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.