

# BMJ Open New device multisegment Mechanical Thrombectomy System for endovascular treatment in acute ischaemic stroke: study protocol for a prospective, multicentre, randomised controlled trial

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**To cite:** Zhong H, Li Z, Zhou T, *et al*. New device multisegment Mechanical Thrombectomy System for endovascular treatment in acute ischaemic stroke: study protocol for a prospective, multicentre, randomised controlled trial. *BMJ Open* 2022;**12**:e063389. doi:10.1136/bmjopen-2022-063389

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-063389>).

HZ and ZL are joint first authors.

Received 01 April 2022

Accepted 22 October 2022



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## ABSTRACT

**Introduction** Endovascular treatment is the standard of care for acute large vessel occlusion (LVO) in the anterior circulation. However, successful complete recanalisation is considerably difficult when the vessels are severely tortuous. At the bend, the stent retriever can distort, collapse and lose its ability to capture the clot due to structural change. The aim of the present study is to evaluate the safety and efficacy of the new thrombectomy device multisegment Mechanical Thrombectomy (MT) System for endovascular treatment of acute ischaemic stroke (AIS).

**Methods and analysis** The present study is a prospective, multicentre, randomised controlled trial conducted in 11 stroke centres in China. The safety and efficacy of vascular recanalisation in patients with AIS who will be treated with a new thrombectomy device—multi-segment MT System or with Solitaire FR within 8 hours of symptom onset will be compared. A total of 238 subjects who met the inclusion and exclusion criteria will be randomised into either a treatment group or a control group by an internet-based Central Random System in a 1:1 manner, and 30 subjects will be recruited into the small sample study. SAS V.9.4 statistical software will be used for statistical analysis of the primary endpoint indicators and other indicators.

**Ethics and dissemination** The study involving human participants was reviewed and approved by the Ethics Committee of Drugs (devices) Clinical Experiment in Henan Provincial People's Hospital (reference number: AF/SC-07/04.0) and other research centres participating in the clinical trial. The results yielded from this study will be presented at international conferences and sent to a peer-review journal to be considered for publication. The Standard Protocol Items: Recommendations for Interventional Trials checklist was utilised when drafting the study protocol.

**Trial registration number** Registry on 10 September 2021 with Chinese clinical trial registry: ChiCTR2100051048.

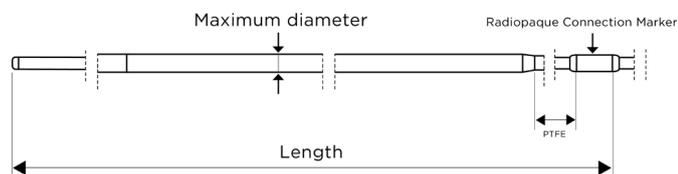
## INTRODUCTION

Stroke is the leading cause of morbidity and mortality worldwide, among which ischaemic

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The small sample study will be the first trial to evaluate the efficacy and safety of the thrombectomy device for subjects with symptoms onset between 8 and 24 hours.
- ⇒ If the trial is successful, it will be the first third-generation thrombectomy device approved in China, and also will considerably reduce treatment costs of stroke caused by large vessel occlusion.
- ⇒ Subjects will be recruited from multiple stroke centres in China.
- ⇒ Since this trial will be conducted in mainland China, where the large artery atherosclerosis stroke subtype is more prevalent among subjects, it may limit generalisability of the study result.
- ⇒ The study will not be blinded to surgeons and nurses, and lacks a uniform standard for the use of adjunct devices among centres.

stroke is the more common type and patients with it account for 60%–80% of patients with stroke.<sup>1</sup> The treatment of acute ischaemic stroke (AIS) mainly includes thrombolysis and mechanical thrombectomy (MT) in order to recanalise the occluded vessels as soon as possible and salvage the ischaemic penumbra. Recombinant tissue plasminogen activator is a common treatment used for ischaemic stroke. The time window for thrombolysis in AIS can be extended to 9 hours by a mismatch between diffusion-weighted imaging (DWI) and fluid attenuated inversion recovery (FLAIR) or automated perfusion imaging, but more than half of the treated patients do not recover completely, or die. With the continuous development of medical technology and interventional materials, endovascular treatment can significantly improve the recanalisation rate of occluded vessels, extend the time window and reduce the haemorrhage transformation rate.<sup>2–5</sup>

