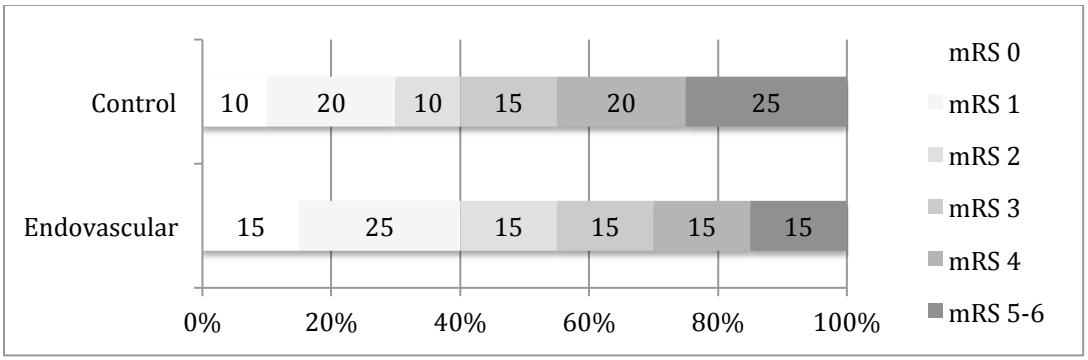
The primary analysis will be an intention to treat analysis. It will use an ordinal logistic regression model to derive the common odds of improvement ("shift") along the mRS scale. The proportional odds assumption will be testing using a Brant test. The analysis will be unadjusted. A secondary analysis using a proportional odds model adjusted for the 6 variables used for minimization (age, sex, NIHSS score, ASPECTS score, occlusion location, intravenous tPA use) will be reported.

A total sample size of 188 ideal patients per group with 90% power is required with alpha at 0.05. The sample size calculation is based upon Whitehead's power formula.[49] The sample size is estimated without the knowing the distribution of pre-specified confounding variables. We assume no cross-overs. Allowing for losses-to-follow-up (of up to 6%, n=24/400), a total required sample size of 400 ideal patients is anticipated. However, we know that the effect size is highly dependent upon very rapid treatment times and have planned to continue enrolling patients until up to 200 endovascular patients have been treated with a CT-to-first reperfusion time < 90 minutes. We conservatively assume that patients treated later than this time window have show no treatment effect. Currently, in our initial patients we are meeting this quality metric in 60% of our patient population, compared to our desired 80% or greater. Therefore,

(1) the trial is powered to detect an effect size based upon 400 ideal patients
(2) the maximum sample size for the trial will be 500 patients to ensure that 200 patients in the endovascular group meet the target treatment times (ie. are ideal patients).

The choice of the shift analysis is based upon empirical evidence that the mRS scale, when categories 5 and 6 are combined, is a true interval scale meaning that any one step increment in the scale is the same; thus, it is unlikely that the proportional odds assumption will be violated and clinical step changes across the scale are meaningful.[47] The proportional odds approach to analysis of the mRS scale is now an accepted methodology in the stroke community and by regulatory agencies.[10] Further, it allows us to include elderly patients (who have a poorer prognosis irrespective of treatment) because a shift from severe to moderate disability will still be recognized as an important outcome. The expected distribution of outcomes is based upon the pooled experience from the literature [SWIFT study, STAR registry, Calgary data, IMS-III study limited to an ESCAPE population, ALIAS part 1 study limited to an ESCAPE population[5,16,24,26,48]] and a 5% increase in favourable outcomes per mRS category.[Figure] A 5% change across each mRS category is judged to be the minimal clinically important difference.

Figure – Projected outcome by mRS category for sample size calculation



Predicted outcomes by mRS category in the ESCAPE trial, modeled on internal Calgary data, STAR study, IMS-III study. This shows an average 5% improvement in outcomes within each mRS category.

All secondary outcomes will be considered exploratory. Post-hoc analyses will be conducted. A formal statistical analysis plan will be finalized prior to the breaking of the blind, which will outline a details analysis plan for the primary, safety and secondary outcomes in accordance with any protocol changes that may have occurred over the course of the study. This statistical analysis plan will be considered the final analysis plan.

