TIGER STUDY

Treatment with Intent to Generate Endovascular Reperfusion

INVESTIGATIONAL PLAN

IDE# G180004

ClinicalTrials.gov ID: NCT03474549

Protocol #: CLN-TI-001

VERSION: 3.0

DATE: Dec 12, 2019

Study Sponsor:
Rapid Medical
P.O. Box 337
Carmel Building
Yokneam 2069205
Israel

CLINICAL INVESTIGATION PLAN (CIP) APPROVAL

Study Title: TIGER Study

CIP Version: 3.0

CIP Date: Dec 12, 2019

Signatures:

Dr. Walid Haddad
VP Clinical Operations
Rapid Medical

Sponsor Representative

Date

Dr. Jeffrey L. Saver
Geffen School of Medicine at UCLA
Director, UCLA Comprehensive Stroke Center 710 Westwood Plaza
Los Angeles, CA 90095

Coordinating Principal Investigator

Date

Dr. Rishi Gupta
WellStar Medical Group
Neuroscience
Atlanta, GA

Co-Coordinating Principal Investigator

Date

CIP SIGNATURE PAGE

Study Title: TIGER Study

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I have read the Investigational Plan and agree to adhere to the research plan contained herein. Deviations from the research plan will not be made prior to sponsor notification, except when necessary to protect the safety, rights, or welfare of study Subjects.

I agree to conduct or supervise the conduct of the described investigation and ensure all participating investigators and research staff are appropriately trained regarding the study conduct prior to participating in any study related activities.

I will ensure that the requirements relating to obtaining informed consent and Institutional Review Board (IRB) review and approval, as they pertain to 21 CFR Part 50, ICH E6 are met.

I agree to maintain adequate and accurate records in accordance with 21 CFR 812.140 and to make those records available for inspection in accordance with 21 CFR 812.145 and ICH E6.

I will ensure that the IRB complies with the requirements of 21 CFR Part 56 and ICH E6 and will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB any changes in research activity and all unanticipated problems involving risks to human Subjects or others. Additionally, I will not make any changes in research without IRB approval, except where necessary to eliminate apparent immediate hazards to human Subjects.

I agree to comply with all other clinical investigator obligations and pertinent requirements in 21 CFR Part 812 and ICH E6.

_____

Site Principal Investigator (please print or use stamp)

_____ _____

Site Principal Investigator Signature Date

LIST OF ABBREVIATIONS

ADE	**Adverse Device Effect**
AE	**Adverse Event**
AIS	**Acute Ischemic Stroke**
AMC-LDS	**Academic Medical Center – Linear Disability Score**
A-P	**Anterior-Posterior**
ASPECTS	**Alberta Stroke Program Early Computed Tomography Score**
CDA	**Confidentiality Agreement**
CEC	**Clinical Events Committee**
CFR	**Code of Federal Regulations**
CMP	**Clinical Monitoring Plan**
CIP	**Clinical Investigation Plan**
CRO	**Contract Research Organization**
CTA	**Clinical Trial Agreement**
CT	**Computed Tomography**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
eCRF	**Electronic Case Report Form**
EDC	**Electronic Data Capture**
EVT	**Endovascular Treatment**
FDA	**Food and Drug Administration**
GCP	**Good Clinical Practice**
GFR	**Glomeruler Filtration Rate**
IA	**Intra-arterial**
ICF	**Informed Consent Form**
ICH	**Intracranial Hemorrhage**
ID	**Identification**
IDE	**Investigational Device Exemption**
IFU	**Instructions for Use**
INR	**International Normalized Ratio**
IRB	**Institutional Review Board**
ISO	**International Organization for Standardization**
ITT	**Intent To Treat**
IV	**Intravenous**
IV t-PA	**Intravenous tissue plasminogen activator**
LAR	**Legally Authorized Representative**
LVO	**Large Vessel Occlusion**
MDR	**Medical Device Reporting**
MRI	**Magnetic Resonance Imaging**

mRS	**Modified Rankin Score**
mTICI	**modified Thrombolysis in Cerebrovascular Infarction**
NIH	**National Institutes of Health**
NIHSS	**National Institutes of Health Stroke Score**
PG	**Performance Goal**
PI	**Principal Investigator**
PRO	**Patient Reported Outcome**
PT	**Prothrombin Time**
PTT	**Partial Thromboplastin Time**
RFA	**Rankin Focused Assessment**
RHV	**Rotating Hemostatic Valve**
rt-PA	**Recombinant Tissue Plasminogen Activator**
SAE	**Serious Adverse Event**
SADE	**Serious Adverse Device Effect**
sICH	**Symptomatic Intracranial Hemorrhage**
SOC	**Standard of Care**
TICI	**Thrombolysis in Cerebrovascular Infarction**
TIMI	**Thrombolysis in Myocardial Infarction**
UADE	**Unanticipated adverse device effect**

PROTOCOL SUMMARY

Title	**Treatment with Intent to Generate Endovascular Reperfusion**
Short title	TIGER Study
Sponsor	Rapid Medical
Coordinating Principal Investigators	Dr. Jeffrey L. Saver Geffen School of Medicine at UCLA Director, UCLA Comprehensive Stroke Center 710 Westwood Plaza Los Angeles, CA 90095, USA. Dr. Rishi Gupta WellStar Medical Group Neuroscience Atlanta, GA
Investigational Product	Tigertriever Mechanical Revascularization Device
Objective	The objective of the TIGER Study is to evaluate the safety and effectiveness of the Tigertriever device in restoring blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke due to a large vessel occlusion (LVO). This study is designed to support substantial equivalence to approved and marketed products such as the Solitaire or Trevo Retriever.
Study Design	This study is a US and EU, multicenter, single arm, prospective IDE study to evaluate the safety (defined as all cause mortality) and effectiveness of the Tigertriever Revascularization Device in Acute Ischemic Stroke (AIS) patients ineligible for IV t-PA treatment or who fail IV t-PA therapy.
Device Description and Intended Use	Tigertriever is a CE marked mechanical revascularization device. The Tigertriever Revascularization Device is indicated to restore blood flow by removing thrombus from a large intracranial vessel in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for IV t-PA or who fail IV t-PA therapy are candidates for treatment.
Primary Endpoints	**Effectiveness**: Successful reperfusion, defined as mTICI Score ≥ 2b at the end of the Tigertriever revascularization procedure. **Safety**: Composite of all-cause mortality at 90 (±14) days and symptomatic intracranial hemorrhage (sICH) within 24 (18-36) hours of the study procedure.
Secondary Endpoints	**Effectiveness**: • Good Clinical Outcomes- Percentage of participants with a modified Rankin Scale (mRS) score of ≤2 at 90 (±14) days post treatment.

	• Successful reperfusion (defined as mTICI 2b or better) at first pass. • Health related quality of life (EQ-5D score) • Degree of disability (Academic Medical Center – Linear Disability Scale score) **Safety**: • Any asymptomatic intracranial hemorrhage within 24h (18h-36h) of the procedure • Neurological deterioration (≥4-point increase in NIHSS score) at 24h (18h-36h) post-procedure. • Embolization to previously uninvolved vascular territories,
Number of Subjects: The maximum Sample size is 160, including up to 60 lead-in Subjects (up to 4 per site). Lead-in Subjects will be used for endpoint analysis.	**Number of Study Centers:** Up to 25 centers total in the US and EU
Population	The TIGER Study will include male or female patients age 18-85 who present with acute ischemic stroke due to a large vessel occlusion confirmed by vessel imaging.
Inclusion Criteria	1. New focal neurologic deficit consistent with being of acute cerebral ischemia origin. 2. Age 18-85 years old (inclusive). 3. Interventionalist estimates that treatment with the Tigertriever (first deployment in target vessel) can be achieved within 8 hours of symptom onset. 4. Patient either: a) eligible for, and received, IV t-PA within 3 hours of symptom onset, at the correct 0.9 mg/kg dose, or b) ineligible for IV t-PA. 5. NIH Stroke Scale score of 8-29. 6. No known significant pre-stroke disability (prestroke mRS 0 or 1). 7. Catheter angiographic confirmation of a large vessel occlusion in the intracranial internal carotid artery, the M1 or M2 segments of the middle cerebral artery, the intracranial vertebral artery, or the basilar artery that is accessible to Tigertriever device. 8. For strokes in the anterior circulation, the following imaging criteria should also be met: a. MRI criterion: volume of diffusion restriction visually assessed ≤50 mL, OR b. CT criterion: ASPECTS 6 to 10 on baseline NCCT or CTA-source images, 9. For strokes in the posterior circulation, the following

	imaging criterion should also be met: pcASPECTS score 8 to 10 on baseline NCCT, CTA-source images, or DWI MRI. 10. Anticipated life expectancy of at least 6 months. 11. A signed informed consent by patient or a Legally Authorized Representative or independent physician in case of oral consent.
Exclusion Criteria	1. Subject already participating in another study of an investigational treatment device or treatment. 2. Use of any other intra-arterial recanalization drug or device prior to the Tigertriever (Tigertriever not as first choice device). 3. Angiographically evident excessive arterial tortuosity precluding device access to the thrombus. 4. For all patients, severe sustained hypertension with SBP >220 and/or DBP >120; for patients treated with IV tPA, sustained hypertension despite treatment with SBP >185 and/or DBP > 110. 5. Glucose < 50 mg/dl (2.78 mmol/L) or > 400 mg/dl (22.20 mmol/L). 6. Known hemorrhagic diathesis. 7. Coagulation factor deficiency or oral anti-coagulant therapy with an international normalized ratio (INR) of more than 3.0. 8. Treatment with heparin within 48 h with a partial thromboplastin time more than two times the laboratory normal. 9. Patients who have received a direct thrombin inhibitor within the last 48 hours; must have a partial thromboplastin time (PTT) less than 1.5 times the normal to be eligible. 10. Platelet count of less than 50,000/uL. 11. History of severe allergy to contrast medium, nickel, or Nitinol. 12. Intracranial hemorrhage. 13. Significant mass effect with midline shift. 14. Intracranial tumor (apart from small meningioma, ≤ 2 cm in diameter). 15. Stenosis or any occlusion in the deployment site or in a

	proximal vessel requiring treatment or preventing device access to the thrombus (for example, stenosis or occlusion in the cervical internal carotid artery). 16. Females who are pregnant or breastfeeding. 17. Known current use of cocaine at time of treatment. 18. Prior recent stroke in the past 3 months. 19. Renal failure with serum creatinine >3.0 or Glomerular Filtration Rate (GFR) <30. 20. Known cerebral vasculitis. 21. Rapidly improving neurological status defined as improvement of greater than 8 points on the NIHSS or improvement to NIHSS of < 6 prior to procedure 22. Clinical symptoms suggestive of bilateral stroke or stroke in multiple territories. 23. Ongoing seizure due to stroke. 24. Evidence of active systemic infection. 25. Known cancer with metastases. 26. Suspicion of aortic dissection, septic embolus, or bacterial endocarditis. 27. Evidence of dissection in the extra or intracranial cerebral arteries. 28. Occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior/posterior circulation). 29. Aneurysm in target vessel.
Study Duration	Enrolment: approximately 24 months Follow-up period: 3 months
Statistical Analysis	The primary efficacy endpoint, defined as successful reperfusion with the Tigertriever device, will be tested against a performance goal (PG) derived from adjudicated trial data for similar devices. The primary safety endpoint, defined as the composite of all-cause mortality at 90 days and symptomatic intracranial hemorrhage (sICH) at 24 hours, will be tested against a performance goal (PG) derived from the same set of trials. Secondary efficacy and safety endpoints will not be subject to hypothesis testing but will be examined using confidence intervals to characterize the relevant population parameter.

