The PLUNGER Stroke Trial

A comparison of cyclic manual direct aspiration thrombectomy (Plunger technique) vs. static manual direct aspiration thrombectomy for treatment of acute large vessel occlusion stroke with the Raptor Aspiration Catheter

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Study Summary

Title	A comparison of cyclic manual direct aspiration thrombectomy (Plunger technique) vs. static manual direct aspiration thrombectomy for treatment of acute large vessel occlusion stroke with the Raptor Aspiration Catheter
Short title	The Plunger Stroke Trial
Objective	To compare the efficacy and safety of cyclic manual direct aspiration thrombectomy (Plunger technique) vs static aspiration for direct aspiration thrombectomy with the Raptor Aspiration Catheter
Design	A randomized, controlled trial of the Plunger technique vs. static manual direct aspiration thrombectomy for treatment of acute large vessel occlusion stroke. At least one pass with aspiration is required.
Sample size	A sample size of 500 subjects will detect a 15% absolute difference in successful first pass rate between the two groups at 90% power.
Duration	With 20 sites, enrollment can be completed in one year (Sites to be decided)
Primary endpoint	First pass effect (FPE) defined as TICI 2c or 3 after the first attempt of direct aspiration thrombectomy
Safety endpoint	Rate of symptomatic intracranial hemorrhage (sICH)
Secondary endpoints	Overall rate of TICI 2b or 3 recanalization with Plunger vs. static aspiration Functional outcome at 90 days based on mRS assessment Rate of successful navigation of aspiration catheter to clot Rate of rescue treatment with stent-retrievers Rate of complete clot ingestion Recanalization rates with the two different sizes of Raptor Rate of recanalization by clot density on CT (hyperdense vs isodense)
Inclusion criteria	Acute ischemic stroke due to occlusion of the terminal ICA or M1 segment of the MCA Treatment can be initiated within 24 hours of symptom onset Age 18 years or older
Exclusion criteria	Evidence of acute intracranial hemorrhage prior to treatment Failure to obtain informed consent

Background

Mechanical thrombectomy is the standard of care for acute ischemic stroke due to large vessel occlusion in the anterior circulation [1]. Improved speed of reperfusion is clearly associated with better patient outcomes [2]..Therefore any device or technique improvements that can optimize efficiency of reperfusion will also lead to improved neurologic outcome.

Recently, several studies have compared direct aspiration thrombectomy with stent-retriever thrombectomy. These studies have shown no difference in reperfusion or patient outcomes between the two approaches [3], though some have found that aspiration thrombectomy achieves reperfusion faster than stent-retrievers [4]. Therefore, aspiration thrombectomy may ultimately provide faster reperfusion, leading to better patient outcomes, particularly if the aspiration technique can be optimized to maximize likelihood of full reperfusion on the first thrombectomy attempt (first pass effect).

The mechanism of aspiration thrombectomy relates to the simple physics of a suction cup. The tip of the catheter comes into contact with the occlusive thrombus and a seal forms around the circumference as a vacuum is applied to the catheter lumen. Thus, a suction cup is formed at the tip of the catheter, and it is this suction cup that transmits the force needed to extract the clot. In mechanical physics, the force of a suction cup is very easily calculated as the product of suction cup area and vacuum pressure (F=A*P). In this context, multiple studies have demonstrated the positive impact of 1) larger catheter size and 2) high vacuum pressures to improve extraction force on the occlusive thrombus and therefore the efficacy of direct aspiration thrombectomy (e.g., Froehler 2017 [5]). In short, larger catheters with maximally negative vacuum pressures should have the greatest clot extraction force.

A more recent frontier in the mechanics of aspiration thrombectomy is acceleration. In particular, jerk, or the derivative of acceleration (the third derivative of position, as expressed in equation below), allows force to be transmitted through the clot, which in turn creates waves and deformation of elastic clot, allowing more clot to be engulfed by the catheter.
Jerk equation:

$$\vec{j}(t) = \frac{\mathrm{d}\vec{a}(t)}{\mathrm{d}t} = \frac{\mathrm{d}^2\vec{v}(t)}{\mathrm{d}t^2} = \frac{\mathrm{d}^3\vec{r}(t)}{\mathrm{d}t^3}$$

This concept can be maximized with an alternating, on/off vacuum (cyclic aspiration). For example, a clogged drainpipe can be cleared using a vacuum created by a suction cup. However, it's common knowledge that a static vacuum is not as effective as an oscillating vacuum, and hence the plumbing technique and device known as the plunger.