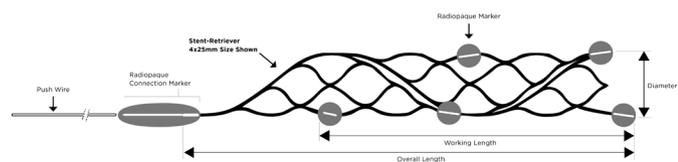


**Figure 2** The diagram of the push rod.

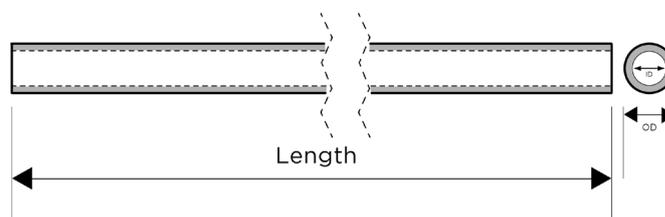
Several randomised controlled trials have shown that the safety and efficacy of endovascular recanalisation therapies by stent retriever over standard medical care in patients with AIS have caused occlusion of vessels of the proximal anterior circulation.<sup>6–10</sup> The Food and Drug Administration of USA approved Solitaire (Medtronic/ev3) and (Stryker) stent retrievers to be mainly used for the treatment of large vessel occlusive (LVO) stroke in 2012. A stent retriever has the advantages of good navigation and rapid recanalisation with a lower risk of long-term complications and uses a temporary stent to capture the thrombus and restore the blood flow by removing the thrombus and directing it to the peripheral vascular wall. During stent withdrawal, the thrombus is captured into the stent space and removed together with the stent.

However, successful complete recanalisation is considerably difficult when the vessels are severely tortuous. Within tortuous vessels, the stent may distort, collapse and lose its ability to capture the clot due to structural change.<sup>11 12</sup> The MT System, designed by NeuroVasc Technologies Inc, includes a multisegment design that allows it to remain stretched even when it is pulled and twisted, so as to attach firmly to the clot as it turns through the tortuous vessels. In addition, the distal end of the multisegment stent remains open during the removal of the clot along with the stent of the body, which is conducive in preventing the broken thrombus from escaping to the distal end.

The multisegment MT System consists of a stent (figure 1), a push rod (figure 2) and an introducer sheath (figure 3). The material of the stent is a nickel–titanium alloy and the material of the label is a platinum–iridium alloy. The pushrod is made of nickel–titanium alloy, and the distal end of the pushrod is mechanically connected with the proximal end. The introducer sheath has a three-layer structure, including an inner layer, a middle layer and an outer layer. The inner layer and outer layers have different functions, while the middle layer is a tie layer that allows the inner and outer layers to bond together. The inner layer needs to provide a low friction surface for interacting with the stent retriever. The outer layer provides structural integrity for the introducer sheath to resist compromising the lumen in normal handling or



**Figure 1** The diagram of the stent.



**Figure 3** The diagram of guiding the sheath. ID, inner diameter; OD, outer diameter.

when compressed by a rotating haemostasis valve. The stent is preinstalled in the introducer sheath. The inner diameter of the compatible micro catheter is 0.165/0.021. According to the stent diameter, it is divided into different specifications of 3.5 mm, 5 mm and 6 mm.

The purpose of the present study is to evaluate, in a prospective, randomised, controlled trial the safety and efficacy of the multisegment MT System conducted by NeuroVasc Technologies Inc for patients with AIS and with anterior circulation LVO, and provide a theoretical basis for the official listing and application of the multisegment MT System.

## METHODS

### Design

This trial consists of a prospective, multicentre, randomised controlled, non-inferiority study and a small sample study. The aim is to evaluate the safety and efficacy of the multisegment MT System conducted by NeuroVasc Technologies Inc for endovascular treatment of patients with AIS due to LVO within 8 hours of disease onset. The planned start date for this study was November 2020, and planned end date is November 2022. The subjects will be recruited in 11 high-volume comprehensive stroke centres in China, and the study protocol has been approved by the Ethics Committee of Drugs (Devices) Clinical Experiment in Henan Provincial People's Hospital and other research centres participating in the clinical trial. A total of 238 subjects who meet the inclusion and exclusion criteria will be randomised into either a treatment group or a control group by a central web-based system in a 1:1 manner, and 30 subjects with symptoms between 8 and 24 hours will be recruited into the small sample study. The treatment group will receive MT with the suitable size of the multisegment MT System (NeuroVasc Technologies Inc), and the control group will be treated with Solitaire FR. The patients with 8–24 hours of symptom onset will be enrolled in the small study. Table 1 is a brief summary of the visits and the assessment schedule.