Schedule of Events							
Elapsed time/Study procedures	**Baseline**	**Procedure**	**24 hours (-6/+12)**	**48 hours (±12)**	**Discharge or 4 days**	**30 (±7) days**	**90 (±14) days**
Informed Consent	X						
Demographics	X						
Medical History and Concomitant Medications	X						
Time of Stroke Symptoms Onset	X						
Brain CT Scan or MRI	X		X				
Vital Signs	X	X	X		X		
NIH Stroke Scale	X		X	X	X		X
Premorbid mRS score	X						
mRS score					X	X	X
Clinical Laboratory	X						
Time of groin puncture		X					
Cath angiography and clot retrieval		X					
mTICI Outcome		X					
Functional activity questionnaire- Barthel Index						X	X
Patient-Reported Outcomes (EQ-5D, AMC-LDS)							X
Prior/concomitant medications	X	X	X	X	X	X	X
AE (including hemorrhage other than sICH)		X	X	X	X	X	X

Summary of Investigational Plan Changes

Revision History	Effective Date
01	01Jan2018
02	01Mar2018
03	

Revision 02, 06Feb2018

Section	Change From	Change To	Rationale for Change
3.1.2- Secondary Endpoint		Added secondary effectiveness endpoint- - Health related quality of life (EQ-5D score) - Degree of disability (Academic Medical Center Linear Disability Scale score)	Correction in response to conditions noted on FDA letter dated 04Feb2018
3.2.1- Prinary Endpoint	All- cause mortality at 90 (±14) days	Composite of all-cause mortality at 90 (±14) days and symptomatic intracranial hemorrhage (sICH) within 24 (18-36) hours of the study procedure	Correction in response to conditions noted on FDA letter dated 04Feb2018
3.2.2- Secondary Endpoint		Added secondary safety endpoint- Embolization to previously uninvolved vascular territories	Correction in response to conditions noted on FDA letter dated 04Feb2018
5.4- Lead-in Phase		Added- Subjects enrolled in the Lead-in phase will be consented, treated and followed according to the	Correction in response to conditions noted on FDA letter dated 04Feb2018

Section	Change From	Change To	Rationale for Change
		clinical protocol, in the same manner as the regular study subjects.	
6.2.2- Exc 15	Intracranial tumor (apart from small meningioma).	Intracranial tumor (apart from small meningioma, ≤ 2 cm in diameter)	Correction in response to conditions noted on FDA letter dated 04Feb2018
6.2.1- Inc 8		1. Added- Inclusion Criteria 8- For strokes in the anterior circulation, the following imaging criteria should also be met: a. MRI criterion: volume of diffusion restriction visually assessed ≤50 mL, OR b. CT criterion: ASPECTS 6 to 10 on baseline NCCT or CTA-source images. 2. Added- Inclusion Criteria 9 – For strokes in the posterior circulation, the following imaging criterion should also be met: pcASPECTS score 8 to 10 on baseline NCCT, CTA-source images, or DWI MRI. Deleted Exclusion criterion 12.	Correction in response to conditions noted on FDA letter dated 04Feb2018
7.2.4- Imaging		Added- ASPECTS and pcASPECTS scores.	In response to conditions noted on FDA letter dated 04Feb2018

Section	Change From	Change To	Rationale for Change
7.3.1- Angiography		Added- The University of California at Los Angeles with the following address: Angiography and Noninvasive Imaging Core Lab David S Liebeskind, MD, FAAN, FAHA, FANA UCLA Department of Neurology Neuroscience Research Building 635 Charles E Young Drive South, Suite 225 Los Angeles, CA 90095-7334	Added Core Lab information
7.3.2- Device preparation, delivery and positionong, 7.3.3- Retrieval			Precautions and clear instructions were added, in response to conditions noted on FDA letter dated 04Feb2018. The instructions are for determining whether there are an unseen stenosis or small caliber bifurcation in the deployment site, including angiographic confirmation.
8- Statistical Analysis			Statistical Analysis section was changed, according to FDA letter dated 04Feb2018. Performance goal was revised (8.2) and subgroup analysis was added (8.5).
9.2- Main Potential Risks		Added risk of ionizing radiation exposure	Correction in response to conditions noted on FDA letter dated 04Feb2018
11.6- Data and Safety		Added- All AEs observed by the site	Correction in response to conditions noted on FDA

Section	Change From	Change To	Rationale for Change
Monitoring Board		investigators will be reported to the DSMB for periodic review.	letter dated 04Feb2018
7. Table 4			Minor corrections and clarifications

Revision 03, 12Dec2019

Section	Change From	Change To	Rationale for Change
Protocol Summary	Sample size 185 plus up to 60 lead-in Subjects. Lead-in Subjects will not be used for endpoint analysis.	Sample size 160, including up to 60 lead-in subjects. Lead-in Subjects will be used for endpoint analysis.	Sample size recalculation due to including the lead-in subjects in endpoint analysis and skipping the planned efficacy interim analysis. See explanations below.
Protocol Summary	Enrollment duration 18 months	Enrollment duration 24 months	Based on actual enrollment rate.
5.1.1 Enrollment and Informed Consent		Added: Consent can be obtained electronically (Electronic Informed Consent)	Allowing electronic informed consent (HIPPA Compliant and IRB approved) can avoid unnecessary waiting time for the legally authorized representative (LAR) of the subject to physically arrive and sign the consent. The electronic informed consent form will have the identical information as the paper form.
5.4 Lead-in Phase	Lead -in Subjects will be summarized separately and will not contribute to the study's statistical evaluation of its primary endpoints.	Lead -in Subjects will be included in the study's statistical evaluation of its primary endpoints.	Per FDA's request, lead-in subjects will be included in the primary analysis.
8.1 General Principles	The primary analysis cohort will include all data collected for all enrolled Subjects (minus Lead-in)	The primary analysis cohort will include all data collected for all enrolled Subjects	Per FDA's request, lead-in subjects will be included in the primary analysis.
8.1 General Principles	SAS software version 9.3 or higher, R version 3.2 or higher	SAS software version 9.4 or higher, R version 3.3 or higher	SAS and R have been updated to new versions.

Section	Change From	Change To	Rationale for Change
8.2 Primary endpoint	In the presence of the planned midway interim analysis, the actual alpha levels used to declare significance at each analysis will be as defined below.	Deleted	FDA requested that Lead in cases be included in the primary analysis sample. Since Lead in cases are now to be included, the company will now reach full enrollment necessary to test the hypothesis more quickly than originally anticipated. For this reason, the interim analysis is no longer necessary. The study protocol and sample size will therefore be adjusted accordingly. Elimination of the interim analysis results in a slight reduction in the required sample size, as described below.
8.4 Sample size and Power	With a hypothesized incidence rate of 75% for revascularization post-procedure and desired power of 80%, and incorporating the planned midway interim analysis, the required evaluable sample size for primary efficacy is 137, or a total of 169 after adjustment for potential missing data or misspecification of the hypothesized rate. For primary safety, under a hypothesized incidence rate of 20% for the composite endpoint and desired power of 80%, the corresponding required evaluable sample size is 150, or 185 after adjustment. As 185 is the larger of these two values, this will be the final required sample size after accounting for up to 10% attrition and an additional 10% as a safeguard against misidentification of the anticipated event rates.	With a hypothesized incidence rate of 75% for revascularization post-procedure and desired power of 80%, and using an exact binomial test with a nominal 0.025 one-sided significance level (equivalent to a two-sided alpha=0.05), the required evaluable sample size for primary efficacy is 135. For primary safety, under a hypothesized incidence rate of 20% for the composite endpoint and desired power of 80%, the corresponding required evaluable sample size is 153. As 153 is the larger of these two values, this will be the required evaluable sample size to reach at least 80% power for both effectiveness and safety analyses.	Since there would be no interim analysis, the type 1 error adjustment to account multiplicity is no longer required. In addition, based on the currently available patient follow-up data, very few losses to follow-up are expected. Therefore, the Sponsor proposes to update the sample size calculation.

<table>
<tr><th>Section</th><th>Change From</th><th>Change To</th><th>Rationale for Change</th></tr>
<tr>
<td></td>
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<table>
<tr><th colspan="2">Table 7: Hypothesized reperfusion rate, safety event rate and sample size requirements.</th></tr>
<tr><td>Hypothesized reperfusion rate</td><td>Total sample size required</td></tr>
<tr><td>73%</td><td>257</td></tr>
<tr><td>74%</td><td>202</td></tr>
<tr><td>75%</td><td>169</td></tr>
<tr><td>76%</td><td>142</td></tr>
<tr><td>77%</td><td>122</td></tr>
</table>

The above table expresses various sample sizes for efficacy under varying hypothesized reperfusion rates. Similar variability applies to the safety objective. As expected, substantial variance is present in sample size based on different reperfusion assumptions. While this risk is present in all study design, the presence of the planned interim analysis mitigates the risk of misidentifying reperfusion effectiveness, as partial results will be known prior to study completion. Under the hypothesized reperfusion rate of 75%, the sample size is 169 for efficacy as shown above, with total sample size set at 185 as above to power for safety.
</td>
<td>Considering a 5% loss to follow-up rate, which is consistent with the observed follow-up rate to date, the Sponsor proposes to adjust the total sample size to 160.</td>
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Section	Change From	Change To	Rationale for Change
8.8 Interim and Final Analysis	Interim and Final Analysis	Indicated that there will not be an interim analysis	See rationale for elimination interim analysis in the previous changes in this table
11.6 DSMB	Stated that DSMB will apply the pre-specified interim analysis	Deleted	There will be no interim analysis.
12 Study Monitoring	The TIGER Study contains a Lead-in cohort that will be monitored for safety only.	Deleted	As noted above, the lead-in subjects will be included in the primary analysis.

Table of Contents

1. INTRODUCTION AND BACKGROUND

Early recanalization of occluded vessels in acute ischemic stroke (AIS) either by intravenous (IV) thrombolysis or endovascular revascularization has been shown to be associated with improved clinical outcome and reduced mortality[1]. Initial works on endovascular treatment (EVT) of AIS were published in the 1980s. Since then, the endovascular techniques for AIS treatment have tremendously improved, advancing from intra-arterial (IA) administration of thrombolytic drugs to first-generation mechanical thrombectomy devices (Merci clot retriever and Penumbra clot aspiration) and more recently to second-generation mechanical thrombectomy devices (stent-retrievers). The introduction of more advanced tools and techniques for EVT for AIS has improved its efficacy and safety.

1.1 Clinical and Economic Impact of Stroke

Stroke is focal injury to the brain due to blockage or rupture of a blood vessel. Ischemic stroke is most common, and is caused by a clot blocking an artery supplying blood to a specific territory of the brain, preventing delivery of oxygen and nutrients. Hemorrhagic stroke is less common, and is caused by a burst blood vessel resulting in blood leak into or around the brain. In the United States, ischemic strokes account for 87 percent of all strokes, intracerebral hemorrhage for 10 percent, and subarachnoid hemorrhage for 3 percent[2].

Stroke is the third most common cause of worldwide death, after myocardial infarction and cancer, the second leading cause of death for people above the age of 60, and the fifth leading cause in people aged 15 to 59. Stroke is also the single most common reason for permanent disability worldwide[3].

Stroke has reached epidemic proportions. One in 6 people worldwide will have a stroke in their lifetime. Fifteen million people worldwide suffer a stroke each year and 5.8 million people die from stroke. Many stroke survivors suffer from permanent disability. Furthermore, survivors of a first stroke are at high risk for a second attack. The burden of stroke is high in both human and economic terms, and action to curb the worldwide trend is clearly of high priority. In the United States alone, stroke afflicts approximately 800,000 patients annually. Total stroke costs (direct and indirect) of treating stroke in the US is approximately $34 billion each year[4]. Given the medical and economic burdens associated with stroke, there is an imminent need to develop therapeutic options that manage and treat acute ischemic stroke in a timely, safe and effective manner.

In AIS, the acute blockage of blood flow (ischemia) to brain cells leads to rapid neuronal injury and death.

In patients experiencing a typical large vessel AIS, 1.9 million neurons are destroyed in each minute. Compared with the normal rate of neuron loss in brain aging, the ischemic brain ages 3.6 years each hour without treatment[5]. AIS leads to regions of brain tissue

with no blood supply and at a risk of permanent tissue damage. However, this progressive tissue injury can be stopped if timely reperfusion is achieved. Thus, the fundamental goal of AIS treatment is to rapidly restore vascular perfusion in the brain by opening up (recanalizing) the occluded vessels. Early and effective recanalization leads to reperfusion of ischemic brain tissue thus preventing further tissue /loss[6,7,8]. Effective recanalization is also strongly associated with improved functional outcomes and reduced mortality[9,10 ,11]. Successful recanalization is associated with a 4 to 5-fold increase in the odds of good final functional outcome and a 4 to 5 fold reduction in the odds of death[8]. Because of the rapid ischemic cell death that AIS causes, earlier initiation of AIS treatment is crucial to maximize therapeutic benefit[12,13,14]. Immediate therapeutic intervention is critical because a delay in treatment significantly reduces the probability of good clinical outcomes for the patient[10].

Thus, the ideal therapeutic intervention is one that can be effectively used immediately after symptom onset, restores vascular perfusion and leads to good functional outcomes.

1.2 Current Stroke Treatments

1.2.1 Thrombolytics

Currently available treatment options for AIS focus on restoring cerebral perfusion to the affected area as quickly as possible, thereby reducing or preventing brain infarction and minimizing long-term disability and stroke-related mortality[15]. Recanalization is a powerful predictor of stroke outcome in patients with arterial occlusion treated with either IV recombinant tissue plasminogen activator (rt-PA) or an endovascular approach[9].