Oscillating, or cyclic, aspiration is now being applied to thrombectomy vacuum pumps and there is preliminary evidence of improved efficacy with these devices [6]. However, many interventional programs do not use electric pumps as they are cumbersome and are felt to be unnecessary [7]. Many operators will simply use a 60 cc syringe to apply a vacuum to the catheter.

We have developed the **Plunger technique**, a manual form of cyclic aspiration introduced by Dr. Michael Froehler. It involves rhythmically pulling and releasing a 60 mL VacLok syringe to generate intermittent suction, mimicking automated cyclic aspiration systems. This technique has been used safely over the past six years at Vanderbilt University Medical Center (VUMC), with no related complications and anecdotal improvements in first-pass effect. In vivo investigations have shown increased clot ingestion compared to static aspiration [10]

The term “plunger” is widely recognized in the neurointerventional community. At VUMC, the technique is used in approximately 75% of thrombectomy cases, with three out of four neuroendovascular attendings preferring it over static aspiration. Nationally, experts such as Dr. Tudor Jovin, Dr. Ramesh Grandhi, and Dr. Brian Jankowitz also favor cyclic aspiration approaches. Both the Plunger and static aspiration techniques are standard of care at VUMC and in broader clinical practice. Their use typically varies by physician preference rather than patient-specific clinical factorsFor example, Dr. Froehler employs the Plunger technique in over 95% of cases, while Dr. Raygor prefers static aspiration and often uses alternatives to the 60 cc syringe. Differences in techniques are likewise not often reported in the medical literature because there is little scientific interest. Instead, experimental investigations of techniques may be reported if there is a measurable outcome. In this case, there is a body of literature investigating cyclic aspiration thrombectomy; Simon et al 2014 (PMID 24235098), Oyekole et al 2021 (PMID 34496311), Patki et al 2023 (PMID 36511815), Bajrami et al 2024 (PMID 38515399).

Note that these references do not include any of our own research or citations. This variability reflects differences in training and institutional experience, which are well-documented contributors to surgical technique selection. Furthermore, all forms of thrombus aspiration are well-represented in the peer-reviewed literature and are recognized by the medical community as appropriate and accepted standards of care.Genuine clinical equipoise exists between the two techniques, as there is no definitive evidence favoring one over the other. The presence of multiple ongoing or planned studies evaluating cyclic aspiration, along with the development of new investigational devices designed for this purpose, underscores the uncertainty and supports the need for a comparative study.

To further evaluate these findings, we are coordinating a multi-site comparative study using FDA-approved devices (Raptor catheters and 60 cc VacLok syringes). Fourteen sites have expressed interest in participating, and additional sites will be contacted following IRB approval. All participating sites must have access to the required supplies. Protocols, consent templates, and REDCap access will be provided to ensure consistency in data collection.

Technique and Devices

Raptor Aspiration Catheter

The Raptor aspiration catheters from Balt are two large-bore catheters designed for distal intracranial access. The two available sizes, 0.071” and 0.074”, are similar to other catheters that are used for direct aspiration thrombectomy, including the Stryker Catalyst 7 (ID = 0.068”), the Penumbra Jet 7 (ID = 0.072”), and the Microvention Sofia Plus (ID = 0.070”). The large ID creates maximal suction cup force by maximizing the cross-sectional area of the catheter tip. We are able

to control for any potential differences between these catheters by using a single catheter type (Raptor) in this study. Both the 0.071" and the 0.074" Raptors are eligible for use.

Navigation technique
All large diameter catheters intended for intracranial use must overcome the tortuosity of the carotid siphon and the lip at the ostium of the ophthalmic artery. While all of these catheters are purposely flexible to overcome these obstacles, difficulty in navigating this anatomic segment is very common. Fortunately, there are several adjunctive devices that are specifically designed to help facilitate easy navigation of large catheters through the carotid siphon and past the ophthalmic artery origin.
The Carrier inner navigation catheter from Balt is specifically designed for use with the Raptor catheters and can be placed in the region of the carotid siphon and ophthalmic origin, allowing the catheter to easily track over it and to the clot face.
Finally, the microwire used for the triaxial navigation of a Raptor to the intracranial vasculature can also counter the difficulty of tortuous anatomy. While any 0.014" neurovascular wire may be used, the Aristotle 18 wire (Scientia Vascular) has particular advantages for this specific purpose. Though it has a diameter of 0.018", it is extremely flexible and can be used quite similarly to a typical 0.014" wire, such as the Synchro2 from Stryker.