### Participants

Detailed study inclusion and exclusion criteria are shown in table 2. Treatment allocation occurs when the study participant meets all of the inclusion criteria and signs the informed consent form.

**Table 1** Brief summary regarding the visits and the assessment schedule

Time	Screening and treatment		Postoperation follow-up		
	Preoperative screening	During operation	24 hours after operation	7 ± 2 days after operation or discharge	90 ± 14 days after operation
Informed consent	×				
Inclusion/exclusion criteria	×	×			
Medical history/demographic data	×				
Vital signs*	×		×		
Blood routine test†	×			×	
Blood biochemistry test‡	×			×	
Routine coagulation test§				×	
Brain CT (CTA) or MRI (MRA)	×		×		
Brain MRI-PWI or CTP-rCBF¶	×				
DSA	×	×			
Pregnancy test**	×				
12-lead ECG	×				
NIHSS score	×		×	×	
mRS score	×				×
Surgery record		×			
Concomitant medication††	×	×	×	×	×
Device defects		×			
Adverse events		×	×	×	×

\*Vital signs: blood pressure, pulse (heart rate), breath, body temperature.

†Blood routine test: WBC, RBC, PLT, Hgb.

‡Blood biochemistry test: ALT, AST, total bilirubin, direct bilirubin, creatinine, RBG.

§Routine coagulation test: APTT, PT, TT, INR.

¶Brain MRI-PWI or CTP-rCBF: subjects who are expected to complete arterial puncture 8–24 hours after symptom onset.

\*\*Pregnancy test: blood HCG or urine pregnancy test for women of childbearing age.

††Concomitant medication: records of the use of anticoagulant, antiplatelet drugs following operation.

ALT, alanine transaminase; APTT, activated partial thromboplastin time; AST, aspartate transaminase; CTA, CT angiography; CTP-rCBF, CT perfusion-relative cerebral blood flow; DSA, digital subtraction angiography; HCG, human chorionic gonadotropin; Hgb, haemoglobin; INR, international normalised ratio; MRA, MR angiography; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PLT, platelet count; PT, prothrombin time; PWI, perfusion weighted imaging; RBC, red blood cell count; RBG, random blood glucose; TT, thrombin time; WBC, white blood cell count.

### Treatment and intervention

Subjects who are eligible for intravenous thrombolysis will be administered 0.9 mg/kg (maximum dose 90 mg) Alteplase according to AHA/ASA, while endovascular treatment is prepared. For all the eligible subjects, a stent retriever should be provided as the first-line approach. Multisegment MT System will be used for the study group and the Solitare FR for the control group. An interventional neurologist will select the intravenous sedation or general anaesthesia based on the subject's clinical condition to ensure the subject's comfort and safety. DSA will be performed to determine the location of the occluded vessels, vascular path and collateral circulation compensation. Stent retriever thrombectomy can be performed three times or less before rescue therapy. If the intracranial occluded blood vessel had significant stenosis or other lesions after MT with stent retriever, the researcher should evaluate whether to perform the

aspiration thrombectomy, balloon dilation, stent implantation or other rescue therapy based on the subject's clinical conditions. extended Thrombolysis In Cerebral Infarction (eTICI) classification will be used to assess and evaluate the condition of recanalisation of the occluded vessels, and the Dyna-CT scan will be performed immediately after the operation to observe whether intracranial haemorrhage has occurred.

### Randomisation

All 238 subjects are randomly allocated into the study group or the control group at a 1:1 ratio based on an internet-based Central Random System. Randomisation will be performed after the completion of brain DSA immediately prior to MT. In order to control for key indicators during grouping, the clinical trial centre and baseline NIHSS scores (NIHSS score <16 and NIHSS score ≥16) were used as stratification factors.