IV fibrinolysis within 3-4.5 hours after stroke onset is the reference therapy for acute ischemic stroke in the Western world. Many predictors of success or failure have been reported in relationship to this treatment[16]. IV-administered t-PA (IV t-PA) has been proven in clinical trials to be effective in improving clinical outcome and reducing subsequent disability. However, the percentage of patients with ischemic stroke who indeed are treated with thrombolytic therapy is exceedingly low, ranging from 2% to 3% in the United States to 4% in Europe[17], primarily because of the narrow time window required from symptom onset to drug administration and the potential for intracranial hemorrhage. Moreover, thrombi within large vessels, which account for 35% of ischemic strokes[18], are relatively resistant to plasminogen activators and IV thrombolysis alone often does not result in rapid recanalization[19,20]. These limitations have led to the exploration of alternative or complementary treatment approaches for AIS.

1.2.2 Mechanical Thrombectomy

Endovascular mechanical thrombectomy has developed over the past 15 years as a safe and effective intervention[21,22,23,24]. Rapid advancement in catheter-based and endovascular device technology has led to an increasing number of patients with AIS being treated when IV t-PA is ineffective or contraindicated[25].

Several types of devices and different techniques have been used for clot retrieval, including looped or corkscrew-like devices, snares or micro-forceps, suction devices, and columnar meshes or retrievable stents. With the aim of improving on the clinical outcomes achieved with the first-generation thrombus retriever devices, introduced in 2004, stent-based retrievers have been developed more recently. Recent studies[26,27,28,29,30] have reported significant superiority of stent-based retrievers compared with "non-stent" devices from both the clinical and technical aspects.

Endovascular mechanical thrombectomy devices offer many potential advantages over pharmacologic thrombolysis, including more rapid achievement of recanalization, enhanced efficacy in treating large-vessel occlusions, and a potentially lower risk for hemorrhagic events[31]. Stent-based thrombus retrievers have been found to provide a safe and reliable treatment option for patients presenting with AIS[17,32]. The concept of stent retrievers combines the advantages of intracranial stent deployment with immediate flow restoration and a thrombectomy device with definitive clot removal from the occluded artery. The complete removal of the device avoids the major disadvantages associated with permanent stent implantation, such as the need for double anti-platelet medication which potentially increases the risk of hemorrhagic complications[33].

1.3 Clinical Outcomes in Recent AIS Studies

Data from recent clinical studies indicate that endovascular thrombectomy reduces disability for patients with large vessel AIS. Analysis shows that modern endovascular thrombectomy achieve faster and more complete reperfusion than older devices, leading to improved clinical outcomes compared with IV t-PA alone. Benefits are seen across a wide range of age and initial stroke severity.

The combination of highly effective reperfusion with modern thrombectomy devices and earlier treatment, has transformed large vessel AIS patient outcomes[30].

T+B3:H14HERAPY TYPE	MECHANICAL THROMBECTOMY					
Drug/Device	Solitaire FR			Trevo		Merci Retriever
Outcome	SWIFT PRIME Study	SWIFT Study (Rand SFR)	NASA Registry	Trevo 2 Study	TRACK Registry	Multi MERCI trial
N	98	58	354	88	629	131
Baseline NIHSS	17	17.3 (4.5%)	18.1 (6.6%)	18.3 (5.3%)	17.4 (6.7%)	19
Complete Successful Recanalization as defined per protocol	88%	69%	256 (72.5%)	60 (68%)	505 (80.3%)	23%
Functional independence (mRS ≤2) at 90 days)	60%	37%	42%	34 (40%)	277 (47.9%)	36%
Mortality Rate at 90 days	9%	17%	30%	29 (33%)	106 (19.8%)	34%
Symptomatic ICH%	0%	2%	9.9%	6 (7%)	44 (7.1%)	10%
No of Passes. Mean (SD)	NA	1.7 (0.9)	1.9 (1.1)	2.4 (1.4)	1.9 (1.2)	NA

Table 1: Efficacy and safety outcomes from recent AIS studies[34, 35, 28, 22, 11, 26]

1.4 Ethical Consideration

The Tigertriever Revascularization Device and the legally marketed comparable devices are stent-based thrombus retrieval devices. The MERCI (Concentric Medical, Mountainview, CA) was the first stroke mechanical thrombectomy device cleared by the US Food and Drug Administration (FDA) in 2004. The MERCI is a flexible corkscrew-shaped device constructed of nitinol memory wires, designed to remove blood clots form the brain in patient with ischemic stroke[20]. The two subsequent stent-based retrieval devices cleared by the FDA were: the Solitaire FR (EV3/Covidien, Irvine, California), cleared by FDA in March 2012; and the TREVO Provue (Stryker Neurovascular, Kalamazoo, MI), cleared by FDA in August 2012.

The Tigertriever utilizes a design similar to the Solitaire FR and TREVO devices. The Tigertriever device has been CE marked in the European Union as of October 2015 and approved for use by the Israel Ministry of Health in July 2016. As of October 2016, more than 400 Tigertriever units had been sold and used across Europe.

The Tigertriever device is only to be used in the US as part of the TIGER Investigational Device Exemption (IDE) Study. The purpose of the TIGER IDE Study is to gather device performance and safety data to support an application for FDA clearance.

2. DEVICE DESCRIPTION

2.1 Investigational Device

The Tigertriever device is available in two sizes: the Tigertriever and the Tigertriever 17. Any mention of the Tigertriever in the current protocol will be inclusive of both the Tigertriever and Tigertriever 17 as they are substantially equivalent. The Tigertriever Revascularization Device is a stent-based thrombus retrieval device.

The Tigertriever (Figure 1) is comprised of a collapsible, fully retrievable, fine wire construction mounted on a wire shaft that expands to comply with the vessel diameter. A finger slide on the handle facilitates precise stent expansion to accommodate vessels of variable size.

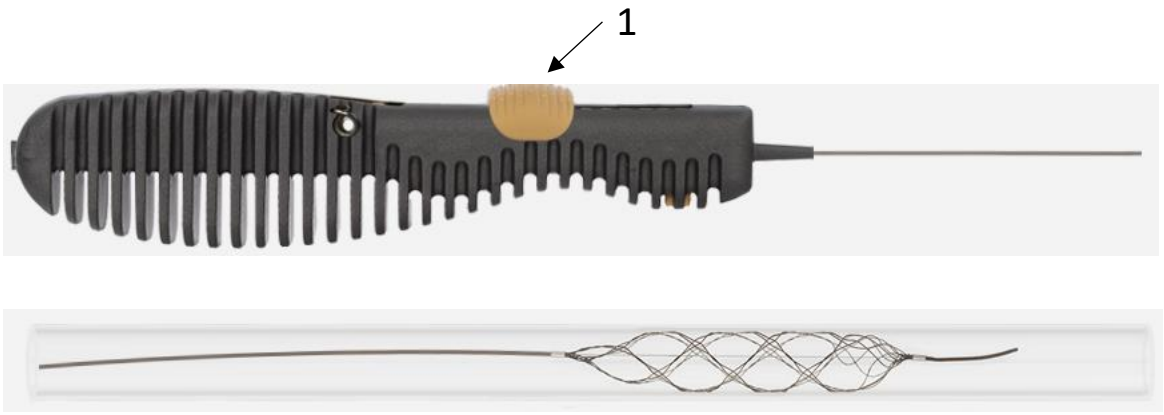

Figure 1. Tigertriever Revascularization Device with integrated handle slider (1).

		Table 2: Tigertriever Revascularization Device Specifications and Recommended Sizing Guidelines				
Model (Cat. Number)	Recommended Vessel Diameter[#] [mm]		Microcatheter Compatibility			Net Length
				MC Inner Dameter	MC Outer Diameter	
	min	max		[inch]	[French]	[mm]
Tigertriever (TRPP3155)	1.5	6.0	Headway 21	0.021	OD Prox./Distal 2.5/2	32
Tigertriever 17 (TRPP3166)	0.5	3.0	Headway 17	0.017	OD Prox./Distal 2.4/1.7	23
[#] Choice of Tigertriever Revascularization Device is based on the sizing recommendations listed in this table and diameter of smallest vessel at thrombus site.						

2.1.1 Device Intended Use

The Tigertriever Revascularization Device is indicated to restore blood flow by removing thrombus from a large intracranial vessel in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for IV t-PA or who fail IV t-PA therapy are candidates for treatment.

2.1.2 Labeling

The Tigertriever device is considered investigational and is required to be used per the protocol and as specified in the Instructions for Use (IFU) document (attached as Appendix A). The device is CE marked and currently available for purchase in Europe. With the exception of the indication statement, no other changes have been made to the device labeling.

3. STUDY OBJECTIVES

The TIGER Study primary objective is to evaluate the safety and effectiveness of the Tigertriever device in restoring blood flow by removing clots in patients who present with AIS due to a large vessel occlusion (LVO).

3.1 Effectiveness Endpoints

3.1.1 Primary Endpoint

- Successful reperfusion, defined as mTICI Score ≥ 2b at the end of the Tigertriever procedure.

3.1.2 Secondary Endpoints

- Good Clinical Outcomes- Percentage of participants with a modified Rankin Scale (mRS) score of ≤2 at 90 (±14) days post treatment.
- Successful reperfusion (defined as mTICI 2b or better) at first pass.
- Health related quality of life (EQ-5D score)
- Degree of disability (Academic Medical Center – Linear Disability Scale score)

3.2 Safety Endpoints

3.2.1 Primary Endpoint

- Composite of all-cause mortality at 90 (±14) days and symptomatic intracranial hemorrhage (sICH) within 24 (18-36) hours of the study procedure. Symptomatic intracranial hemorrhage (sICH) shall be defined as any parenchymal hematoma type 2, remote intracerebral hemorrhage, subarachnoid hemorrhage, or intraventricular hemorrhage that is the predominant cause of ≥4 point NIHSS deterioration at 24 hours

3.2.2 Secondary Endpoints

-
- Any asymptomatic intracranial hemorrhage within 24h (18h-36h) of the procedure
- Neurological deterioration (≥4-point increase in NIHSS score) at 24h (18h-36h) post-procedure
- Embolization to previously uninvolved vascular territories

Additionally, for further evaluation of safety, all adverse events recorded during study conduct will be tabulated and reported, including classification by seriousness and device- and/or procedure-relatedness. These endpoints will be summarized and reported to additionally characterize the clinical performance of the Tigertriever device.

4. ENDPOINT JUSTIFICATION AND RATIONALE

The study design and endpoint selection reflect the common standard in stroke trials evaluating IA therapy (Table 3). There are two major types of outcome measures for acute stroke studies: clinical outcome measures and radiographic measures.

For the primary effectiveness endpoint, the trial will use the broadest and most clinically relevant reperfusion scale, the Thrombolysis in Cerebral Infarction Score. This reperfusion scale has been used in the great preponderance of recent endovascular trials, such as SWIFT, TREVO 2, SWIFT PRIME , NASA registry and Track Registry. Extensive evidence on the validity, reliability and sensitivity of the TICI Score exists across the literature[36].

Additionally, for secondary clinical effectiveness, the study is using the modified Rankin Scale (mRS), a clinician-reported measure of global disability that has been widely applied for evaluating recovery from stroke and as a primary end-point in many clinical trials of emerging acute stroke treatments[37]. Extensive evidence on the validity, reliability and sensitivity of the mRS exists across the literature[38].

In clinical trials that are primarily concerned with recanalization strategies, the safety measures should reflect potential side effects of recanalization agents or strategies. The study uses safety outcome measures widely employed in acute stroke studies of recanalization: mortality and intracranial hemorrhage (ICH), particularly hemorrhage that causes clinical deterioration[39].

Table 3: IA stroke therapy study design and endpoint selection

Study	Goal/ Design	Primary Endpoints
NASA Registry[35]	Retrospective, multi-center registry	Recanalization, Clinical Outcomes (mRS 90 d)
TREVO Study[40]	Prospective, multi-center trial	Recanalization, Clinical Outcomes (mRS 90 d)
TREVO 2 Study[26]	Prospective, Open-label randomized, controlled, multi-center trial	Recanalization, Safety
MERCI[11]	Prospective, single-arm, multicenter trial	Recanalization, Safety
SWIFT PRIME[22]	Multicenter, randomized, prospective, parallel-group trial	Clinical Outcomes (mRS 90 d), Safety
SWIFT[28]	Multicenter, randomized, prospective, parallel-group trial	Recanalization, Safety
MR CLEAN[21]	Multicenter, randomized, prospective, parallel-group trial, open-label with blinded outcome evaluation	Clinical Outcomes (mRS 90 d)
REVASCAT[41]	multicenter, randomized, prospective, sequential, open-label with blinded outcome evaluation	Clinical Outcomes (mRS 90 d)
ESCAPE[42]	multicenter, randomized, prospective, open-label, controlled trial with blinded outcome evaluation	Clinical Outcomes (mRS 90 d)

5. SITES AND SUBJECTS

5.1 Subjects

5.1.1 Enrolment and Informed Consent

Prior to admission to the study, a patient informed consent form (ICF) will be given to each prospective Subject or their Legally Authorized Representative [(LAR); as defined

by the local Institutional Review Board (IRB) or Ethics Committee (EC)]. The ICF will include an explanation of the study, duration, explanation of medical record access and patient anonymity, and how their coded data may be transferred, used for publications or in submissions for reimbursement support. The ICF will contain language that is non-technical and understandable to the patient or his/her LAR.