In the PLUNGER trial the Raptor *must* be used, and it is strongly encouraged that operators utilize the Carrier inner navigation catheter and the Aristotle 18 guidewire. If initial attempts at navigation with a Raptor catheter fails, then other catheters may be used at the discretion of the operator. These will be regarded as protocol deviations and will require description of the anatomy and rationale for device choice. Guide catheter choice is left to the discretion of the operator, including the optional use of balloon guide catheters versus long guide sheaths.

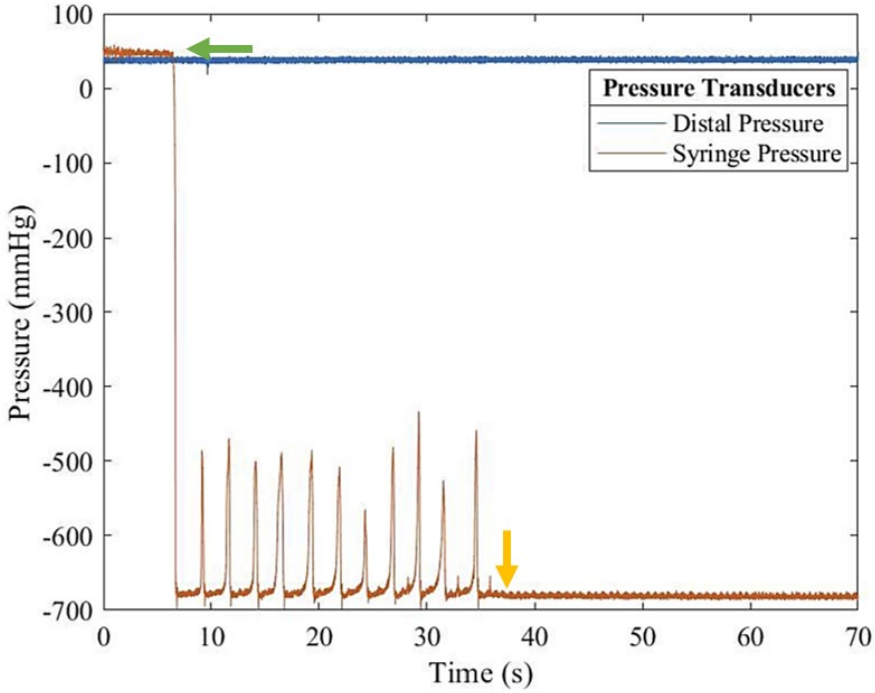
Aspiration syringe and technique
Trial participants will all be treated with direct aspiration thrombectomy, an established endovascular treatment modality for acute ischemic stroke caused by large vessel occlusion. Subjects will be randomized to static aspiration or plunger aspiration, which will be delivered via standardized techniques.
The vacuum source, or 'pump,' will be the Merit Medallion VacLok syringe which is designed to apply aspiration through a catheter. The plunger is pulled back and twisted to lock the syringe in the 'open' position, thereby creating and holding a vacuum in the syringe and the catheter to which it is attached.

In direct aspiration thrombectomy, the catheter is navigated to the clot face and then a vacuum is applied by attaching the VacLok syringe and locking the syringe in the open position, as above. Typically the VacLok syringe will be attached to the open luer connector on the stopcock and rotating hemostatic valve assembly that is already attached to the catheter hub.

For *static aspiration*, the VacLok syringe is opened to create suction on the clot for a minimum of one minute (some interventionalists may prefer a longer 'dwell time' to encourage more clot ingestion, which is fine). Once the syringe is locked open, a timer is used to ensure adequate timekeeping. Once at least 1 minute or more has passed, then the catheter is carefully withdrawn into the guide catheter and removed. The guide catheter is then thoroughly aspirated to clear any fragmented clot. The duration of aspiration will be reported on the case report form (CRF). Other syringes or devices for aspiration may be introduced during the trial at the discretion of the steering committee.

Plunger Technique

The VacLok syringe is also used for the Plunger technique. The catheter is navigated to the clot face and aspiration is applied by drawing the syringe plunger back. However, the syringe is not locked, but instead the plunger is repeatedly pulled back and then released in a cyclic fashion [Froehler, *JNIS* 2023]. There is no need to cycle slowly, as seen in the how-to video. Operators may wish to pull the plunger more quickly than it is released, though our *in vitro* studies have shown that there is always negative pressure at the catheter tip and therefore no risk of 'pushing' the clot. Although obvious, it is important to note that when the plunger is released it should not be actively pushed forward as this could push the clot out of the catheter and into the distal vasculature.