**Table 2** Detailed study inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Randomised controlled trial	<ol style="list-style-type: none"> <li>Age 18–85;</li> <li>Clinical signs consistent with AIS; NIHSS <math>\geq 6</math> and <math>&lt; 30</math> at the time of randomisation</li> <li>Pre-stroke mRS <math>\leq 1</math>;</li> <li>Persistent symptoms within 8 hours from the time point of groin puncture;</li> <li>Imaging demonstrated by MR or CT: core infarct lesion volume <math>&lt; 70</math> mL, or ASPECTS <math>\geq 6</math> and <math>\leq 10</math></li> <li>Large vessel occlusion of anterior circulation demonstrated by DSA (intracranial carotid artery, M1 or M2 MCA, and A1 or A2 ACA)</li> <li>Subjects who meet the requirements have received/are receiving the correct IV-tPA dose within 4.5 hours of onset of stroke symptoms;</li> <li>Subjects or legal representatives should be able to understand the purpose of the experiments, have signed voluntarily the informed consent and should be willing to conduct protocol-required follow-up visits.</li> </ol>	<ol style="list-style-type: none"> <li>Life expectancy may be <math>&lt; 90</math> days;</li> <li>Women who are pregnant or breast feeding, or who plan to give birth within the next 90 days;</li> <li>Allergic to contrast agents, nickel–titanium metals or their alloys;</li> <li>Suspected renal failure defined as serum creatinine <math>&gt; 3.0</math> mg/dL (or <math>264 \mu\text{mol/L}</math>) or GFR <math>&lt; 30</math> mL/min;</li> <li>Severe persistent hypertension that cannot be controlled by medication defined as systolic blood pressure <math>&gt; 185</math> mm Hg or diastolic blood pressure <math>&lt; 110</math> mm Hg;</li> <li>Active bleeding or known bleeding;</li> <li>Platelet count <math>&lt; 50 \times 10^9/\text{L}</math> ;</li> <li>RBG <math>&lt; 50</math> mg/dL (<math>2.78</math> mmol/L) or <math>&gt; 400</math> mg/dL (<math>22.20</math> mmol/L);</li> <li>Subjects with occlusion of multiple vascular areas (eg, bilateral anterior circulation or anterior/posterior circulation);</li> <li>CT or MRI evidence of intracranial haemorrhage or infarction involving greater than 1/3 of MCA territory (or in other territories, <math>&gt; 70</math> mL of tissue on presentation);</li> <li>Angiographic evidence of cervical carotid occlusion due to carotid dissection or arteritis;</li> <li>Angiographic evidence of vessels corresponding to severely tortuous arteries for assessing the ability of group/control group devices to reach the target vessels or to be recycled;</li> <li>Evidence of vessel occlusion caused by septic embolism or bacterial endocarditis;</li> <li>CT or MRI evidence of intracranial tumour (with the exception of small meningioma);</li> <li>Subjects who had a stroke in the past 3 months;</li> <li>Subjects who had a heart, lung and kidney function failure and other serious organic diseases;</li> <li>Other unsuitable conditions for inclusion assessed by the researchers.</li> </ol>
Small sample study	<ol style="list-style-type: none"> <li>Age 18–85;</li> <li>Clinical signs consistent with AIS; NIHSS <math>\geq 6</math> and <math>&lt; 30</math> at the time of randomisation</li> <li>Pre-stroke mRS <math>\leq 1</math>;</li> <li>Persistent symptoms between 8 and 24 hours from the time point of groin puncture;</li> <li>The imaging methods should adhere to the ‘Clinical-Imaging Mismatch’ (core infarct lesion volume mismatch of baseline NIHSS score and MRI-DWI/CTP-rCBF) and are defined as follows: age 80–85, NIHSS <math>\geq 10</math> and core infarct lesion volume <math>&lt; 21</math> mL; age <math>&lt; 80</math>, NIHSS <math>\geq 10</math> and core infarct lesion volume <math>&lt; 31</math> mL and core infarct lesion volume <math>\geq 31</math> mL and <math>&lt; 51</math> mL;</li> <li>Large vessel occlusion of anterior circulation demonstrated by DSA (intracranial carotid artery, M1 or M2 MCA, and A1 or A2 ACA);</li> <li>Subjects who meet the requirements should have received/are receiving the correct IV-tPA dose within 4.5 hours of the onset of stroke symptoms.</li> </ol>	

ACA, anterior cerebral artery; AIS, acute ischaemic stroke; ASPECTS, Alberta stroke program early CT score; DSA, digital subtraction angiography; GFR, glomerular filtration rate; IV-tPA, intravenous tissue plasminogen activator; MCA, middle cerebral artery; MRI-DWI/CTP-rCBF, MRI-diffusion-weighted imaging/CT perfusion-relative cerebral blood flow; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; RBG, random blood glucose; tPA, tissue plasminogen activator.