Data Collection and Management Overview

Data will be housed and managed in a custom database at the Hotchkiss Brain Institute Clinical Research Unit. The data will be supported by an FDA compliant commercial data base (iDATAFAX) which will allow electronic data capture (EDC) or fax-back data capture on a site-by-site basis. EDC will be preferred. A detailed manual will be prepared as part of the Manual of Operations.

All data will be entered into the electronic data capture system. Worksheet/CRFs locally will be considered source documents.

Economic Analysis

A cost-utility analysis will be conducted alongside the RCT. The primary outcome will be the cost per quality-adjusted life year gained with endovascular compared to best standard care. This is most appropriate economic outcome to inform a policy decision about the adoption of endovascular therapy as it allows of comparison with other competing technologies both within stroke care and across other healthcare programs.

A decision analytic model will be developed to model the clinical, cost and utility outcomes over a subject's lifetime. The model will be composed of two parts; the initial 90-days post stroke (informed by the clinical arm of the RCT) and the subject's subsequent trajectory (based on long-term outcome studies of stroke survivors). Costs will be gathered prospectively in the trial for 90 days using the

already established corporate microcosting database available in Calgary. Long-term care costs will be imputed from the literature. Utility scores will be estimated at 30 and 90 days post stroke using the EQ-5D. Long-term utility will be imputed from the literature based on mRS score at 90 days.

Study Documentation, CRFs and Record Keeping

Investigator's Files/Retention of Documents

The Sponsor-Investigator (and any Participating Site Investigators) must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories: (1) Investigator's Study File; and (2) subject clinical source documents.

The Investigator's Study File will contain the protocol/amendments, Case Report and Query Forms, IEC/IRB and governmental approval with correspondence, all versions of ethics approved informed consent forms, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc.

Subject clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, signed ICFs, consultant letters, and subject screening and enrollment logs. The Sponsor-Investigator (and any Participating Site Investigators) must keep these two categories of documents on file according to local clinical trial regulation. For example, at the University of Calgary, for non-Health Canada regulated studies, that period is 5 years from the time of official closure of the study. After that period of time the documents may be destroyed, subject to local regulations.

Source Documents and Background Data

Any Participating Site Investigators shall supply the Sponsor-Investigator on request with any required background data from the study documentation or clinic records. This is particularly important when eCRFs are illegible or when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

Audits and Inspections

The Sponsor-Investigator and any Participating Site Investigators should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor-Investigator or designee after appropriate notification. The verification of the CRF data must be by direct inspection of source documents.

Case Report Forms

For each subject enrolled, a CRF must be completed and signed by the Sponsor-Investigator (and any Participating Site Investigator) or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study (even during a pre-randomization screening period if a CRF was initiated). If a subject withdraws from the study, the reason must be noted on the CRF. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

All forms should be filled out clearly and legibly. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the Sponsor-Investigator (and any Participating Site Investigators) or his/her authorized delegate. The Sponsor-Investigator (and any Participating Site Investigators) should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor-Investigator in the CRFs and in all required reports.

Human Subjects

IRB/REB

This protocol and the informed consent document and any subsequent modifications are reviewed and approved by the IRB/REB or ethics committee responsible for oversight of the study. A signed consent form must be obtained from the subject. For subjects who cannot consent for themselves, a legally authorized representative, or person with power of attorney, may sign the consent form. The consent form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form must be given to the subject, the legally authorized representative, or the person with power of attorney; and this fact must be documented in the subject's record.

Where the subject is unable to consent and a legally authorized representative is not immediately available, a waiver of consent / deferral of consent process will be undertaken. This will be documented in the medical record. It is the intent of this study, that the waiver/deferral of consent process be fully implemented where permissible to reduce time to treatment. It is also expected that a majority of cases will be enrolled in the trial using this mechanism. An Independent physician will be required to review and sign the waiver/deferral inclusion and exclusion criteria prior to enrollment.

In Canada, the Tri-council Policy Statement: Ethical Conduct for Research Involving Humans, governs the IRB and consent processes. Conditions for waiver/deferral of informed consent have been clearly defined. Emergency research where the process of consent can prevent the application of definitive treatment or where time delay prevents enrolment can be approved with external oversight of the IRB under the waiver of consent guidelines. Generally, to allow a process of waiver/deferral of

consent, the situation must be adjudged such that the principles of social justice are upheld at the expense of infringement upon the principle of patient autonomy. Emergency stroke treatment research fits these criteria and this process will be tested in this study.