When using the Plunger technique in the trial, active plunging must be performed for at least 30 s at a time, with pauses of no more than 30 s. When paused, the syringe must be locked in the fully open / full vacuum position. Total aspiration time, including active plunging and static vacuum pauses, must be at least one minute (one cycle of plunging). As with static aspiration, some surgeons may prefer to use a longer total aspiration time, which is acceptable. The VacLok syringe must then be locked in the full vacuum position before the catheter is removed in a fashion identical to that described above for the static aspiration technique.

Rescue treatment

Rescue therapy may be provided to the subject at the discretion of the study investigator. In the event that aspiration thrombectomy fails to achieve successful reperfusion (defined as TICI $\geq$ 2b) after at least one attempt, any other FDA-approved thrombectomy device may be used by the study physician.

Training

All investigators and sub-investigators will receive training on the above techniques prior to site initiation. Training will either be in-person or via video teleconference. Additionally, each site must confirm that they stock the Raptor, VacLok syringe, and Carrier navigation catheter prior to site initiation.

Objective and endpoints

Study objective

The object of this study is to compare the efficacy and safety of the Plunger technique vs static aspiration for direct aspiration thrombectomy using the Raptor aspiration catheter.

Primary effectiveness endpoint

The primary endpoint is the first pass effect (FPE), defined as TICI 2c or 3 after the first attempt of direct aspiration thrombectomy, as determined by core lab assessment (see p. 16)

Primary safety endpoint

The primary safety endpoint is the rate of symptomatic intracranial hemorrhage (sICH) at 24 hours, as defined by 1) new intracranial hemorrhage on CT and 2) neurologic deterioration associated with worsening NIHSS by 4 or more points.

Secondary endpoints

- Overall rate of TICI 2b or 3 recanalization with Plunger technique vs. static aspiration vs. rescue therapy. At least one thrombectomy attempt with the assigned technique will be made prior to rescue treatment with a stent-retriever or other device if needed.
- Functional outcome at 90 days based on modified Rankin scale (mRS) assessment. All patients will be contacted *by phone* at 90 days to assess their functional status.

- Rate of successful navigation of aspiration catheter to clot. This will be reported by the site investigator. If the aspiration catheter cannot be navigated to the clot then rescue treatment with a stent-retriever may be used.
- Rate of rescue treatment with stent-retrievers. This rescue therapy will be employed after **at least** one attempt with aspiration thrombectomy, or if the Raptor cannot be successfully navigated to the clot.
- Rate of complete clot ingestion. Sites will report if the clot is completed ingested through the Raptor and into the syringe, or if it is partially ingested in the tip of the Raptor.
- Recanalization rates with the two different sizes of Raptor: analyses will compare recanalization of the 0.071" vs. 0.074" sizes of Raptor.
- Rate of recanalization by clot density on CT (hyperdense vs isodense). There is evidence that hyperdense clot contains a higher fraction of red blood cells, is softer, and is more readily removed with thrombectomy devices. This has not been assessed in aspiration thrombectomy.

Risk Assessment

- This study poses no more than minimal risk to participants. All subjects will undergo a standard mechanical thrombectomy procedure, with the only difference being the method of aspiration; either static or cyclic (Plunger) technique. Both techniques are widely used in clinical practice, are considered standard of care, and have comparable safety profiles. No investigational devices or procedures will be used. As such, participation in the study does not expose subjects to risks beyond those encountered in routine clinical care.

Investigational plan

Trial design

The Plunger trial is a prospective, multicenter, randomized, controlled trial of the Plunger technique vs. static manual direct aspiration thrombectomy to assess recanalization efficacy for treatment of acute large vessel occlusion stroke. Participants will have a large vessel occlusion in the anterior circulation of the terminal ICA or M1 segment of the MCA.

Ethical Considerations and Informed consent

This study compares two suction techniques: static aspiration and the cyclic aspiration (plunger technique) both of which are standard practices in mechanical thrombectomy. These techniques are routinely employed by physicians based on individual preference and training. All procedures involved are part of routine clinical care and utilize FDA-cleared devices (e.g., Raptor catheters and 60cc VacLok syringes). No investigational devices or experimental procedures are introduced. Importantly, both techniques have similar/identical risk profiles, as they are commonly used in clinical practice and do not introduce additional risks beyond those encountered in standard stroke treatment. Therefore, this study meets the definition of minimal risk research under federal regulations.

Informed consent process:

The patient consent process will be conducted using a REDCap-based electronic consent form. The consent form has been developed in REDCap, a secure, web-based, HIPAA-compliant, data collection platform with a user management system allowing project owners to grant and control varying levels of access to data collection instruments and data (e.g. read only, de-identified-only data views) for other users.