As the TIGER Study is a stroke treatment study, treatment will likely occur in an acute emergency situation. For this reason, informed consent procedures may vary per site IRB/EC requirements. Consent can be obtained electoronically (Electronic Informed Consent).

Each potential Subject will be provided with written and verbal information regarding the nature of the study in an understandable manner. Adequate time will be allowed for the Subject to consider participation in the clinical trial. Signed, written consent will be obtained for each Subject prior to data collection and entry into the study. Coercion or undue influence of potential Subjects to participate will be avoided, and the Subject's legal rights should not be waived. The Investigator or an appropriately designated member of the study staff shall co-sign the consent form, indicating they believe the Subject or LAR understands the nature and risks of the study and scope of the consent. The Investigator must inform Subjects that they are in a controlled clinical trial, apprise them of their rights as set forth in the ICF, and make written documentation that such a discussion took place.

If the Subject is not able to sign the ICF, but has given his/her oral consent to participate, a third party can sign the informed consent for the Subject if allowable per IRB/EC policy. The consenting process will be documented in the medical record and reason for Subject not signing the consent (in case of verbal confirmation). If the Subject is not able to give his/her informed consent to participate in the study, a LAR can sign the informed consent for the Subject if this is approved by the local IRB/EC.

Short form informed consent may be utilized if approved by the IRB/EC. Each institution must follow their institutional IRB/EC policy for obtaining informed consent. If the short form informed consent is used, the summary must include all the basic elements of informed consent (21 CFR §50.25; ICH E6 4.8.10).

The signed consent forms will be retained by the Investigator and made available (for review only) to the study monitor and auditor upon request.

A template ICF is included as Appendix B.

Subjects are considered enrolled once appropriate informed consent has been obtained and a Tigertriever device has first been introduced through the arterial sheath.

5.1.2 Study Subject Numbering

Sites participating in the TIGER Study will each be assigned a site number prior to enrolling Subjects. Each enrolled Subject will be assigned a Subject number. Site study staff will use the electronic case report form (eCRF) assigned Subject number to complete documentation of the screening/enrolment log following appropriate consenting. Subject study identification numbers will consist of the aggregate of site number followed by a sequential number, where “01” is the first enrolled Subject as the corresponding site.

5.1.3 Subject Terminations

Subjects will be considered discontinued from the study if any of the following occur:

1. Subject voluntarily withdraws from the study. Participation in the TIGER Study is voluntary. Subjects may withdraw consent at any time by completing an informed withdrawal form. Reasonable attempts will be made to determine the reason for withdrawal of consent. Data obtained prior to withdrawal enrolled will be included in endpoint data analysis, but no data will be obtained subsequent to withdrawal.

2. Investigator withdraws Subject from the study due to safety concerns. If, during the conduct of research, an Investigator determines that participation in the study may increase the hazard to a subject that is not acceptable, an Investigator may withdraw the Subject from the study due to safety concerns.

3. Lost to Follow Up: In the event that a Subject fails to return for two consecutive follow-up visits and is unable to be reached at the Subject’s last know telephone number, a certified letter will be sent to the Subject’s last known mailing address to remind the Subject of study obligations. Once all reasonable attempts to contact the Subject have been made, including contacting through the Subject’s general practitioner, the Subject is considered lost to follow-up. Each attempt to contact a Subject will be documented.

In this study, death is an endpoint event, not an early termination. If, during the conduct of the study, a Subject dies, all available information related to the event should be obtained. Within 24 hours from study staff becoming aware of the event, an appointed Rapid Medical representative/study monitor should be notified by completing the appropriate study termination forms in the Subject’s eCRF.

- If death occurs while the Subject is in the hospital, a copy of the death summary report should be submitted. If case of autopsy, a copy of the autopsy report should also be submitted.

- If death occurs outside the hospital setting, effort should be made to obtain all information related to the death along with an Investigator's summary of the events associated with the death.

5.2 Site Selection

The TIGER Study will recruit patients at up to 25 sites across the US and Europe. At least 80% of the centers will be located in US whereas up to 20% of the centers will be located in Europe. Sites will be selected based upon the following criteria:

1. Number of stroke procedures annually (min of 30 procedures)
2. Qualifications and experience of Investigators
3. Dedicated and experienced research team
4. Sufficient facilities to conduct stroke procedures
5. Previous experience in mechanical thrombectomy procedures and devices

5.3 Site Training and Initiation

5.3.1 Training

Investigators and Site Personnel will be trained on the Clinical Investigation Plan (CIP) prior to site initiation of enrollment. Training will be documented on the Training Log and cover the following topics:

1. Study objectives
2. CIP review
3. Delegation of authority
4. Process for Informed Consent as well as IRB/EC requirements
5. Electronic case report form use and completion guidelines
6. Enrolment procedures
7. Protocol Deviation documentation
8. AE and SAE event reporting
9. Device malfunction reporting
10. Tigertriever Instructions for Use
11. Device training using a silicon model
12. Device accountability
13. Image collection and core lab submission
14. Investigator responsibilities and obligations
15. General Good Clinical Practice (GCP) guidelines
16. Regulatory requirements including essential documents

Changes to existing TIGER Study staff responsibilities, as documented on the Delegation Log, or addition of new study personnel will require investigational plan training, as appropriate.

5.3.2 Initiation

Rapid Medical, or a representative of Rapid Medical, will conduct study training as described in section 5.3.1.

Prior to actively recruiting/enrolling Subjects, investigational sites must provide the following documentation to Rapid Medical:

1. IRB/EC approval for the Investigational Plan
2. IRB/EC and sponsor approved Informed Consent Form for the study
3. Approval/notification from competent authority, as applicable
4. Investigator(s') *curriculum vitae* (CV)
5. Financial Disclosure(s) for the PI and Sub-I(s)
6. Signed Clinical Trial Agreement (CTA) including Confidentiality Agreement
7. Training Log documentation to verify the appropriate study staff has been trained on the protocol, device, eCRFs and study conduct.

Sites will be officially notified of site activation through receipt of an activation letter or email.

5.4 Lead-in Phase

All Investigators will be trained on use of the Tigertriever Revascularization Device prior to conduct of any procedures on Subjects. A lead-in phase will precede enrolment of patients for primary endpoint analysis. During this phase, up to 4 patients per clinical site will be enrolled. The Lead-in phase will be completed by the site either: 1) achieving two successive successful reperfusions (mTICI 2b or higher), or 2) performing 4 cases, with case review and approval by the Central Neurointerventionalist Principal Investigator. Subjects enrolled in the Lead-in phase will be consented, treated and followed according to the clinical protocol, in the same manner as the regular study subjects.
Lead -in Subjects will be included in the study's statistical evaluation of its primary endpoints.

6. STUDY DESIGN

The TIGER Study is a multi-center, single arm, prospective IDE study. The study will accumulate data in order to evaluate the safety and effectiveness of the Tigertriever mechanical revascularization device.

The study will enroll patients experiencing AIS due to a LVO who are either refractory to or ineligible for IV t-PA treatment. Patients must meet all inclusion criteria and none of the exclusion criteria in order to be enrolled into the study.

Device performance in this study will be compared with criteria performance goal derived from five recent studies of predicate stent-retriever devices, specifically TREVO 2, SWIFT, MR CLEAN, ESCAPE and REVASCAT.

6.1 Study Duration

All patients who are treated with the Tigertriever will be followed for 90 (±14) days post-procedure.

6.2 Subject Inclusion/Exclusion Criteria

Subjects are considered enrolled in the TIGER Study only after having met all inclusion/exclusion criteria, being properly consented, and having a Tigertriever device first introduced through the arterial sheath.

6.2.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria:

1. New focal neurologic deficit consistent with being of acute cerebral ischemia origin.
2. Age 18-85 years old (inclusive).
3. Interventionalist estimates that treatment with the Tigertriever (first deployment in target vessel) can be achieved within 8 hours of symptom onset.
4. Patient either: a) eligible for, and received, IV t-PA within 3 hours of symptom onset, at the correct 0.9 mg/kg dose, or b) ineligible for IV t-PA.
5. NIH Stroke Scale score of 8-29.
6. No known significant pre-stroke disability (prestroke mRS 0 or 1).
7. Catheter angiographic confirmation of a large vessel occlusion in the intracranial internal carotid artery, the M1 or M2 segments of the middle cerebral artery, the intracranial vertebral artery, or the basilar artery that is accessible to Tigertriever device.
8. For strokes in the anterior circulation, the following imaging criteria should also be met:
   a. MRI criterion: volume of diffusion restriction visually assessed ≤50 mL, OR
   b. CT criterion: ASPECTS 6 to 10 on baseline NCCT or CTA-source images,
9. For strokes in the posterior circulation, the following imaging criterion should also be met: pcASPECTS score 8 to 10 on baseline NCCT, CTA-source images, or DWI MRI.
10. Anticipated life expectancy of at least 6 months.

11. A signed informed consent by patient or a Legally Authorized Representative or independent physician in case of oral consent.

6.2.2 Exclusion Criteria

1. Subject already participating in another study of an investigational treatment device or treatment.
2. Use of any other intra-arterial recanalization drug or device prior to the Tigertriever (Tigertriever not as first choice device).
3. Angiographically evident excessive arterial tortuosity precluding device access to the thrombus.
4. For all patients, severe sustained hypertension with SBP >220 and/or DBP >120; for patients treated with IV tPA, sustained hypertension despite treatment with SBP >185 and/or DBP > 110.
5. Glucose < 50 mg/dl (2.78 mmol/L) or > 400 mg/dl (22.20 mmol/L).
6. Known hemorrhagic diathesis.
7. Coagulation factor deficiency or oral anti-coagulant therapy with an international normalized ratio (INR) of more than 3.0.
8. Treatment with heparin within 48 h with a partial thromboplastin time more than two times the laboratory normal.
9. Patients who have received a direct thrombin inhibitor within the last 48 hours; must have a partial thromboplastin time (PTT) less than 1.5 times the normal to be eligible.
10. Platelet count of less than 50,000/uL.
11. History of severe allergy to contrast medium, nickel, or Nitinol.
12. Intracranial hemorrhage.
13. Significant mass effect with midline shift.
14. Intracranial tumor (apart from small meningioma, ≤ 2 cm in diameter)
15. Stenosis or any occlusion in the deployment site or in a proximal vessel requiring treatment or preventing device access to the thrombus (for example, stenosis or occlusion in the cervical internal carotid artery.
16. Females who are pregnant or breastfeeding.
17. Known current use of cocaine at time of treatment.
18. Prior recent stroke in the past 3 months.
19. Renal failure with serum creatinine >3.0 or Glomerular Filtration Rate (GFR) <30.
20. Known cerebral vasculitis.
21. Rapidly improving neurological status defined as improvement of greater than 8 points on the NIHSS or improvement to NIHSS of < 6 prior to procedure.

22. Clinical symptoms suggestive of bilateral stroke or stroke in multiple territories.
23. Ongoing seizure due to stroke.
24. Evidence of active systemic infection.
25. Known cancer with metastases.
26. Suspicion of aortic dissection, septic embolus, or bacterial endocarditis.
27. Evidence of dissection in the extra or intracranial cerebral arteries.
28. Occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior/posterior circulation).
29. Aneurysm in target vessel.

7. STUDY PROCEDURES

All non-investigational procedures will be according to the common practice at each site and determined by the treating physician. Procedures such as routine hospital examinations, brain CT scan or MRI will be performed according to each site's standard management protocol and will be properly documented in the patient's medical records.

7.1 Study

Study flow of Subjects through the TIGER Study is illustrated in Figure 2.