Confidentiality

All imaging, evaluation forms, reports, and other records that leave the site are identified only by the site and subject number to maintain subject confidentiality. All records are kept in a locked file cabinet. Clinical information is not released without written permission of the subject, except as necessary for monitoring by IRB/REB, Health Canada, the sponsor, or the sponsor's designee.

All study investigators at the clinical sites must ensure that the confidentiality of personal identity and all personal medical information of study participants are maintained at all times. Federal legislation in Canada (Personal Information Protection and Electronic Documents Act – PIPEDA), and provincial legislation (eg. Health Information Act – HIA in Alberta) where applicable, must be followed. Additionally, any U.S. clinical sites must follow privacy obligations to study participants under the Health Insurance Portability and Accountability Act (HIPAA). European or Asian/Australasian sites must conform to local privacy and confidentiality law and custom. On the CRFs and other study documents or image materials submitted to the CRU, the subjects are identified only by study identification codes.

Personal medical information may be reviewed for the purpose of verifying data recorded in the CRF by the site monitors. Other properly authorized persons, such as the regulatory authorities, may also have access to these records. Personal medical information is always treated as confidential.

Site Monitoring

To ensure monitoring responsibilities are performed to the fullest extent possible, an elite team of 1 to 2 regionally based, industry experienced independent contractor clinical research monitors perform on site data verification for the trial. All data will be monitored. All data monitored on site are verified for accuracy and thoroughness using the most appropriate source documents for all subjects. In addition, 100% of subjects enrolled are monitored for the presence of signed consent and HIPAA and PIPEDA documentation.

Additional on-site monitoring verification includes: ongoing evaluation of the adequacy of site facilities and staff, site recruitment, subject randomization, the presence of regulatory documents, and specific review of documents and data. The initial performance-monitoring visit to a site takes place after the initial subject(s) are enrolled. Thereafter, it is expected that each site will be monitored at least twice – once during the trial and once at closeout.

During the monitoring visit, any omissions and corrections to data submitted to the database are noted and queries are generated by the monitor on site.

The close-out monitoring visit by a monitor takes place at the completion of subject enrollment and protocol required follow-up visits at the performance site. At that visit, the monitor again reviews the presence of a regulatory file and verifies documents for currency and completion as directed by the CRU. Sites are instructed in the record retention of all trial documents. Principal Investigators are directed to close the trial and issue a final report to the IRB / REB. Finally, any additional special considerations for the auditing of any additional safety issues are made during this final monitoring visit.

Publication and Presentation Policy

The trial executive committee will be co-authors on all publications and presentations. The primary author list for the primary publication will consist of the executive committee and the site principal investigator at each of the sites. A formal publication policy will be presented and developed by the trial executive.

Ancillary Studies Policy

Ancillary or sub-studies may be considered by the trial executive committee. Important principles that guide the addition of ancillary studies are:

(1) no subject shall be enrolled in a concurrent investigational drug/device trial during the study period

(2) concurrent enrollment of an ESCAPE study subject in a site specific observational cohort study is allowable, where the following conditions are met:

   a. the executive committee is notified
   b. the concurrent study does not interfere with any study follow-up procedures or potentially confound the outcome of the ESCAPE trial
   c. the site PI of the concurrent study explicitly acknowledges that the treatment given in the ESCAPE trial may confound the outcome of the site-specific concurrent study
   d. the subject may not be included in any publication or report until the ESCAPE study has been concluded

(3) Ancillary or sub-studies shall be vetted and approved by the trial executive committee.

Data-sharing plan

The Executive Committee will follow the spirit of the NIH policy on data-sharing [http://grants2.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm]. A similar policy is in place at CIHR. In addition, the Executive Committee will follow the CIHR guidelines on public access to trial results and make the results available

as free-access using PubMed. Upon completion of the ESCAPE Trial, a public use database will be prepared by stripping any and all personal identifiers. The public use database, consisting of several data files, should contain: (1) baseline and demographic characteristics; (2) outcomes assessments; (3) CT/MRI data; (4) concomitant medications and procedures; and (5) adverse events. Each data file is made available as a formatted SAS dataset or other electronic format. The data files are distributed along with the data dictionary and a brief instruction ("Readme") file. These data files will be made available to the public only after all major manuscripts (including secondary analysis papers) of the Trial are accepted for publication in peer-reviewed journals.