This study will utilize the electronic consent (e-Consent) framework within the REDCap system. The e-Consent forms will be presented to participants electronically, allowing them to review, complete, and sign the consent form online. The system will ensure that all signed forms are archived as PDF snapshots for compliance and future reference. Version control will be strictly maintained, and any changes to the consent form will be resubmitted to the IRB for approval prior to implementation. The information obtained from participants within the REDCap system during the e-Consent process will align with the information that would have been collected during the paper consenting process.

All consent form versions will be managed using the REDCap version control system. Each version of the consent form will be automatically archived upon participant signature. If a new version of the consent form is required, the previous version will be deactivated, and the new version will be submitted to the IRB for approval before use in the study.

The e-Consent(s) will include the complete and exact contents of the most current, IRB approved study consent(s).

Potential participants will participate in the consent process by :
1. Being approached in-person at a Vanderbilt Clinic and accessing the REDCap survey via iPad or other portable electronic device (OR)

During the in-person consent process, patients will be consented by a member of the key study personnel. Participant signatures will be obtained using a typed signature or, written signature – via stylus/cursor, etc.

The study investigator and/or designated study staff are responsible for obtaining informed consent from each potential participant after confirming eligibility and before any research-related activity, including randomization. This process will comply with all applicable regulatory and institutional guidelines, including those set by the local IRB.

A thorough written explanation of the study will be provided to the participant or LAR, including:

- Purpose of the study
- Alternative treatment options
- Voluntary nature of participation and right to withdraw without penalty
- Potential risks and benefits
- Contact information for questions or concerns

Participants are considered enrolled once the eConsent form is electronically signed using REDCap. No study-specific assessments or data entry into the research database will occur until the signed consent is obtained.

Patient selection
Patients with a large vessel occlusion who are clinically appropriate for thrombectomy will be screened for participation. Subjects who meet selection criteria below will be enrolled. Note that there are no parenchymal imaging criteria; site investigators will determine if individual patients will benefit from thrombectomy. The trial is not intended to assess clinical criteria for endovascular treatment decisions, but rather to assess *technique* of thrombectomy once that decision has been made.

Inclusion criteria
1. Acute ischemic stroke due to occlusion of the terminal ICA or M1 segment of the MCA
2. Treatment can be initiated within 24 hours of onset
3. Age of 18 years or older

Exclusion criteria
Evidence of acute intracranial hemorrhage prior to treatment
Failure to obtain informed consent

Subject withdrawal
Subjects enrolled in the study can discontinue their participation at any time for any reason without prejudice or reduction in the quality of their medical care. The investigator can terminate a subject's participation in the study to protect the subject's health. The Investigator must document this notification of withdrawal from the study in the appropriate CRF and notify the sponsor.

Data collection
Baseline data: At the time of endovascular treatment, the following data will be collected for all subjects:
- Age
- Baseline mRS
- ASPECTS score
- Hyperdense vessel sign (yes/no; site-reported)
- NIHSS
- Location of occlusion (right or left, ICA terminus or M1)

Procedure data: The following will be collected immediately after the procedure:
- Guide catheter used
- Which Raptor used (0.071" or 0.074")
- Microcatheter used (Carrier or other)
- Microwire used
- Successful navigation? (yes/no)

- Total duration of aspiration
- Total duration of plunging (if assigned to Plunger technique)
- Reperfusion (TICI) after each pass (site-assessed)
- Clot ingestion: none, partial, or complete
- Groin puncture time
- On-clot time
- Time of reperfusion
- Rescue treatment? If yes, what device and how many passes

24 hour data: To be collected at 24 hrs post-procedure +/- 6 hours:

- Imaging evidence of hemorrhage? If parenchymal, HI1, HI2, PH1, or PH2; or IVH, SAH, SDH
- Symptomatic ICH?
- NIHSS

90 day follow up: To be collected by phone at 90 days +/- 30 days

- Modified Rankin Score
- PROMIS-10 score (a publically available global health assessment tool that allows measurements of symptoms, functioning, and healthcare-related quality of life for a wide variety of chronic diseases and conditions.

Telephone follow up

Telephone follow-up will be conducted where information related to the subject's mRS assessment and Quality of Life assessment will be collected. If the subject is unavailable for any reason, the subject's family/relative or caregiver/LAR will be requested to provide the applicable information.

