Clinical Investigational Protocol

PROST

pRESET for Occlusive Stroke Treatment

Protocol #: pCT-001-19

Version date: April 2020, Rev 06

Sponsor: Phenox Inc.
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Signature:

This PROST Clinical Study Protocol has been approved by the Sponsor. The following signature documents this approval:

Signature: Gary Brogan,
Director of Clinical and Regulatory Affairs

04-20-2020
MM/DD/YYYY

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Clinical Protocol Signature Page

Prior to participation in this study, the Principal Investigator must obtain written approval from his/her Ethics Committee, and provide a copy to the Sponsor, phenox inc, along with the Ethics Committee approved Informed Consent Form.

The Principal Investigator must also:

- Conduct the study as described in the protocol and in accordance with the relevant parts of the ICH Guidelines for GCP, the ISO 14155:2011, 21 CFR 812, 21 CFR Part 820, 21 CFR Part 50, 21 CFR Part 11, 21 CFR Part 54, 21 CFR Part 56, the Declaration of Helsinki, and the pertinent individual country laws/regulations..
- Agree to participate in an appropriate training program as part of the study initiation.
- Assure that informed consent is obtained from each subject prior to enrolment.
- Assure that no deviation from, or changes to, the protocol will take place without prior agreement from the sponsor and documented approval from the IRB/ethics committee, except where necessary to eliminate an immediate hazard(s) to the trial participants.
- Provide all required data and agree to source document verification of study data with patient's medical records.
- Allow assigned study monitors, as well as representatives from regulatory agencies, to review and inspect any documents pertaining to this clinical investigation.
- Complete all case report forms, study documentation, and relevant imaging assessments promptly and upload to the designated core laboratory tracker for data processing.

The Principal Investigator (PI) may delegate one or more of the above functions to an associate or sub-investigator. However, the PI retains overall responsibility for proper conduct of the study, including obtaining and documenting patient informed consent, compliance with the study protocol, and the collection of all required data.

Investigator Signature

I have read and understand the contents of the clinical protocol. I agree to follow and abide by the guidelines set forth in this document.

Investigator name (print)	Signature	Date (MM/DD/YYYY)

Protocol Summary

Title:	PROST: pRESET for Occlusive Stroke Treatment
Document number:	pCT-001-19
Version:	06 (April 2020)
Investigational device name:	pRESET thrombectomy device
Study design:	Prospective, multi-center randomized clinical trial
Purpose:	Compare the safety and effectiveness of pRESET to Solitaire in the treatment of stroke related to large vessel occlusion
Study duration:	Estimated 18 months
Patient population:	Adults with acute ischemic cerebral stroke due to large vessel occlusion
Sample size:	The target sample size for this clinical investigation is 214 patients; 107 patients per arm. An interim assessment will be performed after 50% of the target enrollment has been enrolled and either completed the 90 day evaluation visit or withdrawn prematurely. The interim assessment, performed under conditional power, may result in the target enrollment being increased to a maximum of 340 patients.
Number of sites:	Maximum number of Sites: 25 in 2 countries (USA and Germany)
Follow-up schedule:	24 hours, 7 days, 30 days, 90 days
Primary effectiveness endpoint:	Global disability assessed via the blinded evaluation of the proportion of patients with a Modified Rankin Scale (mRS) $\leq$ 2 at 90 days after the index procedure.
Primary safety endpoint:	Proportion of subjects with device- or procedure-related symptomatic intracerebral hemorrhage (sICH) within 24 hours (-8/+12 hrs) of the index procedure. *sICH will be defined as per SITS-MOST criteria: local or remote parenchymal hemorrhage type 2 on the post-treatment imaging scan, combined with a neurologic deterioration of 4 points or more compared to baseline NIHSS or the lowest NIHSS value between baseline and 24 h or death within 24 h. Type 2 indicates a hematoma exceeding 30% of the infarct, with substantial space-occupying effect.*

Secondary effectiveness endpoints:	The first secondary effectiveness endpoint will be based on the proportion of patients with eTICI 2b50 or greater flow in the target vessel post-procedure with ≤3 passes of the assigned study device. The second secondary effectiveness endpoint will be based on the proportion of patients with eTICI 2c or greater following the first pass of the assigned study device. The third secondary effectiveness endpoint will be based on overall mortality at 90 days following the index stroke. The fourth effectiveness secondary endpoint is the distribution of mRS shift at 90 days across the entire spectrum of disability.
Pre-specified exploratory endpoints	The first exploratory endpoint is an assessment of global disability assessed via the blinded evaluation of the proportion of patients with a Modified Rankin Scale (mRS) ≤ 1 recorded 90 days after the index stroke. The second exploratory endpoint will be based on the proportion of patients with eTICI 2c or greater with ≤3 passes of the assigned study device. The third exploratory endpoint will be based on the final (last pass) eTICI 2b50 or greater and eTICI 2c or greater proportions by randomized study device. The fourth exploratory endpoint will be based on the proportion of target vessels with first-pass eTICI 2b50, 2b67, 2c or 3 by randomized study device. . The fifth exploratory endpoint will be based on the proportion of patients with "early response" at Day 7/Discharge (whichever is earlier), defined as a NIHSS reduction of ≥10 points from baseline or an NIHSS score 0 or 1. The sixth exploratory endpoint will be based on the proportion of patients with all intracranial hemorrhages using the Heidelberg Bleeding classification by randomized study device. The seventh exploratory endpoint will be based on stroke-related mortality 90 days after the index stroke by randomized study device. The eighth exploratory endpoint will be based on the incidence of neurological deterioration from the baseline NIHSS score through Day 7, or at the time of discharge if discharge is prior to Day 7 post-treatment. Neurological deterioration is defined as ≥ 4-point increase in the NIHSS score from the baseline score. The ninth exploratory endpoint will be based on a comparison of the incidence of procedure-related and device-related serious adverse events (PRSAEs and DRSAEs) through 24 (-6/+24) hours post-procedure. Each event will be adjudicated by the clinical events committee, and defined as: a. Vascular perforation (procedure and/or device related) b. Intramural arterial dissection (procedure and/or device related) c. Embolization to a new territory (procedure and/or device related)

	d. Access site complication requiring surgical repair or blood transfusion (procedure related) e. Intra-procedural mortality (procedure and/or device related) f. Device failure (in vivo breakage) (device related) g. Any other complications adjudicated by the CEC to be related to the procedure (proedure related)
Inclusion Criteria:	1. Age ≥18 2. Clinical signs consistent with acute ischemic stroke 3. Subject is able to be treated within 8 hours of stroke symptom onset and within 1.5 hours (90 min) from screening CT / MRI to groin puncture. 4. Pre-stroke modified Rankin Score of 0 or 1 5. NIHSS ≥6 at the time of enrolment 6. If tPA is indicated, initiation of IV tPA should be administered as soon as possible and no later than 3.0 hours of onset of stroke symptoms (onset time is defined as the last time when the patient was witnessed to be at baseline neurologic status), with investigator verification that the subject has received/is receiving the correct IV tPA dose (0.9mg/kg) for the estimated weight. 7. Expanded Thrombolysis in Cerebral Infarction (eTICI) 0-1 flow confirmed by angiography that is accessible to the mechanical thrombectomy device in the following locations: a. Intracranial internal carotid b. M1 and/or M2 segment of the MCA c. Carotid terminus d. Vertebral artery e. Basilar artery *Note: M1 segment of the MCA is defined as the arterial trunk from its origin at the ICA to the first bifurcation or trifurcation into major branches neglecting the small temporo-polar branch.* 8. Imaging scores as follows: - ASPECTS score must be 6-10 on NCCT or DWI-MRI. If automated core volume assessment software is used: - MR diffusion-weighted imaging (DWI) ≤50cc - Computed tomography perfusion (CTP) core ≤50 cc 9. Subject is willing to conduct protocol-required follow-up visits. 10. A valid signed and dated informed consent by participant or LAR (Legally Authorized Representative) has been obtained. *Note: If approved by the local Ethics Committee and country regulations, an independent physician is permitted to sign consent, to allow enrolment in the study. However, as soon as possible, the patient is informed and his/her consent is requested for the possible continuation of this research.*

Exclusion Criteria:

1. Subject who has received IA-tPA prior to enrolment in the study
2. Female who is pregnant or lactating or has a positive pregnancy test at time of admission.
3. Rapid neurological improvement prior to study enrolment suggesting resolution of signs/symptoms of stroke
4. Known serious sensitivity to radiographic contrast agents
5. Known sensitivity to nickel, titanium metals, or their alloys
6. Subjects already enrolled in other investigational studies that would interfere with study endpoints.
7. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency. (A subject without history or suspicion of coagulopathy does not require INR or prothrombin time lab results to be available prior to enrolment.)
8. Known renal failure as defined by a serum creatinine > 2.0 mg/dl (or 176.8 µmol/l) or glomerular filtration rate (GFR) < 30.
9. Subject who requires hemodialysis or peritoneal dialysis, or who has a contraindication to an angiogram for whatever reason.
10. Life expectancy of less than 90 days
11. Clinical presentation suggests a subarachnoid hemorrhage, even if initial CT or MRI scan is normal
12. Suspicion of aortic dissection
13. Subject with a comorbid disease or condition that would confound the neurological and functional evaluations or compromise survival or ability to complete follow-up assessments.
14. Subject is known to currently use or has a recent history of illicit drug(s) or abuses alcohol (defined as regular or daily consumption of more than four alcoholic drinks per day).
15. Known arterial condition (e.g., proximal vessel stenosis or pre-existing stent) that would prevent the device from reaching the target vessel and/or preclude safe recovery of the device
16. Subject who requires balloon angioplasty or stenting of the carotid artery at the time of the index procedure.
17. Angiographic evidence of carotid dissection

Imaging exclusion criteria

18. CT or MRI evidence of hemorrhage on presentation
19. CT or MRI evidence of mass effect or intra-cranial tumor (except small meningioma)
20. CT or MRI evidence of cerebral vasculitis
21. CT or MRI-DWI showing ASPECTS 0-5. Alternatively, if automated core volume assessment software is used, MRI-DWI or CTP core > 50cc.
22. CT/MRI shows evidence of carotid dissection or complete cervical carotid occlusion requiring a stent
23. Any imaging evidence that suggests, in the opinion of the investigator, the subject is not appropriate for mechanical thrombectomy intervention (e.g. inability to navigate to target lesion, moderate/large infarct with poor collateral circulation, etc.).
24. Occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior/posterior circulation) as confirmed by angiography, or clinical evidence of bilateral strokes or strokes in multiple territories