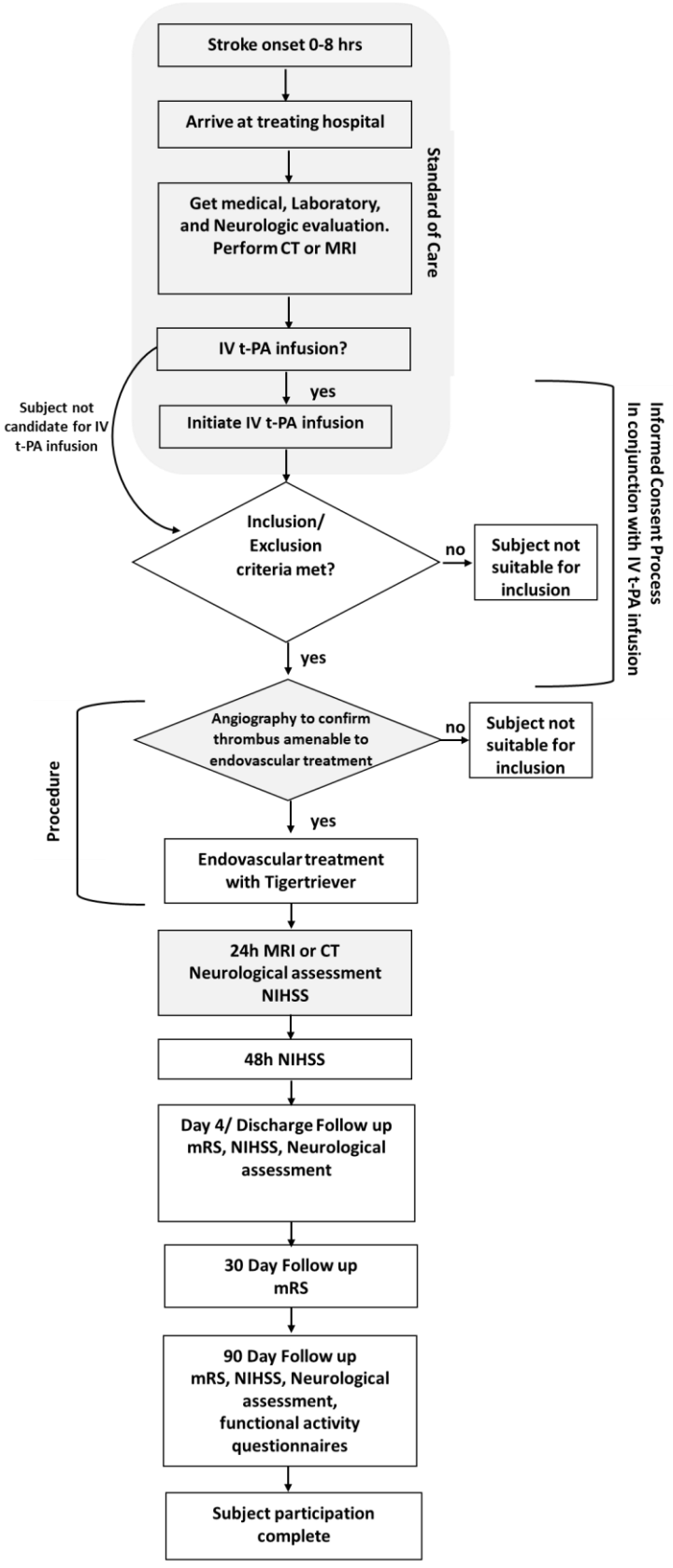

Figure 2. Study Flow

7.2 Screening and Baseline Visit

Screening against study inclusion/exclusion criteria will be completed to determine potential eligibility. Subject screening will be documented on the site specific Screening & Enrolment Log. For patients/LARs who choose not to participate, the reason for non-participation will also be documented.

7.2.1 General Medical Evaluation

- Physical examination and medical history (including time last known well and time symptoms first observed)
- Prior/Concomitant Medications
- Vital signs (Blood pressure and pulse)

7.2.2 Laboratory Evaluation

Blood and/or urine specimens for the following Clinical Laboratory tests:

- Pregnancy (females of childbearing age)
- Hemoglobin, platelet count per site standard of care (SOC)
- Prothrombin time (PT)/International normalized ratio (INR) and partial thromboplastin time (PTT) per site SOC.
- Creatinine or Glomerular Filtration Rate per site SOC
- Serum glucose

Note: Study informed consent not required for lab tests required as per the SOC in assessing acute ischemic stroke treatment.

7.2.3 Neurologic Evaluation

National Institutes of Health Stroke Scale (NIHSS) recorded at screening along with pre-stroke mRS obtained from the Subject or their caretaker. NIHSS and mRS will be performed by certified Study personnel.

7.2.4 Imaging (Brain CT or MRI)

CT or MRI will be used to confirm eligibility. Patients with metal implants or other contraindications to MR will utilize CT exclusively. Baseline imaging will be used to confirm:

1. For anterior circulation strokes, baseline Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of 6-10 on NCCT or CTA-source images, or DWI MR lesion volume ≤ 50 ml.
2. For posterior circulation strokes, pcASPECTS 8-10, on CTA-source images or diffusion MRI
3, No evidence of acute intracranial hemorrhage on presentation
4. No evidence of significant mass effect with midline shift
5. No evidence of intracranial tumor (apart from small meningioma, ≤ 2 cm in diameter)

6. No evidence of cerebral vasculitis
7. No evidence of bilateral stroke or stroke in multiple territories (e.g. Bilateral anterior circulation, anterior/posterior circulation)
8. No evidence of target vessel aneurysm

Subjects who underwent a CT or MRI at a referring hospital and then were transferred to the study hospital for further treatment will need to undergo another CT or MRI at the study hospital to ensure continued absence of extended infarct or acute hemorrhage.

7.2.5 Screen Failures

Subjects who do not satisfy all the inclusion/exclusion criteria prior to signing the ICF will be considered pre-screen failures. If a Subject satisfies initial inclusion/exclusion criteria and has been consented but does not satisfy additional study inclusion/exclusion criteria at time of diagnostic angiography (such as excessive vessel tortuosity evident by angiography), the Subject will be considered a screen failure. Screen fails will receive medical treatment per standard of care and will not enter into the trial population.

7.3 Procedure

7.3.1 Angiography

Diagnostic catheter angiography will be conducted prior to device deployment to confirm inclusion/exclusion criteria and to determine location of occlusion. Diagnostic angiograms will also be obtained after each Tigertriever device pass (maximum of 3) and each pass of rescue therapy. An angiogram will be considered for primary endpoint assessment where a rating of mTICI 2b or greater reperfusion is achieved (for 3 or less passes of the Tigertriever device) or after the third pass of the Tigertriever device. A final post-procedure angiogram (full A-P lateral image) will be obtained once all treatments have concluded, including rescue therapy, if necessary. All images are to be de-identified and submitted to the core lab for review:
The University of California at Los Angeles with the following address:

Angiography and Noninvasive Imaging Core Lab
David S Liebeskind, MD, FAAN, FAHA, FANA
UCLA Department of Neurology
Neuroscience Research Building
635 Charles E Young Drive South, Suite 225
Los Angeles, CA 90095-7334

7.3.2 Device Preparation, Delivery, & Positioning

1. Administer anti-coagulation and anti-platelet medications per SOC.
2. Introduce an 8FR or larger neurovascular balloon guiding catheter.
3. Aided by angiographic fluoroscopy, determine the deployment location and its diameter.

Selectively access the occluded vessel using a microcatheter with a Rotating Hemostatic Valve (RHV) flushed with heparinized saline. With the aid of a guidewire

3.a Advance the microcatheter until the end of the microcatheter is positioned distally to the thrombus, so that the usable length of the Tigertriever will extend past each side of the thrombus in the vessel. Verify the location of the distal side of the thrombus by injecting contrast media through the microcatheter.

3b. Stenosis identification: A suspected stenosis can be evidenced by difficulty crossing the lesion with a wire, poor expansion of the device, or calcium on a CT image.

3c. Small caliber bifurcation identification: Carefully check whether the target occlusion crosses a small caliber bifurcation. For instance opacification of the collateral vessels might indicate such bifurcation. If the clot occludes a bifurcation, prefer the larger division if possible (for example the inferior division of MCA). Perform a contrast injection through the microcatheter to evaluate the sizing of the branch where the device will be deployed.

4. Remove the Tigertriever from the tray according to the Figure 2.

Figure 2. Removal of the Tigertriever from the tray.

5. Carefully advance the Tigertriever until the mesh completely extends from the loading tube.
6. Slowly expand the device by sliding the *Slider* backwards. Do not over inflate. Make sure the device is not damaged.
7. Soak the open mesh in heparinized saline.
8. Deflate the device carefully by advancing the *Slider* until the mesh reaches its minimal form (Figure 3).

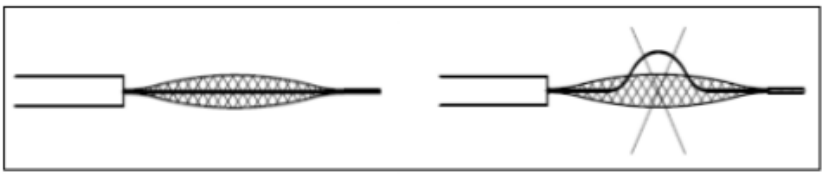

Figure 3. Mesh in minimal form

9. Pull back until the tip is just inside the end of the loading tube (Figure 4).

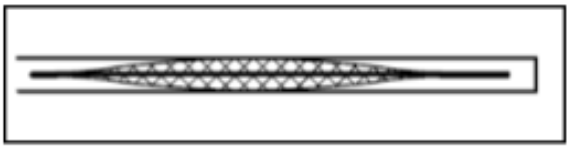

Figure 4. Tip at the end of the loading tube.

10. Insert the loading tube into the microcatheter's RHV and lock it.
11. Slowly advance about 50cm of the Tigertriever through the loading tube into the microcatheter.
12. Slide the loading device back towards the microcatheter's RHV.
13. Continue slowly advancing the device under fluoroscopic visual control until its tip extends out of the microcatheter.
14. Unsheathe the device slowly while following the tip of the device and distal and proximal markers for accurate deployment.
    Important: the proximal marker remains stationary during device expansion while the distal marker and tip move slightly backwards. As a result the proximal marker should be positioned proximally to the thrombus.
15. Under fluoroscopic visual control slowly expand the device by sliding the *Slider* backwards.
    If stenosis or a small caliber bifurcation were idenified as described in steps 3b and 3c above, use extra attention when expanding the Tigertriever, by slowly expansion and avoiding a maximal expansion.
16. Wait 2 minutes to allow device expansion in the thrombus.
17. Position the microcatheter until it is just proximal to the proximal marker of the device. Tighten the RHV to prevent relative movement between the microcatheter and the device.
18. In cases where resistance during device expansion suggests the presence of atherosclerotic plaque at the site of clot, or that the clot and device are crossing a bifurcation and extending into a smaller caliber artery, care should be used not to apply excessively prolonged deployment expansion force to the device in these locations.

7.3.3 Retrieval

1. Inflate the guide catheter balloon to occluded vessel as specified in Balloon Guide Catheter labeling.
2. Slowly withdraw the microcatheter and the Tigertriever device as a unit to the guide catheter tip while applying aspiration to the guide catheter with a 60cc syringe. If needed, adjust the size of the device under fluoroscopic visual control.

If excessive resistance is encountered during the retrieval partially deflate the device before continuing the retrieval.
If stenosis or a small caliber bifurcation were identified as described in steps 3b and 3c in the above, use extra attention when withdrawing the Tigertriever.

3. Apply vigorous aspiration to the guide catheter using syringe and recover Tigertriever device and microcatheter inside the guide catheter. If needed, partially deflate the device prior to inserting it into the guide catheter. Continue aspirating guide catheter until the device and microcatheter are nearly withdrawn from the guide catheter.
4. Open the guide catheter RHV to allow the microcatheter and device to exit without resistance. Use carefully to avoid interaction with the site of the intervention and to prevent air from entering the system.
5. Aspirate the guide catheter to ensure the guide catheter is clean of any thrombus material.
6. Deflate balloon guide catheter.
7. If additional flow restoration attempts are desired:
    - Clot retrieval with Tigertriever devices may be attempted for up to a total of 3 passes.
    - Each Tigertriever device should only be used for a single pass.
8. If flow is not restored after 3 attempts with Tigertriever devices, a rescue device may be used per SOC.

7.4 24 Hour (-6/+12) Follow-up

- Conduct visit at 24 hours (-6/+12 hours) from time of procedure
- Vital signs assessed
- Record concomitant medications
- Perform and record assessment of NIHSS
- Obtain MRI or CT, per standard of care, to assess intracranial hemorrhage

  Note: CT /MRI images will be sent as soon as possible to the Imaging Core Lab for evaluation.
- Record any Adverse Events (AEs), as necessary

7.5 48 Hour (± 12h) Follow-up

- Record concomitant medications
- Perform and record assessment of NIHSS
- Record any Adverse Events (AEs), as necessary

7.6 Day 4 or Discharge

- Conduct visit at 4 days from time of procedure. If Subject is discharged prior to 4 days, conduct the follow up visit at time of discharge.
- Vital signs assessed
- Record concomitant medications
- Perform and record assessment of NIHSS
- Perform and record results of mRS using the Rankin Focused Assessment
- Record any AEs, as necessary

NIH Stroke Scale and mRS should be performed by certified Study personnel.