### Reduction and avoidance of bias

The trial will be conducted in multiple stroke centres, and the case samples from multiple centres will be more representative than that from a single-centre, preventing the systematic error of a single-centre from leading to the bias of the trial results and resulting in more reliable conclusions. At the same time, in order to reduce operational differences among centres, the study-related personnel in each centre will be trained in a unified standard, and the evaluation criteria for efficacy and safety indicators will be adopted. An independent third-party core laboratory will

be used to evaluate the endpoint of successful vascular recanalisation rate (eTICI classification).

### Monitoring plan

Prior to the initiation of the clinical trial, the sponsor/agent, the supervisor and the head of each centre should train the investigator on the study protocol so that the investigator can understand and be familiar with the trial product. The establishment of an inspection plan will be performed as follows: qualified inspectors will be appointed by the sponsor or the agent to conduct regular

on-site inspection visits to each centre and ensure that all contents of the study plan are strictly followed. Monitoring will be performed by the e-CRF to ensure consistency with the content of the original data.

An endpoint Event Committee (CEC) will be established in the present study to conduct a blind review and to evaluate the endpoint events occurring during the trial. The Endpoint Event Committee (CEC) is composed of clinical experts who are independent of the investigator and the sponsor and are not directly involved in the implementation of the clinical trial. These clinical experts are in the relevant clinical research area. No interim analysis will be performed in this study.

### Sample size

The inclusion criteria of the selected subjects were strictly limited in this protocol. All the selected subjects belonged to the same disease and were further divided according to the time of symptom onset as follows: assuming that the rate of successful recanalisation of subjects in the control group after treatment is approximately 88% based on the available clinical evidence and the experience of neuro-interventionists,<sup>8</sup> and it is expected that the study group can achieve the same efficacy. A total of 238 patients are expected to be enrolled in the randomised controlled study within 8 hours of symptom onset, 119 cases in each group with a 12.5% non-inferiority margin, a 5% significance level (two-tailed), an 80% statistical power and a 10% dropout rate. Due to no thrombectomy devices suitable for such indications, the efficacy and safety of the multisegment MT System for subjects with symptoms between 8 and 24 hours cannot be verified in a randomised controlled manner. So a small sample of the subjects with symptoms between 8 and 24 hours will be included in the study with an expected enrolment of 30 patients who all treated with the multi-segment MT System.

The present study will be carried out in multiple stroke centres at the same time. In principle, the number of enrolled centres will be evenly distributed as far as possible to ensure adequate centre representation. However, considering the feasibility and inclusion progress, the number of subjects will be adjusted according to the actual situation to ensure the balance of the inclusion scale of each centre. The final inclusion scale of a specific centre should not exceed 50% of the total number of cases.

### Patient and public involvement

There was no patient and public involvement in this protocol.

## RESULTS

### Primary efficacy endpoint

The primary efficacy endpoint of the study is the successful recanalisation rate. The Core Lab will assess whether the target vessels have achieved successful recanalisation by DSA, which is defined as eTICI 2b or greater

revascularisation. The successful recanalisation rate will be estimated as follows: Number of successful arterial recanalisation/number of targets of stent thrombectomy.

### Secondary efficacy endpoints

The study has the following eight secondary clinical efficacy endpoints: (1) time of arterial recanalisation defined as the time from groin puncture to eTICI 2b or better revascularisation; (2) NIHSS scores, which will be estimated at preoperation,  $24 \pm 6$  hours postoperation and  $7 \pm 2$  days postoperation or before discharge to evaluate the neurological condition; (3) ratio of mRS 0–2 at  $90 \pm 14$  days postoperation, which is used to evaluate the neurological condition and optimal neurological outcome defined as mRS  $<2$ ; (4) rate of device success, which indicates that the thrombectomy device was successfully deployed through the occlusive vessels and that the delivery system was successfully recycled; (5) first-pass successful/near-perfect reperfusion (defined as eTICI  $\geq 2b$ ); (6) rate of surgical success, which is calculated by the proportion of successful surgical cases to all subjects on the basis of eTICI 2b or greater revascularisation; (7) rate of distal vascular embolism, which indicates a new embolisation of the distal end of the occlusive vessels; (8) time of MT.

### Safety outcomes

The present study exhibits the following five safety outcomes: (1) rate of symptomatic intracranial hemorrhage (sICH) at  $24 \pm 6$  hours, which is defined as any ICH event associated with neurological deterioration of an increase of 4 points or more on the NIHSS score compared with that of the preoperative state; (2) rate of asymptomatic intracranial hemorrhage (aICH) at  $24 \pm 6$  hours, which is defined as any intracranial hemorrhage (ICH) event associated with neurological deterioration corresponding to an increase of under 4 points on the NIHSS compared with the preoperative state; (3) rate of severe adverse events related with the device or surgery at  $7 \pm 2$  days postoperation or before discharge; (4) rate of mortality related with surgery at  $7 \pm 2$  days following the operation or before discharge; and (5) rate of all-cause mortality at  $90 \pm 14$  days following the operation.