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Summary of Investigational Plan Changes

Revision History	Details of change	Effective date
01	Initial release of the Protocol	March 2019
02	Update to study required imaging modalities and schedule of assessments Update to the analysis population section to include primary, secondary and tertiary analyses	April 2019
03	Update imaging inclusion and exclusion criteria to clarify that automated software can be used for core volume assessment Update to state that once consent is withdrawn that the patient can no longer be followed under this protocol Update the training section to insert more details about the device training program. Modified the benefits section to clarify the association with the procedure as opposed to the stent retriever.	May 2019
04	Update to the blinded team section to clarify as follows: • Assessor performing the assessments will be independent. • Inclusion of criteria stating how the neurologist must remain blinded. • If a neurologist is not available that a blinded certified and trained assessor (medical professional) can be substituted.	August 2019
05	Inclusion of the pRESET 5x40 device into the study protocol. Modification of sample size to specify a target and maximum patient number based on the planned interim assessment. Reorganization of endpoints to specify secondary effectiveness endpoints and pre-specified exploratory endpoints. Addition of revised study flow chart. Modification of the statistical sections of the protocol to bring in line with the revised Statistical Analysis Plan. Update to align US and German study protocol requirements: • Subject Bias • Informed consent • Insurance • Risk/Benefit Section	February 2020
06	The follow-up assessment for NIH Stroke Scale at the 30 day and 90 day timeframe is being moved to optional.	April 2020

1. Device Description

The pRESET Thrombectomy Device (Figure 1) manufactured by phenox, is a mechanical thrombectomy device mounted on the end of a delivery wire. The device is designed to allow the treating physician to remove blood clot from occluded cerebral arteries in the setting of acute cerebral stroke.

pRESET consists of a self-expanding Nitinol structure that carries one radiopaque platinum/iridium (Pt/Ir) coil-marker on its proximal end and two markers on its distal end. The device has a proximal closed ring design with a helically shaped slit. The ring design ensures stable opening and reduces tapering when withdrawn. The structure is firmly attached to a pusher wire on its proximal end. Proximally, the device is connected to a pusher wire, made from stainless steel (1.4301). The instrument is stored in an introducer tube and is compatible with commercially available 0.021" ID microcatheters. An etched marking on the pusher wire is used to insert the instrument into the microcatheter. This etching allows the device to be loaded into the microcatheter until the etching reaches the hub without the use of fluoroscopy as the device is still contained with the catheter.

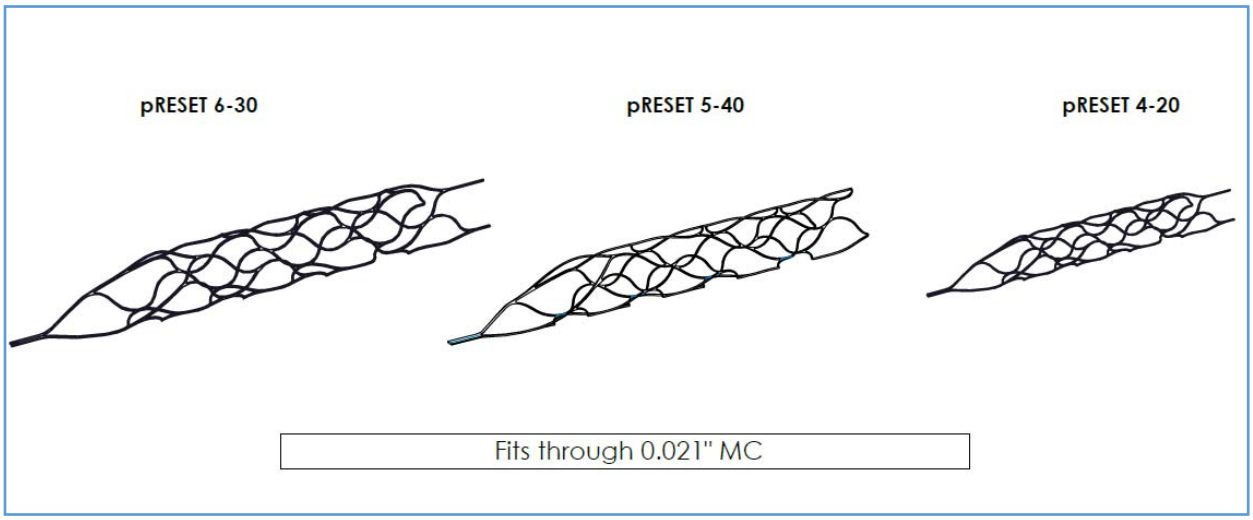

Figure 1. pRESET thrombectomy device.

Model	Device diameter [mm]	Working length [mm]	Indicated Vessel Diameters [mm]
PRE-4-20	4	20	2 – 4
PRE-6-30	6	30	3 – 6
PRE-5-40	5	40	2 - 5

2. Study Objective

To determine the safety and effectiveness of pRESET for the treatment of acute ischemic stroke within 8 hours of symptom onset (defined as time patient was last seen well) due to large vessel occlusion and to compare safety and effectiveness to the predicate device, Solitaire™ revascularization device (Medtronic).

3. Duration

Each enrolled study subject participates for 90 days (± 15 days). Enrolment is expected to take 15 months. Total study duration is approximately 18 months.

4. Rationale for Study Design and Study Population

Mechanical thrombectomy (MT) for acute ischemic stroke (AIS) due to large vessel occlusion (LVO) has been the subject of multiple clinical trials. These trials provide very strong evidence to support the safety and effectiveness of MT for AIS as compared to best medical treatment including intravenous thrombolytic therapy if indicated. As a result of these trials, clinical practice has changed markedly, and MT is now considered standard of care in AIS due to LVO.

4.1. Stent Retriever Trials

Several large prospective randomized controlled trials of stent retrievers in stroke were published in high-impact journals.

- **MR CLEAN** was a large (n=500) prospective multi-center randomized controlled trial conducted in Europe.[1] The target patient population was patients with AIS due to proximal LVO that could be treated with interventional neurovascular procedures within 6 hours of symptom onset. Patients were randomized to receive either usual care (IV alteplase or urokinase) or usual care plus intra-arterial treatment, which could include microcatheterization of the target artery, local delivery of a thrombolytic agent and/or mechanical thrombectomy using commercially available devices. Most (82%) intervention group subjects received stent retrievers. The primary study outcome, modified Rankin Scale (mRS) at 90 days, showed a statistically significant and clinically important benefit of arterial intervention.
- **SWIFT-PRIME** was a multi-center, randomized controlled trial conducted in the US and Europe.[2] The study's goal was to determine whether MT with Solitaire stent retriever in patients with AIS (<6 hours) due to LVO improved functional outcome (mRS) compared to medical therapy. Reperfusion by intraprocedure angiography after Solitaire use was 88%. Successful reperfusion (≥90%) at 27 hours, assessed by perfusion CT or MRI, was more common in the Solitaire group (83% vs. 40%, P<.001). 90-day mRS was substantially superior in the Solitaire group. There were fewer symptomatic intracranial hemorrhages in the Solitaire group but slightly more subarachnoid hemorrhages (p values not significant).
- **EXTEND-IA** was a moderate-sized randomized clinical trial conducted in Australia and New Zealand.[3] The study's goal was to determine the benefit of MT with Solitaire in patients with AIS (<4.5 hours) due to occlusion of the ICA, or M1 or M2 segments of the MCA as seen on CT angiogram. All subjects received intravenous tPA and all showed characteristics on CT or MR perfusion imaging suggestive of recoverable brain tissue. The study was stopped early due to superior efficacy in the MT group (35 patients per group randomized). Reperfusion at 24 hours was greater in the Solitaire group (100% vs. 37%, P<.001) and neurologic improvement at 3 days was greater (80% vs. 37%). Functional outcome

at 90 days was also improved (mRS ≤2 in 71% vs. 40%, P=.01). There were no significant differences in rates of death or symptomatic intracerebral hemorrhage.

- **ESCAPE** was a large international multi-center randomized clinical trial of MT with Solitaire in patients with AIS (<12 hours) due to anterior circulation occlusion.[4] All subjects had a pre-stroke Barthel Index ≥90, noncontrast CT or CTA showing a small infarct core (ASPECTS score 6-10), and an occluded anterior circulation artery with moderate-to-good collateral circulation. All subjects received intravenous tPA within 4.5 hours of stroke onset. mRS at day 90 was superior in the Solitaire group. Mortality at 90 days was lower in the Solitaire group (10.4% vs. 19%, P=.04).
- **REVASCAT** was a large, multi-center randomized control trial conducted in Spain.[5] The study's goal was to determine the functional benefit of adding MT with Solitaire in patients with AIS (< 8 hours) due to anterior circulation occlusion and absence of a large infarct on neuroimaging (ASPECTS ≥7) in whom IV alteplase did not achieve revascularization. The trial was halted early due to loss of equipoise. Solitaire use resulted in reperfusion in 66% (judged by core laboratory). The Solitaire group showed superior improvements in mRS at day 90 (score of 0-2 in 44% vs. 28%), superior dramatic improvement at day 2 (59% vs. 20%), superior median NIHSS score at day 90 (2 vs. 6), superior Barthel index score >95 (57% vs. 26%), superior EQ-5D (0.65 vs. 0.32). Although p-values were not reported, confidence intervals clearly suggest statistical superiority. Differences in trial procedures and patient selection resulted in lower reperfusion rates with Solitaire compared to other trials.

A published meta-analysis[6] reviewing each of the 5 randomized trials[1-5] discussed above was reviewed, in which the effectiveness of the Solitaire device in endovascular thrombectomy over standard medical care was shown. This meta-analysis was referred to as the HERMES collaboration. Of the 633 participants that received thrombectomy, 46.0% (291) achieved a good outcome based on an mRS score ≤ 2 at 90 days. In addition, 71% (402) of 570 patients had a successful revascularization measured by a TICI-score 2b or 3.

Other findings in the meta-analysis collaboration included:

- The common odds ratio for modified Rankin Scale improvement was 2.49 (1.76–3.53). The p-value was reported as P<0.0001.
- The number needed to treat to reduce disability by one level was 2.6.