7.7 30 days (± 7 days), can be performed over the phone

- Conduct visit at 30 days (± 7 days) from time of procedure
- Record concomitant medications
- Perform and record the Barthel Index
- Perform and record the mRS using the Rankin Focused Assessment
- Record any AEs, as necessary

mRS should be performed by certified Study personnel.

7.8 90 days (± 14 days)

- Conduct visit at 90 days (± 14 days) from time of procedure
- Record concomitant medications
- Perform and record assessment of NIHSS

- Perform and record results of mRS using the Rankin Focused Assessment
- Perform and record the Barthel Index
- Perform and record PRO assessments of health-related quality of life (EQ-5D) and degree of disability (AMC-Linear Disability Scale) - Record any AEs, as necessary

NIH Stroke Scale and mRS should be performed by certified Study personnel.

7.9 Unscheduled Visits

When clinically indicated, unscheduled assessments should be completed with corresponding data documented in the eCRF.

7.10 Adverse Events

Adverse events that occur during participation in the TIGER Study will be recorded. See section 11 for more information on AEs.

Table 4: Schedule of Events

Schedule of Events							
Elapsed time/Study procedures	**Baseline**	**Procedure**	**24 hours (-6/+12)**	**48 hours (±12)**	**Discharge or 4 days**	**30 (±7) days[iv]**	**90 (±14) days**
Informed Consent	X						
Demographics	X[ii]						
Medical History and Concomitant Medications	X[ii]						
Time of Stroke Symptoms Onset	X[ii]						
Brain CT Scan or MRI	X[ii]		X				
Vital Signs	X[ii]	X	X		X		
NIH Stroke Scale	X[ii]		X[iii]	X	X		X
Premorbid mRS score	X						
mRS score					X	X	X
Clinical Laboratory	X[ii]						
Time of groin puncture		X					
Cath angiography and clot retireval[i]		X					
mTICI Outcome		X					
Functional activity questionnaire - Barthel Index						X	X
Patient-Reported Outcomes (EQ-5D, AMC-LDS)							X
Prior/concomitant medications	X	X	X	X	X	X	X
AE (including hemorrhage other than sICH)		X	X	X	X	X	X

i. Pre-procedure and post-procedure angiograms will be analyzed by an unbiased core laboratory to make a final determination about TICI Score.
ii. Assessment may be completed during prescreening without obtaining informed consent if assessment at initial evaluation is be part of local standard of care.
iii. NIHSS completed 24h and 48h post procedure. The 48 assessment should be performed at least 12 hours after the 24h assessment.
iv. possible to be performed over the phone

7.11 Clinical Outcomes Assessment

Assessments to be performed as indicated in Table 4 are as follows:

- National Institutes of Health Stroke Scale (NIHSS): Measures stroke-related neurological deficits through 15-item examination. Must be performed by study personnel certified in NIHSS administration (nihstrokescale.org).
- Modified Rankin Scale (mRS): Measures the global degree of disability or dependence of an individual on an ordinal scale. Must be performed by study personnel (who is not the treating physician) who are trained to conduct the mRS assessment using the standardized Rankin Focused Assessment (RFA)
- Barthel Index: Measures performance of activities of daily living on a 10-item, 0-100 point scale.
- Patient Reported Outcome Assesment (PRO):
    - Academic Medical Center – Linear Disability Score (AMC-LDS): Patient-reported measure of disability status on a linear scale.
    - EQ-5D: Patient-reported measure of health-related quality of life, with brief patient-reported ratings along the 5 dimensions of mobility, self-care, usual activities, pain/discomfort, and affect.

8. STATISTICAL ANALYSIS

8.1 General Principles

The primary analysis cohort will include all data collected for all enrolled Subjects, referred to in International Conference on Harmonization (ICH) document E9, “Statistical Principles for Clinical Trials,” as the *full analysis set*.

Continuous variables will be summarized with standard statistics including the mean, standard deviation, median, interquartile range, and range. Categorical variables will be summarized using frequency tables and cross-tabulations. Statistical analysis will be performed using SAS software version 9.4 or higher (SAS Institute, Cary, NC, USA), R version 3.3 or higher (R Foundation for Statistical Computing, Vienna, Austria) or other validated statistical software.

For the primary endpoint analysis, a P-value of less than 0.05 will be deemed statistically significant. For AE reporting, the primary analysis will be based on Subject counts, not event counts. Both Subject counts and event counts will be presented in tabular summaries of results.

8.2 Primary Endpoints

The primary effectiveness endpoint is successful reperfusion, defined as an mTICI score of 2b or better. The performance goals (PG) for evaluating effectiveness is based on outcomes reported from six recent pivotal studies (TREVO 2, SWIFT, MR CLEAN, ESCAPE, REVASCAT and SWIFT PRIME) evaluating the Solitaire and Trevo stent-retriever devices.

Table 5: Summary of criteria from prior studies used for generation of performance goal.			
Study	Reperfusion using study-specific metric as reported	Metric and threshold employed	Converted to mTICI 2b/3
TREVO 2	68%	Original TICI 2b/3	78%*
SWIFT	69%	TIMI 2/3	76%**
MR CLEAN	59%	Modified TICI 2b/3	59%
ESCAPE	72.4%	Modified TICI 2b/3	73.8%***
REVASCAT	65.7%	Modified TICI 2b/3	65.7%
SWIFT PRIME	88%	Modified TICI 2b/3	88%
Pooled estimate			73.4%

* Adjustment for TREVO 2 is performed using Suh et al. (2013)[43], in which 47% (69/146) of cases analyzed and classified as TICI 2a under the oTICI paradigm were found to be TICI 2b under the mTICI paradigm. TREVO 2 results were then adjusted accordingly.
** As reported in secondary publications versus original study endpoint of TIMI 2/3[44]
*** As reported in secondary publication versus original study outcome of oTICI[45]

The PG for the primary effectiveness endpoint of reperfusion post-procedure (mTICI 2b or better) is defined as the incidence in the five trials cited above minus a statistical margin of 10%, the same threshold as in the SWIFT pivotal trial (Saver, 2012, *Lancet*), therefore giving a PG of 73.4% - 10% = 63.4%.

The resulting null and alternative statistical hypotheses are therefore as follows:

H_0: $p \leq PG$

H_A: $p > PG$,

where PG = 73.4% - 10% = 63.4% as above and p is the observed incidence of reperfusion post-procedure with the Tigertriever Revascularization Device. The hypothesis test will be performed at an overall two-sided alpha level of 0.05 using exact binomial methods, in which the lower confidence bound on the observed incidence of reperfusion is compared to the PG.

The primary safety endpoint is the composite of all-cause mortality at 90 (±14) days and symptomatic intracranial hemorrhage at 24 hours (18-36h). The performance goal (PG) for evaluating safety is based on outcomes reported from the same six studies as for primary efficacy as employed above.

Table 6: All-cause mortality and sICH for comparable studies.		
Study	All-cause mortality at 90 days	sICH at 24 hours
TREVO2	33%	7%
SWIFT	17.2%	1.7%
MR CLEAN	21%	7.7%
ESCAPE	10%	3.6%
REVASCAT	18.4%	4.9%
SWIFT PRIME	9%	0%
Pooled estimate	18.2%	4.2%

The performance goal (PG) for the composite primary safety endpoint of all-cause mortality and symptomatic intracranial hemorrhage is defined using the incidence of the individual endpoints in the six trials cited above. For this purpose, the sum of the two pooled event rates is 18.2% + 4.2% = 22.4%; however, as sICH is known to be associated with mortality, this is likely an overestimate of the composite event rate. For conservatism, therefore, only half of the sICH rate will be added to mortality as representing distinct subjects, resulting in a pooled event rate of 20.4%. Adding to this a statistical margin of 10% gives a PG of 20.4% + 10.4% = 30.4%.

The resulting null and alternative statistical hypotheses are therefore as follows:

H_0: $p > PG$
H_A: $p \leq PG$,

where PG = 20.4% + 10.4% = 30.4% as above and p is the observed incidence of revascularization post-procedure with the Tigertriever device. The hypothesis test will be performed at an overall two-sided alpha level of 0.05 using exact binomial methods, in which the upper confidence bound on the observed incidence of revascularization is compared to the PG.

The primary endpoint analysis will be performed using the intent to treat (ITT) population. The ITT population will consist of all enrolled subjects who had at least one Tigertriever device attempt/deployment irrespective of major protocol violation. The per protocol (PP) population is defined as ITT patients who do not have major protocol violations. A major protocol violation includes when a subject does not meet inclusion/exclusion criteria. All protocol violations will be reported.

8.3 Secondary Endpoints

The secondary study endpoints will be examined descriptively in both the ITT and PP populations.

8.4 Sample Size and Power

With a hypothesized incidence rate of 75% for revascularization post-procedure and desired power of 80%, and using an exact binomial test with a nominal 0.025 one-sided significance level (equivalent to a two-sided alpha=0.05), the required evaluable sample size for primary efficacy is 135. For primary safety, under a hypothesized incidence rate of 20% for the composite endpoint and desired power of 80%, the corresponding required evaluable sample size is 153. As 153 is the larger of these two values, this will be the required evaluable sample size to reach at least 80% power for both effectiveness and safety analyses. Considering a 5% loss to follow-up rate, which is consistent with the observed follow-up rate to date, the Sponsor proposes to adjust the total sample size to 160.

8.5 Subgroup Analysis

Analysis of the primary endpoints will be conducted in subgroups of interest, including subgroups defined by device used (Tigertriever versus Tigertriever 17) and subgroups defined by subjects ineligible for IV-tPA administration versus those failing IV-tPA, subjects age 18-69 vs 70-85, and target occlusion location (ICA vs M1 vs M2 vs posterior circulation),

8.6 Missing Data

The number and proportion of Subjects eligible for and compliant with each follow-up examination will be presented. Subjects who withdraw from the study will be tabulated with reasons for withdrawal. Since the primary efficacy endpoint is defined immediately post-procedure, the amount of missing data for this endpoint is anticipated to be very low and necessarily unrelated to subsequent losses to follow-up.

8.7 Poolability Across Investigational Sites

This is a multi-center clinical study, with standardization of Subject enrollment, data entry and adverse event reporting. All investigational sites will follow the requirements of a common protocol, data collection procedures and forms. To present the data from this clinical study in a summary form, a comparison of the primary endpoints across sites will be completed to determine if the generated data can be pooled.

The relevant statistical test for both primary efficacy and primary safety will be Pearson's chi-square test across sites; a p-value less than 0.10 will be considered cause for investigation of non-poolability.

8.8 Interim Analysis

No interim analysis is planned.

8.9 Deviations from the Statistical Plan

Any departure or deviation from these planned statistical methodologies will be documented and discussed in the Statistical Analysis Plan that will include the statistical rationale for change.

9. RISK/BENEFIT ANALYSIS

A risk analysis according to ISO 14971 (Application of Risk Management to Medical Devices) has been conducted as part of the CE Marking process. Risks have been minimized or eliminated through appropriate design control, and confirmed by pre-clinical bench, laboratory and animal testing.

9.1 Main Potential Benefits of the Tigertriever:

Vessel recanalization is one of the strongest predictors of improved functional outcomes and reduced mortality in ischemic stroke patients[46]. It has been further shown that if the vessels can be quickly recanalized, the correlation with good outcomes is even more powerful[47].

There are no guaranteed benefits from participation in this study; however, it is possible that treatment with the Tigertriever Device may improve blood flow through the treated artery. This may result in Subjects experiencing fewer or less severe long term ischemic stroke symptoms and less final disability.

Information gained from the conduct of this study may be of benefit to other persons with the same medical condition and age rages. Study results will be analysed by subgroups based on age.

The following features incorporated into the design of the device, enable the physician to have full control on the device and the process:

- Fully radiopaque, full visibility under fluoroscopy.

- Ability of the physician to control the shape of the mesh and lock it in the required position.