### Statistical analysis

For descriptive analysis, the enumeration data will be described by frequency and component ratio, and the measurement data will be described by mean, SD, maximum, minimum, and median, as well as 25th and 75th quantiles.

For baseline demographic analysis, the likelihood ratio  $\chi^2$  test will be used for comparison of the enumeration data between the groups based on the descriptive analysis, and the Fisher's exact test will be used when more than 25% of the theoretical frequency is  $<5$ ; the normally distributed measured data between the groups will be compared by the group t-test, and the non-normally



distributed measured data between the groups will be compared by the Wilcoxon rank-sum test.

For primary efficacy endpoint of successful arterial recanalisation, the comparison between the groups will be performed using the Cochran-Mantel Haenszel (CMH)  $\chi^2$  analysis of the adjusted centre effect. In addition to the success rate of the study and the control groups, the difference in the success rate between the groups and the 95% CI will also be estimated. The method of other efficacy indicators for between-group comparisons should be the same as that of the baseline analysis. The intra-group comparison of the normally distributed data will be performed by the paired t-test and the Wilcoxon signed-rank test will be used for the intragroup comparison of non-normally distributed data.

For evaluation of safety outcomes, the number and proportion of cases that are normal before treatment and abnormal after treatment will be described. The number and incidence of adverse events will be described, and the proportion will be tested by the likelihood ratio  $\chi^2$  test and Fisher's exact test. Moreover, the specific manifestations and extent of all adverse events in each group and their relationship with the study devices will be described in detail.

For the primary endpoint indicators, statistical analysis will be performed at a unilateral significance level of 0.025 (corresponding to the unilateral confidence limit of 95% CI), and the statistical analysis of the other indicators will be performed at a significance level of 0.05. SAS V.9.4 statistical software will be used for statistical analysis.

## ETHICS AND DISSEMINATION

The protocol of this study has been approved by the the Ethics Committee of Drugs (devices) Clinical Experiment in Henan Provincial People's Hospital (reference number: AF/SC-07/04.0) and other research centres participating in the clinical trial. The study has been registered at Chinese Clinical Trial Registry (registration number: ChiCTR2100051048), and this protocol is accordance with the Declaration of Helsinki and relevant laws and regulations in China. All patients or their legal representatives will have to sign the written informed consent (online supplemental file 1). It is imperative that participants have the right to withdraw from research at any time. Any safety issues related to study, such as modifications of the study protocol or informed consent form of the subjects and serious adverse events during the clinical trial, must be reported to the Ethics Committee in time.

The database used during the study will be available from the corresponding author on reasonable request. The results of the trial will be disseminated through a series of peer-reviewed publications and conference presentations. We used the Standard Protocol Items: Recommendations for Interventional Trials checklist when writing our study protocol.

## DISCUSSION

The development of the new MT devices has enabled the widespread use of the stent retriever for stroke caused by LVO and the significant improvement in the rate of successful recanalisation.<sup>13</sup> However, certain side effects can occur including the escape of the thrombus to the distal end, and the deformation of the stent or its distortion at the bend during the clot. The purpose of the present trial was to evaluate the safety and efficacy of the multisegment MT System conducted by NeuroVasc Technologies Inc. compared with the Solitaire FR in patients diagnosed with AIS.

The multisegment MT System exhibits certain unique characteristics compared with the previously used stent retriever.<sup>14-16</sup> The multisegment design of the multisegment MT System keeps the stent open in the diameter direction under tension, thus improving the ability to capture and remove the clot. Similarly, the multisegment MT System has a stronger grasping ability for the clot compared with other stent retriever systems.<sup>17</sup> In addition, inlaid marks on each stage and throughout the working length provide X-ray visibility of the stent, which can aid the doctor to determine the length and position of the stent and its unfolding shape. This leads to the improvement of the rate of successful recanalisation of the target vessels. Due to the gradual flexibility, the stent can pass through the twists and turns of the internal carotid artery (ICA) and the middle cerebral artery during delivery, such as the cavernous segment of the ICA. The multisegment MT System has different sizes and specifications, which can meet the requirements of the occluded vessels with different diameters. Compared with first-generation devices, Solitaire FR has been confirmed to achieve superior recanalisation rates, faster reperfusion, lower haemorrhagic transformation complications and improved clinical outcomes.<sup>18</sup> Therefore, it is reasonable to select Solitaire FR as a control product in this trial.