Subgroup analysis of these trials showed superior success rates for mechanical thrombectomy across a wide range of pre-specified subgroups. The study drew several important conclusions:

- No heterogeneity of treatment effect across pre-specified subgroups for reduced disability.
- No major safety concerns were noted, with no increase in parenchymal haematoma and symptomatic hemorrhage with no difference also noted for mortality @ 90days.
- Older age has often been used as an exclusion criterion for thrombectomy, and indeed 2 of the 5 trials analyzed had an upper age limit (SWIFT PRIME and REVASCAT). Nonetheless, patients older than 80 years assigned to the thrombectomy had a slightly reduced risk of death – 45% versus 28%. There is, therefore, no justification for exclusion from thrombectomy purely on the basis of age in clinical practice.

All of these initial trials enrolled patients who were within 12 hours of onset (predominantly 0-6 hours) of AIS-related symptoms. However, two recent trials (Dawn & Diffuse 3) have shown that MT for AIS produces important clinical benefits when extended to the 6 to 24-hour time window [7,8].

In summary, the evidence supporting MT for AIS due to arterial occlusion is overwhelming.

The purpose of the trial described herein is to provide confirmatory clinical evidence that the pRESET Thrombectomy Device provides benefits similar to those of the predicate device, Solitaire, for LVO strokes within 8 hours of symptom onset.

5. Prior Investigations

pRESET has been the subject of one prior prospective clinical trial, as well as a number of retrospective case studies. All documented a high rate of revascularization in AIS and a low rate of procedure- or device-related adverse events.

ARTESp was a prospective, single-arm multi-center clinical trial (n=100) conducted in 4 centers in Germany (NCT02437409)[9]. The study's goal was to determine the safety and effectiveness of use of MT with pRESET in patients with AIS (<6 hours) due to LVO of major proximal arteries (ICA, MCA, VA, BA). To be included, subjects had to have NIHSS of 8-30 and lack of a large infarct on CT scan. All subjects had post-treatment angiograms, which were read by an independent and blinded core laboratory according to the original o-TICI system. Successful post-intervention recanalization (o-TICI 2b/3) was achieved in 92 of 109 treated vessels (84.4%). On average, 1.7 passes were used. In a small number of cases other devices were used, including Solitaire FR (n=4), Trevo (n=1), Eric (MicroVention) (n=1), or angioplasty (n=1). In one of these cases, recanalization was improved, resulting in a final revascularization rate of 85.3%. Also observed were marked improvements in NIHSS score and a high rate (62.5%) of good clinical outcome (mRS≤2) at 90 days. The rate of device-related adverse events was low.

Schwaiger et al report a retrospective review of use of pRESET in acute ischemic stroke due to MCA occlusion in 48 cases.[10] TICI 2b/3 flow was achieved in 81.3% of participants. Procedure-related complications occurred in 8.3%. As expected, TICI 2b/3 flow was associated with better outcomes.

Kurre et al report a retrospective review of 271 patients with AIS related to acute LVO using a prospectively maintained database.[11] TICI 2b/3 flow rate was 76.4%. Device-related complications were vessel perforation (1.8%), emboli to unaffected vessels (5.9%), and vessel dissection (1.5%). Many complications were not symptomatic.

In summary, based on both similarity of design, materials, use and clinical data, there is strong prior evidence for the safety and effectiveness of the pRESET device to allow it to be studied further under this proposed clinical study.

6. Information from Commercial Use

The pRESET Thrombectomy Device first obtained market approval (CE Marking) in 2011 and today is the most commonly used device for AIS due to LVO in Germany. To date pRESET has been used in greater than 25,000 procedures in Europe, South Asia, Middle East and Latin America.

7. Study Protocol

7.1. Design

Prospective, multi-center randomized clinical trial.

Because selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias, methods are incorporated in the study design to minimize potential bias including (but not limited) to:

- All investigational site personnel are required to follow this clinical investigational plan (CIP)
- Operators involved in the handling of the device (i.e. surgeon, staff nurse) will be trained by the sponsor on proper usage of the pRESET device
- Subjects will be screened to confirm eligibility for enrolment
- Demographics and medical history will be collected at screening for analysis of subject characteristics that may influence study endpoints
- Data collection requirements and study procedures will be standardized across all study sites
- Regular monitoring visits will be conducted to verify source data and adherence to the CIP and applicable regulations
- An independent clinical events committee (CEC) will be assigned to regularly review and adjudicate all reported (S)AEs.
- A data safety monitoring committee (DSMB) will be assigned to advise the Sponsor regarding the continuing safety of the trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial.

To summarize, potential sources of bias that may be encountered in this clinical study have been considered and minimized by careful study design.

7.2. Number of Sites

Up to 25 study centers may participate in this study in USA and Germany.

7.3. Site Qualification

To participate, a site must meet all of the following:

1. One or more investigators (interventional neurologist, neuroradiologist or neurosurgeon) with expertise in mechanical thrombectomy
2. A dedicated stroke team with demonstrated capability to capture information required in this trial.
3. Dedicated research coordinator staff with sufficient time/experience to fulfil trial requirements.
4. Experience with obtaining informed consent for studies in the acute stroke setting.

7.4. Blinded and Unblinded Teams

This study is planned to incorporate the blinding of the follow-up assessment team. Therefore, each site must provide the following teams:

Unblinded team - consisting of treating physicians and study coordinator who care for the patient/subject up to hospital discharge.
The blinded team - which performs all study assessments during and after hospital discharge (e.g., 24 hours, Day 7/Discharge (whichever is earlier), and 30 and day 90 visits).

The blinded team should meet the following criteria:

1. The assessor will be trained in performing assessments and be independent. Independent means the evaluator will not be an active member of the treating teams for the study subject and has to remain blinded to the study device assignment throughout the duration of the study.
2. Contain a neurologist that usually does not take stroke calls and is trained and certified (where applicable) in performing mRS, National Institutes of Health Stroke Scale (NIHSS), and Barthel Index assessments at all study visits. The blinded physician should not read the patient's actual chart or discuss the patient with colleagues.
3. If a neurologist is not available at any particular study visit, a blinded certified and trained assessor (medical professional) can be substituted for performing the mRS, NIHSS, and Barthel Index assessments.

7.5. Sample Size

Sample size calculations were based on the primary efficacy endpoint (mRS score ≤2 at 90 days).

The target sample size for this clinical investigation is 214 patients; 107 patients per arm.

An interim assessment will be performed after 50% of the target enrollment has been enrolled and either completed the 90 day evaluation visit or withdrawn prematurely. The interim assessment, performed under conditional power, may result in the target enrollment being increased to a maximum of 340 patients. Patient enrolment will continue during the period that the interim assessment is being carried out. See Section 8.5 for more details.

7.6. Study Flow

The different steps during the study are depicted in the study flow-chart (Figure 2) and the schedule of the required assessments in Section 7.18 below (Table 3):

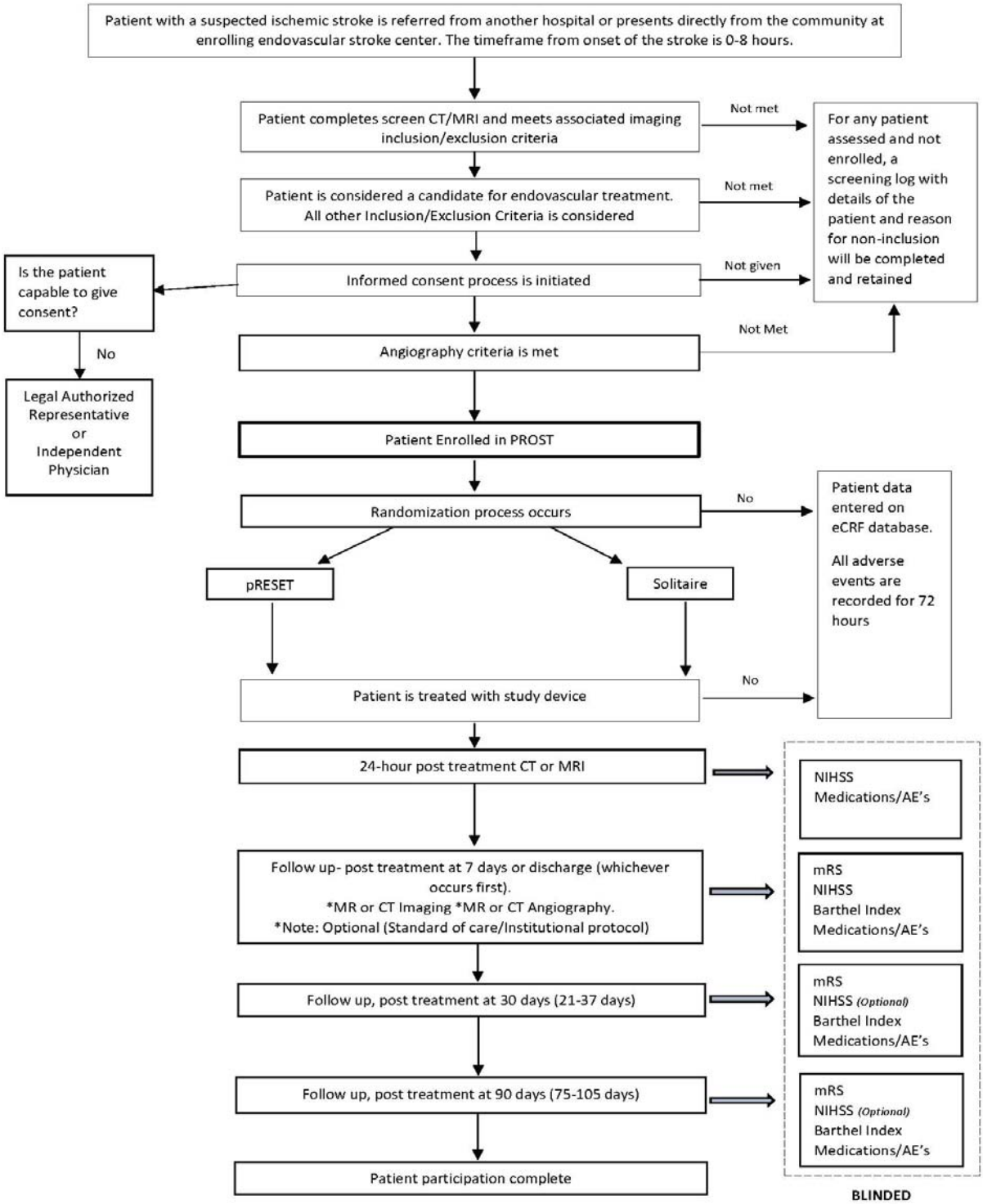

Figure 2. Study Flow-chart

7.7. Study Population

The target patient population is patients presenting with symptoms of acute ischemic stroke within 0-8 hours post onset. To be enrolled, patients must meet all inclusion criteria and no exclusion criteria shown in Table 1.