9.2 Main Potential Risks:

The main possible complications that have been identified in the risk management process for the Tigertriever are risks that are known for any catheterization and thrombectomy procedure, including, but not limited to: hematoma and hemorrhage at puncture site, infection, dissection, vessel perforation, emboli, thrombus, hemorrhage, ischemia, vasospasm, vascular occlusion, pseudo aneurysm formation, post procedure bleeding, distal thrombus formation, distal embolization including to a previously uninvolved territory, adverse allergic reaction to antiplatelet/anticoagulation agents or contrast media, device deformation/collapse/fracture/malfunction, arteriovenous fistula and neurological deficits, including stroke and death. Additional risks might include burning sensation, delay in procedure, (resulting to increase use of contrast, fluoroscopy and anesthesia), peripheral ischemia, incomplete treatment, (unable to treat or no improvement or major injury), organ impairment, fever, local or systemic inflammatory response, shock (traumatic, anaphylactic, hemorrhagic or septic), vassal stenosis or restenosis. General discomfort, tenderness or pain, standard risk of being under general anesthesia (nausea, vomiting), and ionizing radiation exposure.

9.2.1 Minimization of Risk

- The Tigertriever is intended to be used only by physicians who have received appropriate training in interventional neuro-endovascular techniques and neuro thrombectomy techniques.
- The design of the Tigertriever (material used, its visibility, the ability to control it, etc.) minimizes the potential risk to damage blood vessels and enables short and quick procedure.
- Detailed instructions for use that define the procedural steps, warnings of misuse, precautions and guidance for appropriate use of the device will be provided with the device.
- The Tigertriever will be deployed only in patients in whom an endovascular thrombectomy procedure has already been determined as clinically indicated by their clinical physicians. Accordingly, procedure-related risks, including risks of conscious sedation or general anesthesia, arterial puncture and sheath placement, exposure to ionizing radiation, and intra-procedural anticoagulation, are inherent to the patient's clinical state and indicated course of therapy, and not the trial. Only device-specific risks, such as risks of device deformation/collapse/ fracture/malfunction are specific to the trial.

The estimated risks for all identified hazards all meet the defined criteria for risk acceptability. As a result the estimated risk for all identified hazards remains as low as possible.

All of the above suggests that the advantages of mechanical revascularization using the Tigertriever in acute ischemic stroke outweigh its disadvantages and risks.

10. DEVIATIONS FROM THE CLINICAL INVESTIGATION PLAN

10.1 Protocol Deviations

A protocol deviation is defined as any change or alteration from the procedures stated in the clinical investigation plan, consent document, recruitment process, or study materials (e.g. questionnaires) that were originally approved by the IRB/EC where the change or alteration itself is not IRB/EC approved. Protocol deviations can be either major or minor.

All protocol deviations must be reported to Rapid Medical or their authorized representatives (study monitors) through the eCRF protocol deviation form. All deviations, regardless of whether medically justifiable (Subject's safety) or pre-approved by Rapid Medical and/or the IRB/EC of record, shall be reported. In addition, the Investigator is required to adhere to IRB/EC of records' procedures for reporting protocol deviations.

Prior approval for deviation from the CIP shall be obtained by the Investigator from Rapid Medical, except in situations where necessary to protect the safety of a Subject (emergency) or for situations beyond the Investigator's control such as Subjects missing scheduled follow-up visits. Approval for deviations shall be documented in writing and maintained in the Investigator and clinical study management files.

Per 21 CFR §812.140 (a) (4), Investigators are required to maintain accurate, complete and current records, including documentation showing the dates of, and reasons for, each deviation from the CIP. Failure to comply with the CIP may result in Investigator termination of participation [21 CFR §812.46 (a)] in the TIGER study.

10.2 Major and Minor Protocol Deviations

A Major protocol deviation is defined as an event that resulted in an increased risk to a subject or others; affected the right, safety or welfare of a subject; or affected the integrity of the study. Major protocol deviations include, but are not limited to:

- Failure to obtain informed consent prior to patient enrollment
- Enrolled patient did not meet the inclusion/exclusion criteria
- Source data permanently lost

• Introduction of rescue therapy prior to attempting revascularization with Tigertriever for three passes.

Any other events that do not comply with the requirements of the protocol will be considered Minor protocol deviations.
Examples of Minor protocol deviations are:
• Incorrect version of the informed consent form used.
• Patient did not attend follow-up visit or follow-up visit was outside the required window.

11. SAFETY AND ADVERSE EVENTS

Safety of study Subjects is of critical importance for the TIGER study. Site Investigators are responsible for the safety of Subjects under his/her care. In order to more clearly understand data and potential confounders, assessment of all Adverse Events observed by the site investigators will be recorded in the case report form and reported to the Data and Safety Monitoring Board for period review.

11.1 Adverse Event Data Collection

Recording of adverse events commence from time that a Subject is appropriately consented and culminate through the 90-day (± 14) follow up. All available information related to the AE must be obtained by the Investigator so that proper determination of causality and outcome can be made and classification as a SAE can be made if warranted. Adverse Events will be documented on the appropriate eCRF. Data captured include the event description, onset, resolution status, seriousness, severity, causality (if known) and treatment, if done. The Investigator will follow all AEs until resolution or completion of the 90-day follow-up.

11.2 Definitions

11.2.1 Adverse Events

Per ISO 14155:2011 section 3.2, an Adverse Event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in Subjects, users or other persons, whether or not related to the investigational medical device.

In the event that a Subject participates in the TIGER Study with signs of prior disease and/or symptoms, these conditions would not be considered AEs unless the condition recurs after the Subject has recovered from the previously occurring condition or the condition worsens in intensity or frequency during participation in the TIGER Study.

11.2.2 Adverse Device Effect

Per ISO 14155:2011 Section 3.1, an Adverse Device Effect (ADE) is any AE related to the use of an investigational medical device.

11.2.3 Serious Adverse Events

Per ISO 14155:2011 Section 3.37, an SAE is an AE that:

1. Led to death,
2. Led to serious deterioration in the health of the Subject, that resulted in:
    a. a life-threatening illness or injury, or
    b. a permanent impairment of a body structure or a body function, or
    c. in-patient or prolonged hospitalization, or
    d. medical or surgical intervention to prevent permanent life-threatening illness or injury or permanent impairment to a body structure or a body function.
3. Led to fetal distress, fetal death or a congenital anomaly or birth defect

11.2.4 Serious Adverse Device Effect

Per ISO14155:2011 3.36, a Serious Adverse Device Effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a SAE.

Examples of SADE for the TIGER Study include vessel dissections or perforations caused by the Tigertriever Revascularization Device.

11.2.5 Anticipated Adverse Device Effect

An anticipated adverse device effect (AADE) is an effect which by its nature, incidence, severity or outcome has been identified in the study protocol or application.

11.2.6 Unanticipated Adverse Device Effect

As described in 21 CFR §812.3 (s), an Unanticipated Adverse Device Effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the study protocol or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of Subjects.

Rapid Medical will report the results of an evaluation of any UADE to the FDA/CA and all reviewing IRB/EC committees and Investigators within 10 working days from receiving notice of the UADE.

11.2.7 Procedure-Related

Definite Related: Must have all 3 of the following:

1. Has a reasonable temporal relationship to the intervention procedure
2. Could not possibly have been produced by the Subject's clinical state or have been due to environmental or other interventions.
3. Follows a known pattern of response to the intervention procedure.

Possible Related: Must have at least 2 of the following 3 conditions:

1. Has a reasonable temporal relationship to the intervention procedure
2. Could not possibly have been produced by the Subject's clinical state or have been due to environmental or other interventions.
3. Follows a known pattern of response to intervention procedure.

Unlikely Related: Has a reasonable or tenuous temporal relationship to intervention procedure, but also has BOTH of:

1. Could readily have been produced by the subject's clinical state, or environmental or other interventions.
2. Does not follow known pattern of response to intervention procedure.

Unrelated: The temporal relationship between intervention procedure and the adverse event is unreasonable or incompatible and/or adverse event is clearly due to extraneous causes (e.g., underlying disease, environment).

11.2.8 Device-Related

Definite Related: Must have all 3 of the following:

1. Has a reasonable temporal relationship to the intervention device
2. Could not possibly have been produced by the Subject's clinical state or have been due to environmental or other interventions.
3. Follows a known pattern of response to the intervention device.

Possible Related: Must have at least 2 of the following 3 conditions:

1. Has a reasonable temporal relationship to the intervention device
2. Could not possibly have been produced by the Subject's clinical state or have been due to environmental or other interventions.
3. Follows a known pattern of response to intervention device.

Unlikely Related: Has a reasonable or tenuous temporal relationship to intervention device, but also has BOTH of:

1. Could readily have been produced by the subject's clinical state, or environmental or other interventions.
2. Does not follow known pattern of response to intervention device.

Unrelated: The temporal relationship between intervention device and the adverse event is unreasonable or incompatible and/or adverse event is clearly due to extraneous causes (e.g., underlying disease, environment).

11.3 Determination of Event Severity and Relatedness

Using all available information, Site Investigators will independently categorize event severity as Serious or Non-serious, using the above definitions.

Using all available information, Site Investigators will categorize the relationship of non-serious adverse events (NSAEs) and SAEs to study procedure and study device. In addition, a central Clinical Events Committee will independently adjudicate the relationship of all SAEs to study procedure and study device.

11.4 Event Notification

TIGER Study Investigators are required to report all UADEs/USADEs to Rapid Medical, or Sponsor representative, within 24 hours after first learning of the event. In addition, the Investigator must follow the IRB/EC of record's policies for SAE/UADE/USADE reporting. Adverse Event reporting instructions will be included in the Safety Management Plan.

All Medical Device Reporting (MDR) reportable events will conducted in accordance with 21 CRF §803.

11.5 Clinical Events Committee

The Clinical Events Committee (CEC) will be an independent board consisting of stroke Neurologists and Neurointerventionalists who are not participating in the TIGER Study otherwise. The CEC will adjudicate SAEs reported in the study.

Major CEC responsibilities are as follows:

1. Adjudication of all intracranial hemorrhages, documented by the Independent Core Laboratory, as symptomatic or asymptomatic based on Subject neurological status.

2. Adjudication of all dissections/perforations as to relationship to study device of study procedure.

3. Adjudicate of all SAEs as attributable to procedure or device or the natural history of the initial stroke and of patient's other medical conditions.

11.6 Data and Safety Monitoring Board

The DSMB will consist of independent noninvasive Stroke Neurologists, Neurointerventionalists, and a Biostatistician.

All AEs observed by the site investigators will be reported to the DSMB for periodic review.

Major responsibilities of the DSMB are:

1. Monitor the rates of all adverse events
2. Recommend revisions to the TIGER Study CIP regarding safety of the study Subjects
3. Periodically review and monitor aggregated and individual Subject data related to safety, data integrity, scientific validity and overall conduct of the study, to ensure the rights, safety, and welfare of the study participants
4. Monitor Subject accrual and retention
5. Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or on the ethical conduct of the study
6. Ensure the confidentiality of trial data and the results of monitoring

12. STUDY MONITORING

The study will be monitored regularly by trained clinical trial monitors to ensure the protection of Subject rights and safety, as well as, data quality and integrity in compliance with 21 CFR §812 Subpart C.

The monitor will verify information entered into the eCRFs against source documents and the Subject's medical records to ensure validity of data. Source documents may be photocopied if required but will be anonymized prior to a monitor leaving the performance site. The following on-site visits will occur: site initiation visit; first monitoring visit shortly after the first non-Lead-in Subject procedure is completed; additional monitoring visits determined by site enrollment rates.

On the occasion that a monitor requests additional data or clarification of data for the eCRF, the request must be addressed appropriately prior to the next monitoring visit. Once completed eCRF data are verified against source data, the study monitor will electronically sign off

to indicate that data has been monitored for correctness. The Investigator must sign all eCRFs prior to site close.

In the event that a monitor discovers potential SAEs or SADEs which were not previously reported, Rapid Medical or the appointed representative/study monitor will inform the Investigator for their review and submission to the IRB/ethics committee, if applicable.

There will be a site close out visit to ensure all documentation is in place and all outstanding items have been addressed. Record retention policies will be reviewed and post-study Investigator responsibilities discussed.

Device accountability will also be conducted by the study monitor at each monitoring visit. Unused, damaged, malfunctioning, or expired devices will be returned to Rapid Medical prior to or when enrollment closes.

12.1 Source Documentation

Investigators are required to record and maintain adequate and accurate case histories for all Subject observations, assessments, and data pertinent to TIGER Study conduct.

12.2 Access to Source Documents

The Investigator and Institution, as participants in the TIGER Study, will be responsible for providing direct access to source data to Rapid Medical, their designated representatives, and to appropriate authorities for the purposes of monitoring, audit, IRB/EC review or regulatory inspection. Subjects will be notified of such access to study records as part of the consenting process.

13. DATA COLLECTION AND OWNERSHIP

13.1 Protected Health Information and Confidentiality

The Investigator and members of the IRB/EC of record shall consider all data or findings generated during the conduct of the study, other than that information to be disclosed by law, as confidential. Disclosure of such data or findings to any third party shall not occur without the prior written consent of Rapid Medical.