Schedule of assessments

	Baseline	**Procedure**	**24 hours Post Procedure**	**90 days Post Procedure (telephone)**
Eligibility	◆			
Demographics and Medical History	◆			
Location of occlusion	◆			
mRS Assessment	◆			◆
NIHSS Assessment	◆		◆	

Head CT: ASPECTS, hyperdense vessel, hemorrhage	◆		◆	
Devices used		◆		
Successful navigation		◆		
Time of aspiration, plunging, and time to reperfusion		◆		
Reperfusion score (TICI; site-assessed and core lab)		◆		
Rescue treatment, if applicable		◆		
Clot ingestion		◆		
PROMIS-10				◆
Adverse Events		◆	◆	◆

Recording data

Study data will be collected using electronic case report forms and a electronic data capture system (REDCap). The system allows the capability of data collection remotely through the internet so the participating clinical site personnel may log on to the system securely and enter the data. All subjects' data collected in the system will be extensively verified through data validation programs, database integrity rules, and investigation-specific data entry conventions for data accuracy and logical meaningfulness. Periodic analysis of all subjects' data collected will be performed in order to examine the expected distributions of data and to identify outliers for possible data entry errors.

The Investigator is responsible for reviewing all eCRF entries for completion and correctness. Changes in case report forms will be made electronically and the system used will keep an audit trail of changes. If necessary, an explanation for the change(s) may be provided. The Investigator will electronically approve all eCRF data.

All study staff that enter data into eCRFs will undergo appropriate training for use of eCRFs.

Loss to Follow-up

A participant will be considered lost to follow-up for the secondary end-point, mRS, if he or she is unable to be contacted by the study site staff, either via telephone or an in-person meeting at 90-days after randomization. When all reasonable attempts to locate the subject have been exhausted, the subject will be considered lost to follow-up and their data will be excluded from the data analysis from the time of last contact onward. All data collected prior to last contact will be included in data analysis.

Statistical analysis

Sample size calculation

The true rate of successful FPE with aspiration thrombectomy can be estimated based on several prior studies. The COMPASS trial reported an 83% rate of TICI 2b or 3 after the first attempt with aspiration thrombectomy [4]. Similarly, Kang et al reported TICI 2b or 3 in 82% of patients after the first pass with aspiration thrombectomy [8], but that rate dropped to 19% when limiting the definition of successful FPE to TICI 2c or 3 [8]. Similarly, the ETIS investigators reported a 24% rate of TICI 3 FPE with the Sofia catheter [9]. Synthesizing these results, we estimate the predicted FPE (TICI 2c or 3) rate of static aspiration thrombectomy to be 25%.

While it is difficult to predict the treatment effect of the Plunger technique, our experience is that there is significantly more total clot ingestion with this technique. Total clot ingestion would be expected to particularly impact the TICI 2c/3 rate of FPE. Therefore, we estimate that the Plunger technique may increase FPE rate by 15% over static aspiration (predicted Plunger FPE of 40%).

A minimum sample size of 462 would be required to detect a difference of 15% between these two groups with 90% power at alpha of 0.05. Given that the actual FPE rates are difficult to estimate and accounting for inability to access the lesion with the Raptor and missing data, we plan for a total minimum sample size of 500.

Population for analysis

A modified intention-to-treat (mITT) analysis will be employed, wherein all subjects for whom navigation of the Raptor to the clot failed will be excluded from the subsequent ITT analyses. This is because those subjects will not be treated by either of the techniques being studied in this trial. Once navigation failures are excluded, the remainder of the population will be compared based on assigned treatment technique per randomization.

Analysis of primary effectiveness endpoint

The primary endpoint is the first pass effect (FPE), defined as TICI 2c or 3 after the first attempt of direct aspiration thrombectomy, as determined by core lab assessment. The rate of successful FPE will be compared between the Plunger group and the static aspiration group per the mITT population as above.

Null hypothesis: the rate of successful FPE is not different between static and plunger aspiration. The rate of FPE will be compared between the two groups by chi-square analysis. If there is a significant difference between the two, then the null hypothesis will be rejected.

Analysis of primary safety endpoint

The primary safety endpoint is the rate of sICH at 24 hours compared between the static and Plunger aspiration groups. A chi-square test will assess for differences in rate of sICH between the two treatment groups in the mITT population. Secondary analyses will account for ASPECTs score and time to treatment between the two groups.

Analysis of secondary endpoints

Overall rate of TICI 2b or 3 recanalization with Plunger vs. static aspiration will also be compared using chi-square analysis on the mITT population.