Table 1. Inclusion/exclusion criteria.

Inclusion criteria

1. **Age ≥18**
2. Clinical signs consistent with acute ischemic stroke
3. Subject is able to be treated within 8 hours of stroke symptom onset and within 1.5 hours (90 min) from screening CT / MRI to groin puncture.
4. Pre-stroke modified Rankin Score of 0 or 1
5. **NIHSS ≥6** at the time of enrolment
6. If tPA is indicated, initiation of IV tPA should be administered as soon as possible and no later than **3.0 hours** of onset of stroke symptoms (onset time is defined as the last time when the patient was witnessed to be at baseline neurologic status), with investigator verification that the subject has received/is receiving the correct IV tPA dose (0.9mg/kg) for the estimated weight.
7. Expanded Thrombolysis in Cerebral Infarction (eTICI) 0-1 flow confirmed by angiography that is accessible to the mechanical thrombectomy device in the following locations:
    a. Intracranial internal carotid
    b. M1 and/or M2 segment of the MCA
    c. Carotid terminus
    d. Vertebral artery
    e. Basilar artery

Note: M1 segment of the MCA is defined as the arterial trunk from its origin at the ICA to the first bifurcation or trifurcation into major branches neglecting the small temporo-polar branch.

8. Imaging scores as follows:
    - ASPECTS score must be 6-10 on NCCT or DWI-MRI.

    If automated core volume assessment software is used:
    - MR diffusion-weighted imaging (DWI) ≤50cc
    - Computed tomography perfusion (CTP) core ≤50 cc
9. Subject is willing to conduct protocol-required follow-up visits.
10. A valid signed and dated informed consent by participant or LAR (Legally Authorized Representative) has been obtained.
    Note: If approved by the local Ethics Committee and country regulations, an independent physician is permitted to sign consent, to allow enrolment in the study. However, as soon as possible, the patient is informed and his/her consent is requested for the possible continuation of this research.

Exclusion criteria

1. Subject who has received IA-tPA prior to enrolment in the study
2. Female who is pregnant or lactating or has a positive pregnancy test at time of admission.
3. Rapid neurological improvement prior to study enrolment suggesting resolution of signs/symptoms of stroke
4. Known serious sensitivity to radiographic contrast agents
5. Known sensitivity to nickel, titanium metals, or their alloys
6. Subjects already enrolled in other investigational studies that would interfere with study endpoints.
7. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency. (A subject without history or suspicion of coagulopathy does not require INR or prothrombin time lab results to be available prior to enrolment.)
8. Known renal failure as defined by a serum creatinine > 2.0 mg/dl (or 176.8 µmol/l) or glomerular filtration rate (GFR) < 30.
9. Subject who requires hemodialysis or peritoneal dialysis, or who has a contraindication to an angiogram for whatever reason.
10. Life expectancy of less than 90 days
11. Clinical presentation suggests a subarachnoid hemorrhage, even if initial CT or MRI scan is normal
12. Suspicion of aortic dissection
13. Subject with a comorbid disease or condition that would confound the neurological and functional evaluations or compromise survival or ability to complete follow-up assessments.
14. Subject is known to currently use or has a recent history of illicit drug(s) or abuses alcohol (defined as regular or daily consumption of more than four alcoholic drinks per day).
15. Known arterial condition (e.g., proximal vessel stenosis or pre-existing stent) that would prevent the device from reaching the target vessel and/or preclude safe recovery of the device
16. Subject who requires balloon angioplasty or stenting of the carotid artery at the time of the index procedure.
17. Angiographic evidence of carotid dissection

Imaging exclusion criteria

18. CT or MRI evidence of hemorrhage on presentation
19. CT or MRI evidence of mass effect or intra-cranial tumor (except small meningioma)
20. CT or MRI evidence of cerebral vasculitis
21. CT or MRI-DWI showing ASPECTS 0-5. Alternatively, if automated core volume assessment software is used, MRI-DWI or CTP core > 50cc.
22. CT/MRI shows evidence of carotid dissection or complete cervical carotid occlusion requiring a stent
23. Any imaging evidence that suggests, in the opinion of the investigator, the subject is not appropriate for mechanical thrombectomy intervention (e.g. inability to navigate to target lesion, moderate/large infarct with poor collateral circulation, etc.).
24. Occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior/posterior circulation) as confirmed by angiography, or clinical evidence of bilateral strokes or strokes in multiple territories

7.7.1. Justification for inclusion of vulnerable subjects

As indicated by the inclusion criteria, the population under investigation consists of severely ill patients with an acute brain disease which need immediate emergency treatment. Acute cerebral dysfunction, ischemic stroke, accompanied by a reduced level of consciousness and neurological deficits imply that the affected patients are vulnerable. There is no substitute group for the trial cohort.

7.8. Recruitment

Potential study participants may come from a treating hospital or a referring hospital. Potential participants are identified by the study site Investigator and/or the study center's stroke team.

7.9. Screening

During the screening phase, the stroke and research study teams evaluates the patient per standard institutional guidelines against eligibility criteria in Table 1. The study sponsor considers that all eligibility criteria are standard care.

Clinical studies require obtaining informed consent from study participants. Study consent for patients with AIS may be complicated by neurologic dysfunction preventing obtaining informed consent directly from potential participants. Sites will use standard institution-based guidelines for obtaining consent in the emergent/urgent setting, similar to that used in other stroke studies. The patient is considered a study subject and patient data is entered onto the eCRF when study-specific consent is obtained and the patient is determined to meet all eligibility criteria.

At this stage if the patient is not randomised, the site is still required to record all AE's for a period of 72 hours of enrolment or discharge.

If the subject retroactively rejects consent and withdraws from the study at any time prior to day 30 after treatment, the withdrawn patient will no longer be followed under the study protocol.

7.10. Baseline Evaluation

Due to the requirements for rapid AIS treatment, there is no additional baseline evaluation. The goal of treatment is to perform MT as quickly as possible after diagnosis and confirmation of eligibility.

7.11. Endovascular Treatment

The treatment phase begins when the subject enters the endovascular procedure room for the index mechanical thrombectomy procedure. The study procedure is performed under general anesthesia or conscious sedation as per standard local practices. Access to the cerebral circulation is obtained via standard access techniques using devices provided by the study site and the target vessel is catheterized.

7.11.1. Documentation of LVO

The treating physician will document the presence of LVO through catheter angiography. AP/Lateral angiographic views must be obtained at (1) baseline, (2) after up to 3 passes with the assigned device, and (3) at the end of the procedure.

7.11.2. Randomization

The treatment team will obtain a randomization assignment using a web-based randomization system. Randomization (1:1 ratio) is stratified by Age, Site of occlusion, NIHSS, IV t-PA usage, Time to symptom onset and study centre to either pRESET or Solitaire.

7.11.3. Mechanical Thrombectomy

Any study subject who has received a randomization assignment but who does not undergo the index procedure will be withdrawn from the study, but will be followed up for 72 hours post enrolment. Reason for non-completion of the study procedure will be documented in CRFs.
MT is performed with the assigned device and associated tools according to the device's Directions for use. Depending on the randomization assignment, the relevant device size is chosen according to the subject's specific anatomy and the documented sizing criteria in the DFU. The assigned device must be used for at least the first 3 passes.

An AP/Lateral angiogram showing the target vessel must be recorded after each MT device pass.

Use of a balloon guide catheter is encouraged. Optionally, a distal access catheter may be used.

If MT with the assigned device fails to restore adequate cerebral blood flow (TICI 2b50 to 3) after 3 passes, the treating physician can decide what treatment therapy (if any) is deemed appropriate for the patient at this stage. This will be recorded in the Case Report Form as a device failure and as a result a failure to the primary effectiveness endpoint analysis.

In addition, any subject who has been administrated IA-tPA as part of the treatment strategy will be considered a failure for the primary effectiveness endpoint analysis.

A final, AP/Lateral angiogram showing the target vessel must be recorded.

All imaging performed during the study procedure must be captured and sent in pseudonimized DICOM format to the independent core laboratory.

7.12. Post-Procedure Imaging

During index hospitalization, mandatory and optional imaging is shown in Table 2. All optional imaging is to be completed only as part of the standard of care/ institutional protocol. All imaging must be labelled appropriately and sent to the study sponsor in pseudomized DICOM format.

Table 2. Study-required imaging.

24 Hour	7 days (or Discharge if this occurs first)	Any timepoint if patient has had a significant deterioration
Mandatory: Brain MRI (preferable) or head CT (if brain MRI is not possible). **Optional:** Head MRA, Head CTA, Perfusion imaging (only if done as part of the standard of care/ institutional protocol	**Optional:** Brain MRI or head CT **Optional:** Head MRA, Head CTA, Perfusion imaging (only if done as part of the standard of care/ institutional protocol)	Whatever CT/MRI modality was performed as clinically indicated.

7.13.Discharge

The subject will be discharged from the hospital when medically stable. Sites should provide standard discharge instructions, including a proposed follow-up visit schedule with the blinded follow-up study team. Post-operative medications are at the discretion of the study investigator and will be recorded on study CRFs.

7.14.Follow-Up Visits

All post-discharge study visits/telephone calls are performed by the blinded study team only. Subjects undergo follow-up at 24 hours, 7 days (or discharge, whichever occurs first), 30 days and 90 days. At each follow-up timeframe, the blinded investigator/coordinator assesses modified Rankin Scale (mRS), medications, adverse events and resource utilization (see schedule of assessments, Table 3). Healthcare resource utilization may involve review of hospital charts. The blinded team should take efforts not to become unblinded through review of hospital charts.

7.15.Unscheduled Visits

If any unscheduled visit to the study investigator occurs that is deemed an adverse event, an adverse event CRF(s) will be completed.