There are some limitations in the study design. First, since this trial will be conducted in mainland China, where the large artery atherosclerosis stroke subtype is more prevalent among subjects, it may limit generalisability of the study result. Second, the study will not be blinded to surgeons and nurses, and lacks a uniform standard for the use of adjunct devices among centres.

In conclusion, the results of this trial will provide information on the safety and efficacy of the multi-segment MT System. The success of this trial will provide a new MT device for the treatment of AIS in China.

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**Contributors** TL and YH conceived the study. ZL designed the study. HZ contributed to the draft of the manuscript. ZL, TZ and YH contributed to the revision of the manuscript. All authors read and approved the final manuscript.

**Funding** The present trial was funded by the National Stroke High-risk Population Intervention Technology Research and Promotion Project (GN-2018R0007) Provincial and Ministerial Joint Project of Henan Provincial Medical Science and Technology (SBGJ202002001). The present trial was supported by NeuroVasc Technologies Inc. (no grant number), and the company provided the stent retrievers for free.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Consent obtained from parent(s)/guardian(s).

**Provenance and peer review** Not commissioned; externally peer reviewed.

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ICF version No.: V1.1

NeuroVasc Technologies Inc.

## Informed Consent Form (ICF)

<b>Name of investigational medical device:</b>	mechanical thrombectomy system
<b>Specification/Model of investigational device:</b>	FG-004-001-CH, FG-004-002-CH, FG-004-003-CH, FG-004-014-CH, FG-004-016-CH, FG-004-018-CH, FG-004-035-CH, FG-004-037-CH, FG-004-039-CH
<b>Sponsor:</b>	NeuroVasc Technologies Inc.
<b>Agent:</b>	Neurovasc (Weihai) Medical Device, Ltd.
<b>Name of clinical trial protocol:</b>	A prospective, multicenter, randomized controlled clinical study to evaluate the safety and efficacy of mechanical thrombectomy system for endovascular treatment of acute ischemic stroke
<b>Clinical trial protocol No.:</b>	NWSKLC-202001
<b>ICF version No.:</b>	V1.1
<b>ICF version date:</b>	2020-11-13
<b>Clinical trial institution:</b>	Henan Provincial People's Hospital
<b>Principal investigator:</b>	Li Tianxiao

### Distinguished sir/madam,

We would like to invite you to participate in a clinical trial, "A prospective, multicenter, randomized controlled clinical study to evaluate the safety and efficacy of mechanical thrombectomy system for endovascular treatment of acute ischemic stroke", sponsored by NeuroVasc Technologies Inc. The study protocol number is NWSKLC-202001. The clinical study should be approved by the Ethics Committee of Henan Provincial People's Hospital. The study will be carried out by Li Tianxiao, Professor in the Department of Cerebrovascular Disease. The study should be performed upon the approval of Human Genetic Resource Administration of China. You are invited to participate in this study as you are eligible to be enrolled in the acute ischemic stroke study. Your study doctor or investigator will fully explain the contents of the informed consent form to you.

The following items describe the study background, purpose and method of the investigational medical device, benefits and risks or inconveniences that may arise from the study process, and your rights and interests. Please read them carefully before you participate in the clinical trial. The informed consent form provides you with information that can help you decide whether to participate in this clinical trial. The study doctor will answer your questions about the test product and the study. When your doctor or investigator discusses the informed consent form with you, you can always ask the investigator questions in case of any doubt or any content that cannot be fully understood, so as to ensure full understanding of related contents. Please inform us if you are participating in other drug or medical device trials/studies.

Your participation in this trial is based on voluntary principle. Please sign the statement in the informed consent form after reading the following data, if you participate in the clinical study of your own accord.

The background, purpose, process and other important information of this study are as follows:

## **I. Background**

Cerebral stroke is one of the diseases that cause the greatest damage to human beings. Acute ischemic stroke accounts for 60%-80%.