For the following additional binomial secondary efficacy endpoints, treatment groups will be compared using logistic regression models as appropriate:

- Rate of successful navigation of aspiration catheter to clot
- Rate of rescue treatment with stent-retrievers
- Rate of complete clot ingestion
- Rate of recanalization by clot density on CT (hyperdense vs isodense)

The 90-day functional outcomes, including mRS and PROMIS-10, will be compared between the two groups using ordinal shift analysis.

Randomization
Patients will be randomized (1:1; permuted block randomization) once the decision is made for patient to go for thrombectomy using the REDCap randomization tool.

Adverse events
Throughout the course of the clinical investigation, all adverse events will be recorded on the applicable Adverse Event CRF. The date of onset, date of resolution, severity, and action taken will be evaluated by the Investigator. The relationship to the technique or device, relationship to the procedure, and clinical significance will be evaluated. The neurological outcomes and adverse events will be reported.

Adverse Event Classification and Definitions
An Adverse Event (AE) 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 procedure.
A Serious Adverse Event (SAE) is an AE that:

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

For the current study, detailed and narrative reports of the following specific adverse events will be obtained:

- Incidence of death 24 hours post procedure
- Vessel perforation
- Vessel dissection
- Failure to navigate to target

Adverse Event Assessments
<u>Relatedness:</u>

- Procedure-related: Event has a strong temporal relationship to the study procedure. This includes AEs attributable to any device(s) used at procedure, such as access devices, delivery microcatheters, non-ionic contrast, guidewires, or any other adjunctive, approved/cleared device for neurovascular procedures.
- Technique-related: Event has a strong temporal relationship to the use of aspiration for thrombectomy.
- Unknown: Event relationship cannot be attributed to any of the above categories and remains undetermined.

Event Reporting Requirements

Any adverse event that occurs during the course of the study must be recorded and reported using the appropriate Adverse Event eCRF. These will include events occurring from the point of consent until a subject exits the study. The Investigator must sign each AE eCRF report. Investigators must obtain all information available to determine the causality and outcome of the AE and to assess whether it meets the criteria for classification as serious and the relationship of each adverse event to the procedure or device.

Pre-existing medical conditions or symptoms occurring prior to the start of the procedure should not be reported as adverse events. In the situation where there is a worsening of a pre-existing medical condition or symptom due to a study related procedure, an adverse event should be reported.

The Investigator is required to report all SAEs within 72 hours after first learning of the event. The primary method of reporting SAEs will be through the eCRFs. All SAEs will also be reported to the local IRB.

Site selection

Potential clinical sites will be assessed to ensure the investigator and his/her staff have the facilities, expertise required for the study and ability to conduct the study according to the clinical protocol.

To participate in this trial a clinical site must have, at a minimum, the following:

- 24/7 stroke interventional capabilities
- CT-based acute stroke imaging protocols (MRI is not acceptable)
- Ability to support timely data collection via an Internet-based EDC system
- Resources for conducting the informed consent process
- Willingness to adhere to the study protocol

Angiographic core lab

The procedural angiograms will be submitted by each site with all subject identifiers removed and only the assigned subject study number on the images. Each angiogram will be blindly assessed by the core lab for:

- Reperfusion score after first pass
- Reperfusion after final aspiration pass
- Reperfusion at end of procedure

Oculus Imaging, LLC, will serve as the core lab. The core lab services will include:

1. Trial Specific Website Design
    a. We will customize a user accessible website on our server specifically for the requested study. All imaging aspects of the study will be managed through this site.
    b. The primary functions of the site include electronic image submission, de-identification, and analysis.
    c. The website may also allow users or sponsors to review subject images and the dynamic trial reports as needed.
    d. Our study websites are secure, HIPAA, FDA, (CFR part 11) and E-Union compliant. Daily backups are performed.
    e. Studies are stored in at least two separate off-site archive sites.
    f. After launch of the trial website, any requested changes to the data collection for this trial may require a database change. Such requests would be reflected in a new version of the trial guidelines. Database changes may require revalidation of the trial imaging reports and additional fees may apply.
2. Imaging Protocol
    a. Oculus Imaging will write the Imaging Guidelines detailing imaging modalities to be used, imaging acquisition protocols, and procedures for image transfer.
    b. Oculus Imaging physicians and contractors will perform interpretations for trial submissions. All required data points will be finalized with the Sponsor by approving the Reading Guidelines prior to implementation. After finalization of the Reading Guidelines, the imaging report templates will be created and submitted to the trial sponsor for approval.
    c. Review Guidelines will be created to address the review of images for protocol adherence and core lab required measurements.
    d. All documents will be provided in English.
3. Site Qualification and Training
    a. Each site will be trained live via a webinar with our staff unless they have been previously trained on our system.
    b. Sites not previously qualified by Oculus may upload a qualifying imaging exam to the core lab as a part of site training. The qualifying exam will be a training tool to address promptly any potential imaging or transmission problems requiring attention prior to study enrollment. These exams will not be kept.
    c. Throughout trial duration, each site will receive feedback regarding submitted studies as needed. The Oculus Imaging staff will participate in teleconferences with sites after the initial training to resolve queries and track missing procedures.
    d. We will maintain a continuous quality assessment of images based on the study protocol as well as Good Clinical Practice Guidelines, FDA, and EU requirements.