7.16.Study Exit

The subject's participation in the study finishes when the 90-day evaluation is complete. Other than study completion, valid reasons for early study withdrawal include:

- Subject Death
- Medical reason/subject non-compliance/investigator´s decision
- A study subject may withdraw consent to participate in the study at any time without providing specific reasons. Withdrawal does not influence the quality and quantity of medical care given to that individual. Date of withdrawal will be noted in the study files.
- Lost to follow-up (A study patient is considered lost to follow-up if he/she misses two consecutive visits. A missed visit is defined as being more than one month late and not contactable via telephone). Three attempts should be made to contact the patient either by telephone or mail.

NOTE: For those patients considered lost to follow-up (see definition above), the site will, at a minimum, make a concerted effort to confirm that the patient is not deceased (e.g., active search of death indices will be performed to ensure the patient remains alive). Sites should consider that patients at high risk for loss to follow-up for any reasons (see exclusion criterion #13) should not be enrolled.

7.17.Study Assessments

The following study assessments will be documented on the study-specific eCRFs:

- **Demographics, medical history and physical examination**. CRF pages that collect standard demographic and medical information.
- **Procedure**. Aspects of the study procedure, device use, and technical complications.
- **Adverse events**. At each study visit, the investigator or designee will determine whether an adverse event (see definition below) has occurred and complete.

- **Modified Rankin Scale (mRS)**. mRS is a validated, commonly used scale to assess global neurologic status related to stroke.
- **NIH Stroke Scale (NIHSS)**. NIHSS is a commonly used validated scale to assess neurologic function after stroke.
- **Barthel index.** This is an ordinal scale used to measure performance in activities of daily living (ADL).

7.18.Schedule of Assessments

Table 3 shows the study's schedule of assessments along with allowed study windows.

Table 3. Schedule of assessments.

	Screening	Procedure	24-hour post-procedure	7 days	30 days	90 days
Timeframe / Assessment	0 hrs	Index	16-36 hrs	5-7 days	21-37 days	75-105 days
Eligibility criteria	X					
Demographics and medical history	X					
NIH Stroke Scale	X		X	X	X*	X*
Prestroke mRS	X					
mRS	X			X	X	X
MR or CT Imaging	X		X	X*		
Catheter angiogram	X	X				
ASPECTS (0-8 hr symptom onset)	X					
Core infarct size	X					
MR or CT Angiography	X*			X*		
Procedure characteristics		X				
Medications/AE's	X	X	X	X	X	X
Barthel Index	X			X	X	X

* Optional assessments:
- Imaging based on Standard of Care / Institutional Protocol
- NIH Stroke Scale not required if follow-up is completed over the phone

7.19.Imaging Core Laboratory

The imaging and angiography core lab readers will be blinded to all clinical data and treatment assignment. The readers will be experienced in prior stroke studies or trials of AIS treatment. The primary angiographic and imaging metrics to be used in the study objectives regarding safety and efficacy will be conducted by 2 independent readers with demonstrated expertise in this role. In cases of discrepancies for these measures, the 2 readers will re-review all subjects with discrepant findings and conduct a consensus conference to resolve and finalize these metrics.

The reader's adjudication of eTICI[13] flow in the target vessel post procedure will be used as the study's first secondary endpoint. See table 4 below:

Table 4. Expanded Treatment in Cerebral Ischemia Scale

Grade	**Definition**
TICI 0	No perfusion
TICI 1	Minimal antegrade reperfusion past the initial occlusion
TICI 2a	Antegrade reperfusion of less than 50% of the occluded target artery
TICI 2b50	Antegrade reperfusion of between 50-66% of the occluded target artery
TICI 2b67	Antegrade reperfusion of between 67-89% of the occluded target artery
TICI 2c	Near complete perfusion (>90%) except for slow flow in a few distal cortical vessels, or presence of small distal cortical emboli'
TICI 3	Complete antegrade reperfusion of the previously occluded target artery

The core laboratory readers will remain blinded to treatment assignment.

The readers will undergo training and assessment of reading reproducibility prior to any reads of study subjects' images.

The core laboratory readers will evaluate the following:

- Initial CT/MRI for presence of infarct core size and to confirm pre-treatment ASPECTS, presence of target penumbral pattern, and presence of proximal vessel occlusion in the target vessel.
- Catheter angiograms before, during and after the MT procedure, including assessment of the expanded thrombolysis in cerebral infarction (eTICI) scale.

Intracranial hemorrhage, if observed on any CT/MRI, will be classified as per table 5 below:

Table 5. Intracranial hemorrhage definition

Category	Definition
HT 1	Small petechiae within ischemic field without mass effect
HT 2	Confluent petechiae within ischemic field without mass effect
PH 1	Hematoma within ischemic field with some mild space-occupying effect but involving ≤ 30% of the infarcted area
PH 2	Hematoma within ischemic field with space-occupying effect involving > 30% of the infarcted area
RIH	Any evidence of intraparenchymal hemorrhage remote from the ischemic field
IVH	Any evidence of intraventricular hemorrhage
SAH	Any evidence of subarachnoid hemorrhage.

7.20.Device Accountability

pRESET is this study's investigational device. Study teams and the sponsor will carefully track pRESET device receipt, use and disposal by listing all lot numbers in the Case Report Form. The device used in the control arm, Solitaire, will also have the batch details by way of a lot number recorded as required in the Case Report Form. The control arm device will be used as per the study sites' standard procedures and off the shelf.

In the event of a device deficiency, all details will be added to the eCRF, and in the case of the study device, contact should be made with the sponsor as soon as possible and no later than 10 days from learning if it. If deemed necessary by the sponsor, the study device may be requested for return for analysis. Site standard procedures will be employed.

7.21.Blinding

This randomized trial will ensure that the assessing study team along with the Core Laboratory readers are blinded to treatment assignment. Due to the nature of the treatment, and patient access to records, the treatment team and the patient are not required to be blinded.

All steps should be made to ensure that there are limited study-related subject-specific interactions between the unblinded (treating) and blinded (pre/post-discharge assessing) teams.

8. Study Outcomes

8.1. Primary Efficacy Endpoint

The study's primary efficacy endpoint (PEE) is global disability assessed via the evaluation of the proportion of patients with a Modified Rankin Scale (mRS) $\leq$ 2 at 90 days after stroke. mRS is determined by a blinded assessment team. If the subject cannot attend the 90-day visit, mRS may be assessed by telephone call. Any subject who is dead at 90 days will be assigned an mRS of 6. The cause of death (if known) should be recorded on the Case Report Form.

Modified Rankin Scale, measures the degree of disability or dependence in the daily activities of persons who have suffered a stroke. It has been chosen as the primary efficacy endpoint in this study as it has for many years been universally considered the best clinical outcome measure for AIS trials. The successful outcome threshold of less than or equal to 2 while also been widespread utilized for many years is the level when the patient is considered functionally independent and as such is considered the most reasonable measure of a successful treatment.

8.2. Primary Safety Endpoint

The study's primary safety endpoint (PSE) is the proportion of patients experiencing symptomatic intracerebral hemorrhage (sICH), defined as per SITS-MOST criteria[12] (e.g. local or remote parenchymal hemorrhage type 2 on the post-treatment imaging scan, combined with a neurologic deterioration of 4 points or more compared to baseline NIHSS or the lowest NIHSS value between baseline and 24 h or death within 24 h. Type 2 indicates a hematoma exceeding 30% of the infarct, with substantial space-occupying effect) within 24 hours (-8/+12 hrs) post-procedure.

8.3. Analysis Populations

Primary Analysis

The primary analysis set of all study outcomes will be intent-to-treat (ITT), under which data from all enrolled subjects who have signed the ICF, meet the eligibility criteria, and are randomized in the study will be analysed irrespective of the treatment actually delivered. The intention-to-treat principle defines that every patient randomized to the clinical study should enter the primary analysis. Accordingly, patients who drop out prematurely, are non-compliant to the study treatment, or even take the wrong study treatment, are included in the primary analysis within the respective treatment group they have been assigned to at randomization.

Secondary analysis

The secondary analysis set of all study outcomes will be per-protocol population (PPP), under which data from all enrolled subjects will be analysed who met all eligibility criteria and who had the primary endpoint assessments according to the protocol (i.e. underwent treatment with the pRESET thrombectomy device or Solitaire device & received a clinical 90 days post-procedure event review for the efficacy endpoint analysis). In the PPP-analysis patients will be analysed and included in the group in which they were randomized.

Tertiary analysis
The tertiary analysis set of all study outcomes will be as-treated (AT), under which data from all enrolled subjects who actually received treatment will be analysed according to the treatment these subjects actually received irrespectively of the treatment they were assigned to.

8.4. Missing Data

Missing data, which in this instance is defined as data that was not entered into the EDC system for analysis, may have an impact upon the interpretation of the trial data.

The primary presentation of the results for the ITT population will be based on the observed data with multiple imputation for missing endpoint data using SAS PROC MI. This procedure uses an iterative modeling approach to generate estimates for patients who withdraw prematurely, or the data is just not recorded, incorporating multivariate imputation by fully conditional specification (FCS) methods. The discriminant function method will be used for classification variables. With the function method of classification, the missing values will be imputed sequentially in the following order:

Additional sensitivity analyses will also be conducted as a secondary examination of the primary analysis using the last observation recorded following the procedure observation carried forward. A tipping point analysis will also be conducted.

If a patient did not have solicited adverse events of special interest [incidence by type of event] prior to withdrawing prematurely from the study, the patient will be considered as not having experienced the event.

8.5. Primary Endpoint Statistical Analysis

The primary effectiveness endpoint of this study attempts to address the following research question:

After 90 days following the stroke, is the lower bound of the 1-sided 95% confidence interval of the difference (pRESET minus Solitaire) in global disability (mRS < 2) above the a priori threshold of -12.5%?

The hypothesis is that the proportion of good outcomes (mRS ≤ 2) at 90 days after treatment with the pRESET thrombectomy device in patients with cerebral infarction is non-inferior to the rate of good outcome at 90 days after treatment with the Solitaire device. The largest clinically acceptable effect to be able to declare non-inferiority is 12.5% (non-inferiority margin). The null and alternative hypotheses can be defined mathematically as follows:

- Ho: Treatment with pRESET is inferior to treatment with Solitaire for good outcomes defined as an mRS ≤ 2 at 90 days based on a non-inferiority margin of 12.5% (good outcome with pRESET < [good outcome with Solitaire – 12.5%]).
- Ha: Treatment with pRESET is non-inferior to treatment with Solitaire for good outcome defined as an mRS ≤ 2 at 90 days based on a non-inferiority margin of 12.5% (good outcome with pRESET ≥ [good outcome with Solitaire – 12.5%])

The summary statistics will be conducted by treatment assignment and the resulting proportions from the individual treatment groups will be used to calculated the confidence interval of the difference.