All reports and communications relating to Subjects in the study will identify Subjects by their Subject ID number only.

13.2 Data Management

Every effort will be taken to ensure the accuracy and reliability of data including the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigator and associated personnel before the study commences, and periodic onsite monitoring visits by the Sponsor, or their representatives, as deemed appropriate by the Sponsor. Guidance for eCRF completion will be provided and reviewed with the study personnel prior to the start of the study. The Sponsor will review eCRFs for accuracy and completeness and any discrepancies will be resolved with the Investigator or designee, as appropriate.

13.3 Electronic Case Report Forms

Study staff, as indicated in the Delegation log, who will use the EDC system will have adequate training in order to perform assigned tasks (21 CFR §11.10(i)). Training will be conducted by Rapid Medical and/or their qualified designated appointee as part of the Site Initiation Visit or as needed.

Data collected during the conduct of the TIGER Study will be entered into a 21CRF §11 compliant eCRF database. Accuracy and data quality will be ensured through implementation of data edit checks. Responses to requests for clarification of eCRF recorded data will be answered, dated, and electronically signed by the Investigator or designee. Any required changes to the Sponsor's eCRF/database will be followed by data review and validation procedures.

Once the study is closed and all data has been monitored and signed by study Investigators, the database will be locked and analyzed for statistical evaluation and reporting.

13.4 Record Retention and Storage

13.4.1 Sponsor Record Retention

Rapid Medical will retain all study documentation for a period of at least five (5) years or in accordance with GCP regulations in force in the Sponsor's jurisdiction, whichever is greater, following formal discontinuation of the TIGER Study.

13.4.2 Investigator Record Retention

The Investigator shall retain all study documentation for a period of at least (3) years or in accordance with retention policies of the IRB/EC of record, whichever is longer.

13.5 Publication Policy

As part of the TIGER Study, information related to the Tigertriever Revascularization Device (such as pre-clinical data and other device materials) may be supplied to TIGER Study Investigators. Any information not previously published is considered confidential and shall remain the sole property of Rapid Medical. The Investigator agrees to use any such information as it pertains to study conduct and not use data generated from the study for other purposes without first obtaining the written consent of Rapid Medical.

Every effort will be made to publish the results of this study regardless of whether the findings are in favor of the Tigertriever device. To achieve this goal, and to avoid publication bias, the TIGER study will be registered, prior to enrollment commencing, on the clinicaltrials.gov database.

Rapid Medical will form a Publications Committee for the purpose of reviewing and publishing data from the study. This committee will include, at a minimum, the TIGER Study Principal Investigators (PIs) and a representative of Rapid Medical. The Publications Committee will be tasked with creating a publication policy describing the authorship criteria. Abstracts and manuscripts will be written and/or reviewed by the Publication Committee prior to submission for journal or meeting acceptance.

14. AUDITS OR INSPECTIONS

Representatives of Rapid Medical or any regulatory body reviewing study results may visit study sites to conduct a TIGER Study audit in compliance with company policy and regulatory guidelines. Audits will require access to all study related documentation for inspection. Investigators will immediately notify Rapid Medical upon learning of announced audits or inspections by regulatory agencies.

15. REFERENCES

1. Pierot L, Soize S, Benaissa A, Wakhloo AK. Techniques for endovascular treatment of acute ischemic stroke: From intra-arterial fibrinolytics to stent-retrievers. *Stroke*. 2015;46(3):909-914. doi:10.1161/STROKEAHA.114.007935.
2. W.L. B, J.A. C, V. T, et al. Neurothrombectomy devices for the treatment of acute ischemic stroke: State of the evidence. *Ann Intern Med*. 2011;154(4):243-252.
3. Wolfe, Charles, Rudd, Tony. The Burden of Stroke White Paper, SAFE Stroke Alliance for Europe, March 2007.
4. http://www.uhnj.org/stroke/stats.htm.

5. Saver JL. Time is brain--quantified. *Stroke*. 2006;37(1):263-266. doi:10.1161/01.STR.0000196957.55928.ab.
6. Group TNI of ND and S rt-PSS. Tissue Plasminogen Activator for Acute Ischemic Stroke. *N Engl J Med*. 1995;333(24):1581-1588. doi:10.1056/NEJM199512143332401.
7. Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet*. 2010;375(9727):1695-1703. doi:10.1016/S0140-6736(10)60491-6.
8. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke. *N Engl J Med*. 2008;359(13):1317-1329. doi:10.1056/NEJMoa0804656.
9. Joung-Ho Rha MD MJLS. The Impact of Recanalization on Ischemic Stroke Outcome. *Stroke*. 2007;38:967-973. doi:10.1161/01.STR.0000258112.14918.24.
10. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial Prourokinase for Acute Ischemic Stroke. *JAMA*. 1999;282(21):2003. doi:10.1001/jama.282.21.2003.
11. Smith WS, Sung G, Saver J, et al. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. *Stroke*. 2008;39(4):1205-1212. doi:10.1161/STROKEAHA.107.497115.
12. Marler JR, Tilley BC, Lu M, et al. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. *Neurology*. 2000;55(11):1649-1655. doi:10.1212/WNL.55.11.1649.
13. Saposnik G, Young B, Silver B, et al. Lack of improvement in patients with acute stroke after treatment with thrombolytic therapy: predictors and association with outcome. *JAMA*. 2004;292(15):1839-1844. doi:10.1001/jama.292.15.1839.
14. Lansberg MG, Schrooten M, Bluhmki E, Thijs VN, Saver JL. Treatment time-specific number needed to treat estimates for tissue plasminogen activator therapy in acute stroke based on shifts over the entire range of the modified rankin Scale. *Stroke*. 2009;40(6):2079-2084. doi:10.1161/STROKEAHA.108.540708.
15. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest*. 2008;133(6 SUPPL. 6). doi:10.1378/chest.08-0720.
16. Gascou G, Lobotesis K, Machi P, et al. Stent retrievers in acute ischemic stroke: Complications and failures during the perioperative period. *Am J Neuroradiol*. 2014;35(4):734-740. doi:10.3174/ajnr.A3746.
17. Grunwald IQ, Wakhloo AK, Walter S, et al. Endovascular stroke treatment today. *Am J Neuroradiol*. 2011;32(2):238-243. doi:10.3174/ajnr.A2346.
18. Smith WS, Tsao JW, Billings ME, et al. Prognostic significance of angiographically confirmed large vessel intracranial occlusion in patients presenting with acute brain ischemia. *Neurocrit Care*. 2006;4(1):14-17. doi:10.1016/j.jhsb.2006.03.124.
19. Saqqur M, Uchino K, Demchuk AM, et al. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. *Stroke*. 2007;38(3):948-954. doi:10.1161/01.STR.0000257304.21967.ba.
20. Balasubramaian A, Mitchell P, Dowling R, Yan B. Evolution of Endovascular Therapy in Acute Stroke: Implications of Device Development. *J Stroke*. 2015;17(2):127-137.

21 .Berkhemer OA, Fransen PSS, Beumer D, et al. A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke. *N Engl J Med*. 2015;372(1):11-20. doi:10.1056/NEJMoa1411587.
22 .Saver JL, Goyal M, Bonafe A, et al. Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke. *N Engl J Med*. 2015;372(24):2285-2295. doi:10.1056/NEJMoa1415061.
23 .Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387(10029):1723-1731. doi:10.1016/S0140-6736(16)00163-X.
24 .Badhiwala JH, Nassiri F, Alhazzani W, et al. Endovascular Thrombectomy for Acute Ischemic Stroke. *JAMA*. 2015;314(17):1832. doi:10.1001/jama.2015.13767.
25. Hassan AE, Chaudhry SA, Grigoryan M, Tekle WG, Qureshi AI. National trends in utilization and outcomes of endovascular treatment of acute ischemic stroke patients in the mechanical thrombectomy era. *Stroke*. 2012;43(11):3012-3017. doi:10.1161/STROKEAHA.112.658781.
26. Nogueira RG, Lutsep HL, Gupta R, et al. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): A randomised trial. *Lancet*. 2012;380(9849):1231-1240. doi:10.1016/S0140-6736(12)61299-9.
27. Broussalis E, Trinka E, Hitzl W, Wallner A, Chroust V, Killer-Oberpfalzer M. Comparison of stent-retriever devices versus the merci retriever for endovascular treatment of acute stroke. *Am J Neuroradiol*. 2013;34(2):366-372. doi:10.3174/ajnr.A3195.
28. Saver JL, Jahan R, Levy EI, et al. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): A randomised, parallel-group, non-inferiority trial. *Lancet*. 2012;380(9849):1241-1249. doi:10.1016/S0140-6736(12)61384-1.
29. Jovin TG, Saver JL, Ribo M, et al. Diffusion-weighted imaging or computerized tomography perfusion assessment with clinical mismatch in the triage of wake up and late presenting strokes undergoing neurointervention with Trevo (DAWN) trial methods. *Int J Stroke*. 2017;12(6):641-652. doi:10.1177/1747493017710341.
30. Campbell BC V, Donnan GA, Lees KR, et al. Endovascular stent thrombectomy: the new standard of care for large vessel ischaemic stroke. *Lancet Neurol*. 2015;14(8):846-854. doi:10.1016/S1474-4422(15)00140-4.
31. Thomassen L, Bakke SJ. Endovascular reperfusion therapy in acute ischaemic stroke. *Acta Neurol Scand Suppl*. 2007;187:22-29. doi:10.1111/j.1600-0404.2007.00842.x.
32. Gralla J, Schroth G, Remonda L, Nedeltchev K, Slotboom J, Brekenfeld C. Mechanical thrombectomy for acute ischemic stroke: Thrombus-device interaction, efficiency, and complications in vivo. *Stroke*. 2006;37(12):3019-3024.
33. Levy EI, Mehta R, Gupta R, et al. Self-expanding stents for recanalization of acute cerebrovascular occlusions. *Am J Neuroradiol*. 2007;28(5):816-822.
34. Zaidat OO, Castonguay AC, Nogueira RG, et al. TREVO stent-retriever mechanical thrombectomy for acute ischemic stroke secondary to large vessel occlusion registry. *J Neurointerv Surg*. 2017:neurintsurg-2017-013328. doi:10.1136/neurintsurg-2017-013328.
35. Zaidat OO, Castonguay AC, Gupta R, et al. North American Solitaire Stent Retriever Acute Stroke registry: post-marketing revascularization and clinical outcome results. *J Neurointerv Surg*. 2014;6(8):584-588. doi:10.1136/neurintsurg-2013-010895.

36. Kleine JF et al. “Time to redefine success? TICI 3 versus TICI 2b recanalization in middle cerebral artery occlusion treated with thrombectomy”, J Neurointerv Surg. 2016 Feb 17.
37. Sulter G et al.” Use of the Barthel index and modified Rankin scale in acute stroke trials”, Stroke. 1999;30:1538 –1541.
38. Banks et al. “Outcomes Validity and Reliability of the Modified Rankin Scale: Implications for Stroke Clinical Trials. A Literature Review and Synthesis”, Stroke. 2007;38:000-000.
39. Higashida et al. “Trial Design for Thrombolysis of Acute Stroke”, *Stroke*. 2003;34:e109-e137.
40. Jansen O et al, Neurothrombectomy for the Treatment of Acute Ischemic Stroke: Results from the TREVO Study. Cerebrovascular Dis. 2013;36:218-225. doi: 10.1159/000353990.
41. Jovin TG, Chamorro A, et al. Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke. *N Engl J Med* 2015;372:2296-306. DOI: 10.1056/NEJMoa1503780.
42. M. Goyal, A.M. Demchuk et al. Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke. *N Engl J Med* 2015;372:1019-30. DOI: 10.1056/NEJMoa1414905.
43. Suh et al, Clarifying Differences Among Thrombolysis in Cerebral Infarction Scale Variants: Is the Artery Half Open or Half Closed? Stroke. 2013;44(4):1166-1168. doi:10.1161/STROKEAHA.111.000399.
44 Jahan R et al. Abstract 163: TICI success Rates In Swift: Comparisom Between Randomized Arms And Coorrelation To 90 Day Neurologic Outcomes. Stroke. 2013;44:A163
45 Brigdan M, D. Hill M, et al. Novel Interactive Data Visualization- Exploration of the ESCAPE Trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times) Data. Stroke. 2018;49:00-00. DOI: 10.1161/STROKEAHA.117.018814
46. Rha et al, The impact of recanalization on ischemic stroke outcome: a meta-analysis. *Stroke*. 2007;38(3):967-73.
47. Mederos et al Speed of tPA-Induced Clot Lysis Predicts DWI Lesion Evolution in Acute Stroke. *Stroke* 2007;38;995-960.