Financial Considerations

Routine care is expected to be paid for by the existing standard medical insurance system. This will include but is not limited to:

- Admission to hospital
- Baseline laboratory testing, ECG, baseline NCCT and CTA
- Follow-up brain imaging at 24 hours
- Follow up ECG at 24 hours
- Follow-up laboratory testing
- Physician fees
- Treatment processes in the endovascular lab since they are considered standard of care
- Nursing care
- Rehabilitation and home care if relevant
- Outpatient clinic follow-up at 90 days (routine)

The study fees are designed to cover the costs of study personnel, data collection, research study processes and treatments, the 4-8 hour CT angiogram, the 30 day follow up visit, the 90-day follow-up visit. The study fees are inclusive of any local institutional overhead/indirect costs.

Appendix 1 – Guidance on Endovascular Treatment

Notes on the Components of success with intra-arterial therapy in acute stroke with large proximal artery occlusion:

- short time from onset
- short ED to start of imaging time
- understanding imaging
- short imaging time
- excellent overall organization to reduce CT to groin puncture time
- short, precise consent or try to get waiver of consent
- short CT to recanalization time
- aim for TIMI 3 (as opposed to TIMI 2b) recanalization of the arterial occlusive lesion and TICI 3 reperfusion
- control BP as soon as recanalization achieved
- keep complication rate low

Short time from onset:
This has been shown in many studies and intuitively makes sense. However, from the perspective of this study it is not a controllable factor. On average, for major acute ischemic stroke, it takes 60 minutes from door – ED arrival.

Short ED to start of imaging time:
Encourage the creation of a system that includes communication from the ambulance to ED. Use NIH score and other markers of large strokes and training to facilitate the process. If possible, communicate to CT scanner about the upcoming subject. Create a system of prioritization within the CT scan list.

The process of electronic records and computerization can sometimes be a limiting factor. This would need to be studied at each institution and get a better understanding if this can result in delays. As an example, CT scan cannot be done till the time there is an order in the electronic registration system.

Electronic records can also facilitate information gathering. While the subject is en route by ambulance, information on past history, medications etc. may be gathered prior to arrival. These data can be very helpful in facilitating fast arrival-to-imaging times.

Understanding imaging:
There is significant variation across the world as to what imaging modalities people feel comfortable with in deciding appropriate patients for intervention.

Overall, CT shall remain the mainstay from the perspective of this trial. This would include

- NCCT

- CTA from arch to head

NCCT quality:

- Minimum power: 120-140 kV, 170-200 mA
- 2 second scanning time
- 5 mm section thickness
- Appropriate algorithm reducing bone artifacts and high SNR for gray-white differentiation
- Contiguous axial sections from skull base to vertex parallel to the inferior orbitomeatal line (IOML)
- A good quality stroke protocol scan is defined by the following two criteria on the unaffected side: Lateral margin of the lentiform nucleus well discriminated in the absence of previous infarction.
- Insular ribbon is well defined in the absence of previous infarction.
- CTA should use minimum contrast media –75cc is the recommended amount
- Helical acquisition
- Reformats should include: thin (3mm) axial, sagittal, coronal MIPS, thick (25 mm)axial and sagittal MIPS

NCCT:

ASPECTS is less unreliable early in stroke (ie. within 90 minutes of onset); however, at later time windows it should be easy to recognize large areas of irreversible damage. Having a good quality scan and optimization of scanner is key. Further information is available at: www.aspectsinstroke.com

A teaching slide set and module will be available for use within the trial.

CTA:

The importance of contrast bolus timing should be emphasized. Using single-phase CTA, it is important to have a sufficiently venous weighted study to be able to visualize the collateral circulation adequately. The CTA must include the aortic arch to allow the interventionalist a view for planning.

Multi-phase (3 or 4 phase) CTA may be used to show the evolution of the blood flow. This technique is particularly useful in demonstrating regional blood flow hang-up and implicated distal circulation occlusions.

CT perfusion and MR perfusion imaging

These techniques are only for centres that have a well-oiled machinery. The time taken for imaging and image interpretation may make it impossible to meet the thresholds for imaging to recanalization times. It is not advisable to spend 20 minutes acquiring and post processing CT perfusion images when this time could be best spent treating the subject. In centres with well-groomed processes, these things happen in parallel.