8.6. Sample Size Calculation

The objective of this trial is to demonstrate similar performance after treatment with the pRESET device compared to the expected proportion of good outcomes at 90 days in the Solitaire arm. The expected proportion of good outcomes in the pRESET arm was estimated based on earlier results with Solitaire. A 12.5% non-inferiority margin (NIM) will be used to examine the lower bound of the 1-sided 95% exact binomial confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with a 90 day mRS of 0-2. The null hypothesis and alternative hypothesis is presented below.

H_o: pRESET – Solitaire ≤ -12.5%
H_a: pRESET – Solitaire > -12.5%

If the lower bound of the 1-sided 95% exact binomial confidence interval of the difference (pRESET minus Solitaire) in the proportion of patients with a 90 day mRS of 0-2 is greater than -12.5%, then non-inferiority will be established.

The planning estimates for the PROST study considered the lower bound of the 2-sided 95% (asymptotic) confidence interval from the SWIFT PRIME study for estimation (50.5%). Sample size estimates were prepared for this parallel design study assuming a non-inferiority margin of -12.5% (pRESET successes [%] minus Solitaire successes [%]). Under the alternative hypothesis, non-inferiority would be claimed if the lower bound of the 1-sided 95% confidence interval of the difference is less than the non-inferiority margin of -12.5%.

For planning purposes, the estimated effectiveness of the Solitaire device was based on a previously published meta-analysis of 5 randomized trials in which the effectiveness of endovascular thrombectomy over standard medical care was shown. This study was referred to as the HERMES collaboration. Of the 633 included participants that received thrombectomy, 46.0% (291) achieved a good outcome based on an mRS score ≤ 2 at 90 days. The expected effectiveness of the pRESET thrombectomy device was based on the SWIFT PRIME study where 98 patients were treated with the Solitaire FR (Flow Restoration) or Solitaire 2 device. In total, 59 out of the total 98 patients who were treated achieved an mRS score less than or equal to 2. As the reported 60% patients with good outcome in the SWIFT PRIME study might be an overestimation of the actual result, the lower bound of the 95% CI was calculated based on a normal approximation. The construction of a confidence interval around the estimate of SWIFT PRIME yielded a 95% CI of [50.5% - 69.9%]. The overview of the data used for the statistical analysis is detailed in table 6.

Table 6. Overview of study-outcomes.

	SWIFT PRIME	**HERMES meta-analysis**
Primary outcome (mRS ≤2 at 90 days)	59/98 (60%)	291/633 (46.0%)
Primary outcome (mRS ≤2 at 90 days) *(95% Lower bound CI applied to SWIFT PRIME)*	(50.5%)	291/633 (46.0%)

Assuming 46% of the Solitaire patients and 50.5% of the pRESET patients have an mRS score ≤ 2 at 90 days, 214 total patients will be required.

8.7. Additional Analyses

Several additional analyses will be performed. A safety analysis will look at the following additional safety endpoints:

- Number of procedure- or device-related adverse events per subject rated as probably or definitely related to the study device/procedure prior to day 7.
- Number of procedure- or device-related serious adverse events per subject rated as probably or definitely related to the study device/procedure occurring 1) prior to day 30, and 2) up to day 90.
- Number of severe procedure or device-related adverse events rated as probably or definitely related to the study device/procedure occurring 1) prior to day 30, and 2) up to day 90.

Additional analyses will look at device performance, total number of device passes, the distribution of baseline parameters, and other procedure-related variables.

8.8. Pre-Planned Subgroup Analysis

The following pre-planned subgroups are proposed for analysis, however it is recognised that this list may not be exhaustive:

- Age >80 years at the time of the procedure
- Age >70 years at the time of the procedure
- Age ≥65 years at the time of the procedure
- Site of occlusion: ICA
- Site of occlusion: MCA
- Site of occlusion: BA
- Baseline/Enrollment NIHSS score: <17
- Baseline/Enrollment NIHSS score: ≥17
- Prior IV t-PA usage
- No prior IV t-PA usage
- Time to symptom onset: ≥4 hours
- Time to symptom onset: <4 hours

8.9. Clinical Events Committee

All neurologic AEs and all events meeting the definition for SAE (see below) will be adjudicated by a clinical events committee (CEC). The CEC will consist of 3 non-investigator independent physicians. At least one member will be a vascular neurologist, all 3 with experience in acute stroke care. The CEC must come to agreement on each evaluated event. In the event of a disagreements, a consensus of 2 out of the 3 members is needed. The CEC will use the same rating scale for AE relatedness as listed below. To the extent possible, the CEC will be blinded to study device. All statistical analysis will use AEs as adjudicated by the CEC.

8.10.Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) is responsible for the oversight and safety monitoring of the study. The DSMB advises the Sponsor regarding the continuing safety of the trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. The DSMB members are leading experts in neurology who are not participating in the trial and have no affiliation with the Sponsor. Please see the DSMB charter for specifics on the conduct and responsibilities of the DSMB.

9. Adverse Event Definitions

9.1. Adverse Event

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.

Adverse Events, regardless of relationship to the device or procedure, should be recorded in the Case Report Forms during all scheduled assessments.

The following definitions will be used by both investigators and the clinical events committee.

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

A **serious adverse event** (SAE) is defined as any AE that:

- led to a death,
- led to a serious deterioration in the health of the subject that
- resulted in a life-threatening illness or injury,
- resulted in a permanent impairment of a body structure or a body function,
- required hospitalization or prolongation of existing hospitalization,
- resulted in medical or surgical intervention to prevent permanent impairment to body structure or function,
- led to fetal distress, fetal death, a congenital abnormality, or birth defect.

Note that a planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered to be an SAE.

A **serious adverse device effect** (SADE) is an AE related to the study device that also meet the definition of an SAE.

An **anticipated serious adverse device effect (ASADE)** is a serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

An **unanticipated serious adverse device effect** is a SADE which was not previously identified in nature, severity, or degree of incidence in the clinical study documentation 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.

A **device deficiency** (DD) is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance, this includes malfunctions, use errors and inadequate labelling.

Note: The investigator is responsible for reporting any device deficiency related to the pRESET thrombectomy device to the sponsor via the appropriate CRF as soon as possible and no later than 10 days from learning if it. Only these device defeciences that resulted in an adverse device effect (ADE) to the subject should be captured as an AE on CRF.

9.2. Adverse Event Severity

The investigator will be asked to characterize the severity of each AE as mild, moderate or severe as follows:

- **Mild:** The AE is transient and easily tolerated by the subject.
- **Moderate:** The AE causes the subject discomfort and interrupts the subject's usual activities.
- **Severe:** The AE causes considerable interference with the subject's usual activities; may be incapacitating and may require hospitalization.

9.3. Adverse Event Association

The investigator and the CEC will judge the relationship of AEs to the study device and device placement procedure as follows:

- **Not related**: The AE is due to an underlying or concurrent illness or effect of another device, drug or intervention and is not related to the study device, device procedure or general surgery.
- **Unlikely to be related**: While the AE could be due to a device, an alternative explanation is more likely.
- **Possibly related**: The causal and/or temporal relationship to the study device, device procedure or general surgery, is equally or less likely than other plausible explanations.
- **Probably related:** The causal and/or temporal relationship to the study device, device procedure or general surgery, is likely or significantly more likely than other plausible explanations.
- **Definitely related**: A clinical event that can only be attributed to the device, device procedure or general surgery.

10. Risks/Benefits

10.1. Determination of Risk

The following are risks, some of which could be fatal or cause serious temporary or permanent neurologic disability related to brain bleeding or ischemia, with the use of the pRESET thrombectomy device including the associated procedure, all these risks have been reviewed by an independent physician and all can be either device or procedure related:

- Air-, Catheter-, Plaque-, Thrombus- Emboli;
- Allergic / Toxic Reaction;
- Cerebral Ischemia;
- Extracranial Haemorrhage / Complications during procedure;
- Hematoma and Haemorrhage at the puncture site;
- Infection;
- Intracranial Haemorrhage;
- Inflammation;
- Ischemic Stroke/Haemorrhagic Stroke;
- Neurovascular/Neurological complications;
- Severe Harm (permanent disability/death);
- Vasospasm;
- Vessel Perforation / Occlusion / Dissection / Thrombosis / Damage.

Risks associated with Solitaire as used in the study's target population are similar.

The frequency of risks according to the phenox limited risk management file is low, all of the above clinical complications have an occurance rating of 2 or lower. An occurance rating of 2 is considered rare (≥1 in 10,000 to <1,000).

A Risk Analysis was performed for pRESET, as per phenox Quality Management System procedures. This process involved a multi-functional team that identified risks associated with the design, processing and use of the device, and identified the characteristics related to its safety The Risk analysis process itself comprises of three principle components; Identification of qualitative and quantitative characteristics of the device, analysis of Risk using – Failure Mode Effects Analysis (FMEA) and Risk Acceptability. This complies with key elements of ISO 14971.

Risk analysis was carried out on all designs prior to design freeze and appropriate actions were taken and documented. The Risk Assessment was reviewed at each Design Review Phase and where possible changes made to improve the file.

Failure Mode and Effects Analysis (FMEA) is the technique adopted by phenox to evaluate risk.

Design & Use Hazards:

An FMEA was carried out on both the clinical/use risks and the design risks.

The hazards are Identified, Estimated and Evaluated in the FMEAs. A severity score and an occurrence score of 1-5 are assigned to each risk pre- and post-Risk Reduction activities. The severity and occurrence rankings determine a Risk Index to be used for risk acceptability decisions and evaluation of residual risk.

The clinical complication risks associated with the clinical investigation are the same as the risks outlined above in section 10.1. Possible interactions with concomitant medical treatments is not applicable for this device.

Residual Risk:

During residual risk evaluation each risk is reviewed and all reasonable steps are taken to mitigate against this risk. Once completed, all residual risks which fall into each category is presented to the team and acceptance of the residual risk is approved.