4. Image Transfer, Analysis, and Storage
    a. Images primarily will be redacted and submitted electronically via our web accessible uploader. We will make every attempt to facilitate electronic image transfer, given its timeliness and cost-effectiveness. We can accept CDs, DVDs, or Flash Drives should the need arise.

   b. When images are received, they are reviewed by our personnel. Images are assessed for completeness of image transmission, quality, and protocol compliance. If additional images or information is needed, the sending site will be notified to resubmit images with specific input as to missing data.
   c. Data is de-identified and the reader(s) are notified of pending interpretations.
   d. All data and images are stored in at least two separate locations. Daily backups of the server are performed.
   e. The website access to our server uses secure 2048 bit HIPAA-compliant encryption.
5. Image Interpretations
   a. A board-certified radiologist will interpret all images as required by the protocol. All reads will be interpreted in a blinded fashion. Dr. Woodward would be the primary reader unless the sponsor requests a different physician.
   b. Summary images and image interpretations will be uploaded to the study-specific server site. All reads will be immediately available to the sponsors. Images and any interpretation data can be reviewed by site users as required by the protocol.
   c. The core lab will select images of interest during review. These will be immediately available for review by the sponsor or sponsor's designee from any web enabled device.
   d. The sponsor or any sponsor designee will have access to the entire imaging dataset once it has been validated for HIPAA compliance via download from our server. Our standard imaging turn-around time is 14 days from submission.
6. Imaging Data Reporting
   a. All imaging data collected during the trial will be saved on our secure database.
   b. Images and draft imaging reports are available via secure web access.
   c. These may be downloaded in PDF or excel format. These may also be downloaded in csv format to allow importing into other EDC systems.

Study Management and Oversight

Vanderbilt University Medical Center (VUMC) will serve as the coordinating center for this study. The VUMC team will be responsible for:

- Study protocol development and amendments
- Informed consent templates and revisions
- IRB approvals and correspondence
- Site initiation and training materials
- Case Report Forms (CRFs) and data collection tools
- Monitoring reports and audit documentation
- Adverse event and protocol deviation reporting
- Regulatory compliance (e.g., certifications, CVs, signature pages)
- Communication logs with participating sites
- Final study report and data safety monitoring documentation

Institutional review boards

The site investigator must submit this clinical protocol and subject informed consent form to the appropriate IRB. The study will not start at a clinical site and subjects will not be enrolled until a copy of written and dated approval/favorable opinion has been issued by the site.
Any amendment or modification to the clinical protocol must be sent to the IRB. The IRB must also be informed of any event likely to affect the safety of subjects or the conduct of the study. If the IRB imposes any additional requirements (e.g. safety reports, progress reports etc.), this will be followed, if appropriate.

A **Data and Safety Monitoring Board (DSMB)** will oversee participant safety and data integrity throughout the study. DSMB members will include experts in neuro intervention, biostatistics, and clinical trial execution. Their responsibilities will include:

- Reviewing safety and efficacy data at regular intervals
- Advising on study continuation, modification, or termination

Electronic Data Capture and Monitoring
VUMC will oversee data management using Redcap, a secure electronic data capture system. The system includes built-in checks to support data accuracy and protocol compliance. The Project Manager will conduct monthly data reviews to identify and resolve discrepancies. All study personnel will be trained in data entry procedures and Good Clinical Practice (GCP) standards.

The Project Manager (PM) will conduct monthly data reviews to identify outliers, inconsistencies, and missing information. Discrepancies will be addressed through open queries in REDCap and resolved in a timely manner to maintain data quality.

Staff Training: All study personnel involved in data entry and protocol implementation will receive training on the protocol, REDCap use, and Good Clinical Practice (GCP) standards.

Protocol Adherence Monitoring: Compliance will be assessed through monthly check-ins and quarterly oversight meetings. Any deviations will be documented, reviewed, and reported to the IRB as required.

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