CTP should be done after CTA as it is not critical to randomization. Very low CBV should be used as an exclusion criterion for the trial. Further, for CTP, radiation dose should be a consideration and a reason to avoid its use since it is not required for randomization.

Short imaging time:
The total imaging time starts from the time the subject reaches the door of imaging suite to when the subject is out of there and ready to move to next step. It includes putting subject on table, setting IV line, connecting to pump etc. In the case of MR it would include the time taken to exclude presence of pacemaker etc. It includes post-processing time. Imaging time should not exceed 15 minutes.

Excellent overall organization to reduce CT to groin puncture time
This is likely where the waiver of consent will play a big role since it is a bottleneck, once the subject has met the appropriate inclusion and exclusion criteria. There are multiple steps to get from imaging to the groin puncture and these may include:

-image interpretation
-blood draw
-ECG
-anesthesia involvement for conscious sedation
-prepping the angiography suite
-availability of nurse and technician
-availability of respiratory technician and anesthetist if appropriate
-ability to move the subject from the CT rapidly to the interventional suite

Consent:
Ideally deferral of consent will take place with most patients. We will provide a training module on how to take consent, provide information about deferral of consent for all study participants.

Groin puncture-to-Recanalization time:
From the time the subject is on angio table:

- Puncture the groin while the subject is getting draped. Do not wait.
- Have a stroke kit ready
- Have a pre-decided division of labour: who is going to do what?
- Simple things like shaving the groin: is it needed?
- Foley catheter. Draining the bladder improves subject comfort and help reduce BP
- Assess need for anesthesia; overall general anesthesia should be avoided. Involvement of an anesthetist for conscious sedation is ideal.
- Training on use of other drugs to hold subject still: consult with local anesthetist
- 8F sheath
- Go straight to vessel of interest
- Choice of catheter dependent on CTA
- Whether common carotid artery run needed on not dependent on CTA

- Try to use standardized microcatheter and wire
- Plan an entire kit of stuff that is needed included things like a 60 cc syringe

TIMI 3 / TICI2c or 3 flow
Aim for complete recanalization (TIMI 3) and reperfusion (TICI 3). A few small distal emboli are an acceptable outcome and are generally tolerated well by collateral flow.

Control BP
While the artery remains occluded, SBP 150 or greater is probably useful in promoting and keeping collateral flow adequate. Indirect evidence supports this assertion. Once reperfusion has been achieved, BP often falls naturally. Controllng blood pressure once reperfusion has been achieved aiming for a normal BP for that individual is sensible. Labetalol or an IV B-blocker such as metoprolol in low doses is preferred.

Keep complication rate low
Be prepared to stop and back out. Do not take unnecessary risks. Remember that you do not necessarily need a "perfect" angiographic outcome to have a good clinical outcome.

Medical Management
Designate one person to observe and manage the subject's vital signs. Follow the SaO2, pulse and blood pressure. Manage accordingly. In an ideal circumstance, an anesthetist helps manage this aspect of care.

In the absence of an anesthetist, the standard of care is that the attending neurologist or stroke fellow will have a lead apron on and be in the neuro-angiosuite managing the medical and neurological condition of the subject.

Blood pressure management is described above. There are no clear guidelines that are based upon level 1 evidence.

Conscious Sedation Management
We strongly recommend that all sites avoid general anesthesia. The vast majority of endovascular stroke treatment can be completed under conscious sedation. Several case series support the concept that general anesthesia is associated with poorer outcomes. A possible explanation is prolonged blood pressure lowering resulting in more rapid progression to infarction.

A simple conscious sedation paradigm for adult patients is as follows:
-2.5 mg midazolam IV
-25 µg fentanyl IV

These drugs should be given together since this avoids the occasional paradoxical agitation seen with IV benzodiazepines alone. They can be given q10-15min. Follow the RR and SaO2 to avoid trouble with respiratory suppression. Managing conscious sedation can be done by the neurologist or stroke fellow in the room.

It is often additionally helpful to pre-treat patients with anti-nausea agents:
-25-50 mg dimenhydrinate (gravol) IV

This drug is very mildly sedating and may help avoid an episode of aspiration.

The only patients who typically will require intubation include those with paradoxical agitation associated with a Wernicke's aphasia, or those who develop respiratory compromise due to aspiration or other event arising after randomization.