10.2.Benefits

Mechanical Thrombectomy (MT) is an accepted treatment for AIS due to LVO. Well-known benefits of MT treatment in AIS include:

- High recanalization rates and low complications rates
- Decreased rate of death and neurologic disability
- Increased quality of life through increased rates of functional independence

10.3.Further Risk Mitigation

As a further risk mitigation during the course of the PROST study, all personnel involved in the handling of the device (i.e. surgeon, staff nurse) will be trained on proper and safe usage of the pRESET thrombectomy device according to the device accompanying documents.

10.4.Risk-Benefit Rationale

Mechanical recanalistaion with a stent retriever system is safe and effective method for reopening an occlusion of a major cerebral artery and thus considerably improving the patients outcome. The treatment assigned to the study is the standard treatment for acute stroke. Whether or not the patient participates has no consequences for continuing therapy since it is essentially a data collection for an authorised therapy.

Weighing up disadvantages and risks against expected benefits

1. Consideration of the principle that the interests of the study participants must always be accorded to priority. Since interventional stroke treatment is only conducted in fewer than 1% of patients, this study can help deliver data that support the safety and efficacy of that therapy, which can ultimately only be in the patients interests.
2. Restriction of number of study participants to the absolute minimum. A maximum of 340 Patients will be recruited to allow a definitive statement to be made using statistical analysis.
3. Studies of healthy subjects who do not have any therapeutic benefits from the study are subject to stricter requriements on the suitability of the research project than apply to novel studies on patients.
4. Specical considerations are necessary for blind and double-blind studies on patients in view of the unequal treatment of the two subject groups.

A risk-benefit profile will be drawn up at the end of the study taking into consideration points 1 – 4 above.

11. Study Management

11.1. Study Monitoring

As the study sponsor, Phenox has the overall responsibility to conduct the study according to applicable regulations (21 CFR 812, 21 CFR Part 50) and guidelines (Good Clinical Practice (GCP) Guidelines, the Declaration of Helsinki, ISO 14155:2011) and conditions imposed by the reviewing IRB/EC, FDA and all applicable regulatory requirements. For this study, Phenox will assume some responsibilities and will delegate other responsibilities to appropriate consultants and/or contract research organizations (CROs). Together, Phenox, consultants and CROs will ensure that the study is conducted according to all applicable regulations. All personnel to participate in the conduct of this clinical trial will be qualified by training, education and/or experience 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 information in 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 pseudonimized prior to the monitor leaving the site. The following on-site visits will occur: site initiation visit, first monitoring visit shortly after the first subject is enrolled, additional monitoring visits determined by enrolment rate and CIP adherence.

Once completed eCRF data are verified, the monitor will electronically sign off to indicate that data have been monitored for correctness. The principal investigator must sign all eCRFs prior to site closure.

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 monitor at each monitoring visit. Unused, damaged, malfunctioning or expired devices will be returned to Phenox.

11.2. Investigator List

A complete list of participating investigators will be maintained and will be available upon request.

11.3. Investigator Responsibilities

The Investigator(s) is responsible for the day-to-day conduct of the investigation as well as for ensuring that the investigation is conducted according to all signed agreements, applicable elements of local or international regulations, the Clinical Investigational Plan, the principles that have their origin in the Declaration of Helsinki, and any conditions of approval imposed by the IRB/EC, FDA or relevant competent authorities.

The investigator is also responsible for having control of the device under investigation, for protecting the rights, safety and welfare of subjects under the investigator's care and for obtaining informed consent in accordance with 21 CFR Part 50. Each Investigator must sign the Investigator Agreement and Financial Disclosure forms prior to patient enrolment. No investigator will be added to the investigation until a signed Investigator Agreement is provided.

Additional Investigator responsibilities include:

- Ensuring IRB/EC approval is obtained prior the participation of a subject in a clinical trial. Such participation includes obtaining written informed consent
- Ensuring that the Investigational device is used only under the supervision of a trained study investigator
- Providing the study sponsor with accurate and complete financial information per 21 CFR Part 54
- Returning or disposition of the study supplies at the sponsor's request
- Ensuring that all personnel assisting with the clinical trial are adequately informed and understand their trial-related duties and functions
- Providing a study coordinator with experience and time to complete study responsibilities. The study coordinator is charged with day-to-day activities related to the trial.
- Provide access to source documents to enable trial-related monitoring.

11.3.1. Required Documents from the Investigator

At a minimum, the following documents will be provided by the investigational site to the study sponsor:

- Signed Clinical Trial Agreement
- Written and dated IRB/EC approval
- Written and dated IRB/EC approved ICF document
- IRB/EC approval for any other written documents to be provided to the study subject (e.g., advertising)
- Investigator and Co-Investigator's current Curriculum Vitae
- Any other relevant documents requested by the study sponsor or the reviewing IRB/EC or other regulatory authority(ies)
- Financial Disclosure Form
- Training documents and overview of delegated responsibilities (Delegation of Authority)

A site may not begin study participation until all of the above listed documents have been provided to the study sponsor.

Once the required regulatory approvals are in place, the study site may be activiated. No additional Investigators may participate until a copy of their CV has been provided to the study sponsor and they are properly trained on the study and if deemed necessary on the use of the investigational device.

11.3.2. Investigator Records

The Investigator is responsible for maintaining medical and study records for every subject participating in the clinical study (including information maintained electronically such as digital imaging). The Investigator will also maintain ***original*** source documents from which study-related data are derived, which include, but are not limited to:

- all correspondence including required reports,
- records of receipt, use, or disposition of the investigational device,
    - type and quantity of device
    - date of receipt
    - batch number or code
    - name of person that received, used, or disposed of each device
    - why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of
- records of each subject's case history and exposure to the device which must include,

- signed and dated consent forms
- condition of each subject upon entering the study
- relevant previous medical history
- record of the exposure to the investigational device, including the date and time of each use and any other therapy
- observations of adverse device effects
- medical records (physician and nurse progress notes, hospital charts, etc.)
- results of all diagnostic tests
- case report forms
- any other supporting data

- the protocol and documentation (date and reason) for each deviation from the protocol.
- any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

The Investigator must ensure that all study subject records are stored per local retention requirements after the end of the clinical study or the records are no longer required to support regulatory approvals, whichever date is later. For European sites this must be a minimum of 10 years. To avoid error, the study site should contact Phenox prior to the destruction of study records to ensure that they no longer need to be retained. In addition, Phenox should be contacted if the Investigator plans to leave the investigational site so that arrangements can be made for the handling or transfer of study responsibilities.

The Investigator will also maintain ***original*** source documents from which study-related data are derived, which include, but are not limited to:

- Clinic progress notes recording subject's medical history and medications
- Medical charts with operative reports and condition of subject upon discharge
- Medical records regarding AEs, including treatment and clinical outcome
- Results of diagnostic examinations
- Imaging (such as x-rays, MRIs), as well as the report of the radiologist's reading/interpretation of diagnostic imaging
- Notes of phone calls and/or correspondence indicating investigational site's attempts to follow study subjects at the required follow-up visits until subject's participation in the study is complete or terminated
- Records relating to patient death (e.g., death certificate, autopsy report/terminal medical records)
- Print-outs of source data generated by technical equipment (e.g., x-rays, MRIs) must be filed with the patient's records.

11.3.3. 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 procedure with the investigator and associated personnel prior to 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.

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

Data collected during the conduct of the PROST study will be entered into a 21 CFR §11 compliant eCRF database, Accuracy and data quality will be ensured through implementation of data edit checks. Responses to requests of clarification of eCRF recorded data will be answered, dated and electronically signed by the investigator or designee.

Any required changes to the eCRF/database will be followed by data review and validation procedures

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

11.3.4. Reporting of Adverse Events

All Serious Adverse Events (SAEs) must be reported to Phenox (or designee) within the eCRF, without delay, not to exceed **24 hours** after the investigator first learns of the event. In the event of technical problems with the eCRF, a paper SAE form is available to be manually completed and sent to the Safety management team by fax or email.

All SAEs need to be followed until the event is resolved (with or without sequelae). In case of death, all possible information that is available, e.g. autopsy or other post-mortem findings, including the possible relationship to the device, should be provided.

The investigator must submit to Phenox (or designee) any unanticipated adverse device effect **within 24 hours** after the investigator first learns of the effect. The investigator must also report the unanticipated adverse device effect to the EC/IRB within its pre-specified timeline.

The Investigator will report all of the above to the reviewing EC/IRB *(as applicable)* according to the local reporting requirements.

NOTE: Reports must identify subjects using the study's unique identifier to protect patient's confidentiality.

Expedited reporting processes and responsibilities will be outlined in the Safety Management Plan.

All Medical Device Reporting (MDR) reportable events will be conducted in accordance with 21 CFR §803, where applicable, for the clinical sites in the United States and MEDDEV 2.12-1, Vigilance reporting for sites in the European Union.

11.4.Sponsor Responsibilities

Phenox Ireland Ltd (Phenox) is the manufacturer of the pRESET device and study sponsor. Phenox' responsibilities include but are not limited to:

- Selecting qualified investigators (qualifications will be documented)
- Providing investigators with the information necessary to conduct the investigation properly
- Providing appropriate training to each study site and all study personnel (monitors), as necessary
- Documenting training where appropriate

- Selecting monitors qualified by training and experience to monitor the investigational study in accordance with FDA regulations (21 CFR 812.43(d))
- Ensuring that the IRB/EC approval is obtained
- Submission of an IDE application to FDA and any subsequent reports
- Establishment of an independent DSMB and CEC to oversee ongoing safety and scientific validity of the study
- Ensuring that any reviewing IRB/EC or FDA are informed of significant new information
- Providing and tracking investigational product to qualified investigators
- Obtaining signed Investigator Agreement for each investigator prior to their participation in the study
- Obtaining sufficient and accurate financial disclosure information (21 CFR Part 54)
- Reporting per 21 CFR 812.150 (b)

The sponsor may delegate responsibilities to contractors or CROs as they deem appropriate but will have ultimate study responsibility.

11.4.1. Training

pRESET is intended for use by interventional neuroradiologists or neurosurgeons who are trained in endovascular procedures and who have experience with AIS. All investigators, primarily US based, that do not have experience with the pRESET device, will undergo a standardized training program prior to study participation. This training will be conducted and documented as part of the Site Initiation Visit. The outline of this training program is as follows:

- pRESET Thrombectomy device, Directions for Use.
  a. Discuss and identify device description of the pRESET Thrombectomy Device.
  b. Indications for Use
  c. Contraindications for Use
  d. Precautions
  e. Compatibility
  f. Recommended Procedure
  g. Including review of procedural warnings.

- Hands-on practice with an in-vitro stroke model, if deemed necessary, to confirm understanding ofdevice Usage
  a. Follow recommended procedure steps as defined in the Directions For Use.
  b. Demonstrate proficiency utilizing an anatomical in-vitro model.

In addition to device training, each study center will undergo protocol initiation training which will include, but is not limited to, a review of the following:

- Device overview (for non-investigator research personnel)
- Clinical Investigational Plan (CIP)
- Regulatory files
- Consenting procedures
- Directions for Use (DFU)
- Safety Reporting requirements
- CRF completion and correction procedures

- Device handling procedures
- Protection of patient confidentiality
- Study supplies
- PI responsibilities

Site training will be documented and training records maintained by the study sponsor.

11.4.2. Adverse Event Review

The study sponsor will immediately conduct an evaluation of any unanticipated adverse device effect (21 CFR 812.46(b)) and will ensure the necessary reporting of the event(s) to regulatory authorities, investigators and reviewing IRBs/ECs as necessary.

If an investigation shows that an unanticipated adverse device effect presents an unreasonable risk to subjects, the sponsor will terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the sponsor first receives notice of the effect (21 CFR 812.46(b)(2)).

The sponsor will only resume a terminated investigation after obtaining EC/IRB and CA/FDA approval.

11.5.Ethical Considerations

The rights, safety and well-being of clinical investigation subjects will be protected consistent with the ethical principles laid down in the Declaration of Helsinki.

It is expected that all parties will share in the responsibility for ethical conduct in accordance with their respective roles in the investigation. The Sponsor and the Investigator(s) will avoid improper influence or inducement of the subject, monitor, the clinical investigator(s) or other parties participating in or contributing to the clinical investigation.

11.5.1. Ethical considerations – United States

The pRESET Thrombectomy device is not FDA cleared in the US. It is an investigational device that may be used in the U.S. within the confines of the PROST IDE Study. The purpose of this study is to determine the safety and effectiveness of pRESET for the treatment of acute ischemic stroke to support an application for clearance to FDA.

11.5.2. Ethical considerations – Europe

The pRESET Thrombectomy device is a CE-marked, approved device. It will only be used during the study within its approved indicated use in line with the instructions for use. The collection and analysis of the data requires ethical approval; however, the use of the pRESET Thrombectomy device under this trial protocol in Europe does not introduce any new ethical concerns beyond those present when treating any acute stroke patient with an approved mechanical thrombectomy device.

11.5.3. Compensation for Injury

The Sponsor has an insurance policy covering the subject's costs of treatment in the event of clinical investigation related injuries in accordance with national regulations. This insurance covers any damage to health proven as related from participation in the study. The insurance policy will be provided to the patient at time of consent, as applicable by national and/or local requirements.

11.6.Protection of Patient Confidentiality

To the extent possible, patient confidentiality will be observed by all parties involved at all times. All study-related data will be secured against unauthorized access. Privacy and confidentiality of information about each subject will be preserved in study reports and in any publication. Each subject participating in this study will be assigned a unique identifier. All CRFs will be tracked, evaluated, and stored using only this unique identifier.

The Investigator will maintain a confidential study subject list identifying all enrolled subjects. This list will contain the assigned study subject's unique identifier and name. This list will not be provided to the study sponsor and is only to be used at the study center and will be filed in a secure location.

While on site, monitors and auditors will have access to the study subject list and other personally identifying information of study subjects to ensure that data reported in the CRF corresponds to the person who signed the ICF and the information contained in the original source documents.

NOTE: Subject name, medical record number or address will NOT be recorded in the monitor's visit report or the database.

Any source documents copied for monitoring purposes by the Sponsor will be identified by using the assigned patient's unique identifier in an effort to protect subject confidentiality.

11.6.1. Ethics Committee/Institutional Review Board Approval

Institutional Review Board (IRB) or Ethics Committee (EC) approval is required prior to study commencement. The IRB or EC must approve a consent form specific to the study. The consent form should have all of the required informed consent elements and the site must provide a copy to Phenox for review prior to IRB/EC submission.

The Investigator must also obtain renewal of IRB/EC approval as dictated by local requirements during the entire duration of the study. The Investigator is responsible for fulfilling any conditions of approval imposed by the reviewing IRB/EC, such as regular reporting, study timing, etc. The Investigator will provide the study sponsor with copies of such approvals and reports.

Withdrawal of IRB/EC approval must be reported to the study sponsor immediately following the investigator's knowledge of the withdrawal.

The informed consent form (and any other written information to be provided to the study subject) should be updated whenever new information becomes available that may impact the patient's consent. Any such revision or update must be approved by the reviewing IRB/EC before being provided to the study subject. Should it be necessary that such information is verbally provided to the study subject (in the case that the information may impact the patient's willingness to continue study participation), communication of the information must be documented.

11.6.2. Quality Assurance and Supervision by Authorities

All clinical sites are subject to audit by study sponsor personnel or designee for protocol adherence, accuracy of CRFs and compliance with applicable regulations. Any evident pattern of non-compliance with respect to these standards will be cause for the site to be put on probation until appropriate corrective action is taken.

All documents and data will be maintained in such a way to assure control of documents and data to protect the subject's privacy as far as reasonably practicable. The Sponsor and representatives of the FDA or other regulatory authorities are permitted to inspect the study documents (e.g., study protocol, CRFs, and original study-relevant medical records/files) as needed. All attempts will be made to preserve subject confidentiality.

Investigators will immediately notify Phenox upon learning of announced audits or inspections by regulatory agencies.

11.7.Study Suspension or Early Termination

The study can be discontinued at site level, at the discretion of the study Sponsor for reasons including, but not limited to, the following:

- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary
- Insufficient recruitment of subjects
- Persistent non-compliance with the protocol
- Persistent non-compliance with EC/IRB or regulatory requirements

If the study is discontinued or suspended prematurely, the Sponsor will promptly inform all clinical investigator(s)/investigational center(s) of the termination or suspension and the reason(s) for this. The EC/IRB will also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the clinical investigator/investigation center(s). Regulatory authorities and the personal physicians of the subjects may also need to be informed if deemed necessary.

11.8.Protocol Deviations

A protocol deviation is defined as any study action taken by the clinical Investigator or site personnel in conflict with the Study Protocol. In this study, deviation degree is defined as:

- *Major deviation*: Any deviation from subject inclusion and exclusion criteria, subject informed consent procedures or unauthorized device use.
- *Minor deviation*: Deviation from a protocol requirement such as incomplete/inadequate subject testing procedures, follow-ups performed outside specified time windows, etc.

Investigators and research coordinators will document protocol deviations on a specific form in the eCRF. Non-subject specific deviations (e.g. unauthorized use of an investigational device) should also be reported to Phenox via the eCRF. Investigators will also adhere to procedures for reporting study deviations to their IRB/EC in accordance with their specific IRB/EC reporting policies and procedures.

Investigators must obtain prior approval from Phenox clinical study management before initiating *major* deviations from the investigational plan, except where necessary to protect the life or physical well-being of a subject in an emergency. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g. subject was not available for scheduled follow-up office visit, blood sample lost by laboratory, etc.); however, the event is still considered a deviation and will be reported on the appropriate CRF.

Per 21 CFR §812.140 (a)(4), investigators are required to maintain accurate, complete and current records, including documentation showing the dates of, and reason for, each deviation from the CIP. Failure to

comply with the CIP may result in investigator termination of participation [21CFR §812.46 (a)] in the PROST study.

11.9.Protocol Amendments

Only Phenox is allowed to modify the protocol. Any changes made to the protocol after a favorable opinion by the accredited Ethics Committee and Regulatory Authority has been given, will be in the form of a protocol amendment. All amendments will be submitted for review and approval to the Ethics Committees and relevant authorities that gave the initial favorable opinion.

11.10.Final Report

It is the goal of phenox inc. to prepare one or more study reports suitable for publication in the peer-reviewed literature and for submission to regulatory authorities. As detailed in the Clinical Trial Agreement, Investigators are not permitted to publish single-center results before the multi-center results are published.

11.11. Information Confidentiality

All information not previously published concerning the test device and research, including patent applications, manufacturing processes, basic scientific data, etc., is considered confidential and should remain the sole property of Phenox. All information and data generated in association with this study will be held in strict confidence and remain the sole property of Phenox. The Investigator agrees to use this information for the sole purpose of completing this study and for no other purpose without written consent from Phenox.

11.12. Trial Registration

The study will be registered in a publicly accessible trial database (e.g., clinicaltrials.gov) prior to study initiation.

11.13.Abbreviations

Abbreviation	**Definition**
ADE	Adverse device effect
ADL	Activities of daily living
AE	Adverse event
AIS	Acute ischemic stroke
ARTESp	Acute Recanalization of Thrombo-Embolic Ischemic Stroke with pREset
ASPECTS	Alberta Stroke Program Early CT Score
BA	Basilar Artery
CEC	Clinical events committee
CFR	Code of federal regulations

CI	Confidence interval
CRF	Case report form
CRO	Clinical research organization
CT	Computed tomography
CV	Curriculum Vitae
DFU	Directions for use
DSMB	Data safety monitoring board
EC	Ethics committee
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good clinical practice guidelines
GFR	Glomerular filtration rate
ICH	Intracranial hemorrhage
IRB	Institutional review board
IA-tPA	Intra-arterial tissue-type plasminogen activator
IV-tPA	Intravenous tissue-type plasminogen activator
LVO	Large vessel occlusion
MCA	Middle cerebral artery
MRI	Magnetic resonance imaging
mITT	Modified intent-to-treat
mRS	Modified Rankin Scale
MT	Mechanical thrombectomy
eTICI	Expanded Thrombolysis in Cerebral Infarction
NCCT	Non-contrast CT
NIHSS	National Institutes of Health Stroke Scale score
NIM	Non-inferiority margin
PEE	Primary efficacy endpoint
PP	Per-Protocol
PSE	Primary safety endpoint
SADE	Serious adverse device effect

SAE	Serious adverse event
SD	Standard deviation
sICH	Symptomatic ICH
SWIFT-PRIME	Solitaire™ With the Intention For Thrombectomy as PRIMary Endovascular Treatment trial
TICI	Thrombolysis in Cerebral Infarction scale
UADE	Unanticipated adverse device effect
VA	Vertebral artery

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