Carotid artery stenting

Some interventionalists prefer to stent a stenosed carotid artery either during or at the end of a case. We recommend that this not be done.

Tandem occlusion of the extracranial carotid at the bifurcation associated with an M1-MCA occlusion is common. The target lesion initially is the M1-MCA occlusion. Advance a catheter past the ICA lesion and deal with the M1-MCA first. Very often, in this process, the proximal ICA is open at the end of treating the M1-MCA because of the mechanical manipulation of the occlusive lesion at the carotid. What was initially a 99% stenosis is reduced to 60 or 70%.

At this point stop. Treat the subject with ASA per rectum (since they cannot swallow) and bring the subject back the following day to decide on whether to stent or pursue endarterectomy. It is simply not necessarily true that forward flow in the carotid is required to keep the M1-MCA open.

The major potential difficulty with leaving a carotid stent in place is the need for antiplatelet therapy, which will increase the chance of major symptomatic bleeding.

Very occasionally, a stent is required – either intracranially or at the carotid bifurcation. In these circumstance, we recommend using ASA and clopidogrel rather than IV abciximab or eptifibatide. Give ASA per rectum and as soon as possible give 600 mg clopidogrel per NG.

Use of IA tPA

The study protocol does not forbid the use of IA tPA. However, note that tPA is not indicated for direct IA catheter delivery. Thrombolytic may be particularly useful once some flow is re-established. The maximum dose we recommend is 10 mg.

Reconstitute tPA is sterile. We recommend using 2mg vials of CathFlo™ (alteplase) to keep cost low. Dilute 2cc of tPA (2mg in 2cc of sterile water) with 4 cc of saline. Draw up 3cc of this solution in 3cc syringes and give additional tPA by very gentle pulse-spray technique through the microcatheter.

Number of Devices / GP2b3a Inhibitors / When to stop

Some lesions are too difficult to treat and adequate recanalization may not be achieved. The more devices that are used and the most antithrombotic agents that are used, the greater the risk of major adverse events. Use of intravenous GP2b3a inhibitors in the setting of acute ischemic stroke, is associated with a very high risk (up to 40%) of hemorrhage. Please do not use them. Please make every effort to achieve recanalization within 90 minutes of imaging. If this is clearly not going to be achievable, the interventionalist and team must make a judgment as to whether to continue. Spending more than 90 minutes working on an intracranial lesion is a recipe for major adverse events. Stop and call it.

Chasing distal M2, M3 or A2, A3 occlusions

Once the arterial occlusive lesion is open, there will remain visible distal occlusion approximately 10-20% of the time. Do not chase these. Do not give regional tPA infusion. A perfect angiographic outcome is not necessary for a good clinical outcome and there is a greater risk of doing harm.

Appendix 2 – Further Details on Inclusion and Exclusion Criteria

Details Explanation of the Inclusion and Exclusion Criteria
Checklist for the Enrolling Team

1. Subject meets all inclusion and exclusion criteria.
2. Subject fits the intent of the trial.
3. Subject can return for in-person follow-up at 90 days or site personnel are willing to go to the subject to obtain follow-up or the subject resides in a city where there is a known ESCAPE clinical site.
4. Subject has a good functional status. Subject is independent for all activities of daily living immediately pre-stroke.
5. In the case of in-hospital stroke, the immediate pre-stroke state is one of functional independence. This means that typically only patients admitted for elective outpatient procedures and who suffer stroke as a complication o the procedure are eligible.
    a. major neurological, abdominal, thoracic or limb surgery will typically be an exclusion. Patients are bed bound as they recovery. Stroke as a complication in this circumstance rarely results in a good outcome because the pre-morbid condition combines with the stroke to produce a poor outcome
    b. stroke as a complication of elective coronary angiography or cerebral angiography would be potentially eligible
    c. stroke as a complication of percutaneous aortic valve replacement, percutaneous device placement, mitral valve commissurotomy, angioplasty for unstable angina or recent MI will be an exclusion if patients are not independent immediately prior to intervention, or if their cardiac prognosis is not adequate.
6. Subject can be treated rapidly within the time targets. Interventionist and neurologist agree and facilities are available.
7. Deferral of consent processes will include the documentation by a second independent physician that the process is acceptable.

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