The Report on the Third National Retrospective Sampling Survey of Death Causes in China showed that acute ischemic stroke has become the first cause of death in China with the aging of the population and 75% of survivors still had different degrees of disability. Cases aged over 40 years with cerebral stroke in China have exceeded ten million, showing a tendency of younger patients, of which cases with ischemic stroke account for 80%. The disease has constituted heavy social and economic burdens. At present, the intravenous recombinant tissue plasminogen activator (rt-PA) is an effective approach to treating acute ischemic stroke. However, the treatment time window is narrow, only 4.5 hours, so patients beyond the time window cannot be treated in time. In addition, for stroke caused by large vessel occlusion and cardiogenic embolism, the recanalization rate using intravenous thrombolysis is low and the therapeutic effect is poor. With the development of interventional materials and technologies in recent years, endovascular treatment has significantly improved the recanalization rate of occluded vessels and expanded the treatment time window, showing a good application prospect. Mechanical thrombectomy and emergency angioplasty were developed relatively late. As to advantages, these techniques can avoid or reduce the use of thrombolytic drugs and have a higher recanalization rate for large vessel occlusion and cardiogenic embolic stroke, which become important treatments for acute ischemic stroke. "Mechanical thrombectomy" attracts widespread attention due to many theoretical advantages including rapid recanalization, low bleeding conversion rate, and extended time window of interventional therapy for stroke. For thrombectomy devices, a temporary stent is used to capture the thrombus and restore blood flow by moving the thrombus through squeezing against peripheral vessel wall. In stent withdrawal, the thrombus is captured into the stent space and removed with the stent. The treatment has advantages of navigation and rapid recanalization, and lower risk of long-term complications. Therefore, the invention of thrombectomy devices is a great advance in the endovascular treatment of stroke.

The current treatment results have demonstrated that the endovascular treatment of mechanical thrombectomy can bring additional benefits, including significantly decreased disability rate, faster and more complete reperfusion, and increased survival rate and functional independence in patients with ischemic stroke. However, successful recanalization is very difficult when the pathway vessel is seriously tortuous. At the turn of vessels, the stent will twist, collapse, and lose its ability to catch the thrombus due to structural changes. Since 2004, the US Food and Drug Administration (FDA) has approved Merci<sup>TM</sup> Retrieval and Penumbra Aspiration Systems<sup>TM</sup> as the first generation of mechanical thrombectomy devices successively. In 2012, FDA approved Solitaire<sup>TM</sup> and Trevo<sup>TM</sup> as thrombectomy devices.

The mechanical thrombectomy system manufactured by NeuroVasc Technologies Inc. is of multi-section design. The system still remains stretched even when being pulled and twisted and can hold onto the thrombus when passing through the turns of vessels. In addition, when the multi-section stent loaded with the thrombus is withdrawn, its distal end remains open, which is helpful to prevent broken thrombus from escaping to the distal end.

ICF version No.: V1.1

NeuroVasc Technologies Inc.

The mechanical thrombectomy system has been subject to the type test in the National Institutes for Food and Drug Control and granted the test qualification report. Furthermore, the animal experimental studies have been completed for the product. Based on the above conditions, this clinical study is planned to be performed.

## **II. Name and Purpose**

### **(I) Study name:**

A prospective, multicenter, randomized controlled clinical study to evaluate the safety and efficacy of mechanical thrombectomy system for endovascular treatment of acute ischemic stroke

### **(II) Purpose**

To verify the safety and efficacy of the mechanical thrombectomy system manufactured by NeuroVasc Technologies Inc. for endovascular treatment of patients with acute ischemic stroke.

## **III Scope, Method and Related Information:**

### **(I) Number of subjects:**

The study will be conducted in multiple clinical trial institutions in China. The competitive enrollment model will be adopted across China. A total of 268 subjects are planned to be enrolled, including 238 subjects for the randomized controlled study and 30 subjects for the small sample study. It is expected that 30 subjects are enrolled in the randomized controlled study and the small sample study respectively in our center.

### **(II) Scope and method:**

This trial is mainly to verify the safety and efficacy of the mechanical thrombectomy system manufactured by NeuroVasc Technologies Inc. for the surgery for intracranial vascular acute stroke and evaluate its usability.

The study consists of two parts: (1) Patients with acute ischemic stroke within 8h of symptom onset are enrolled in the randomized control study. Based on randomized results, thrombectomy is carried out with the experimental device or the control device. (2) Patients with acute ischemic stroke within 8-24 h of symptom onset are included in the small sample study and receive thrombectomy with the experimental mechanical thrombectomy system.

### **1. Randomized controlled study:**

In this part, a prospective, multicenter, randomized controlled, non-inferior study is designed. Subjects who meet the inclusion criteria within 8 hours after symptom onset are enrolled and randomized into the experimental group and the control group at a ratio of 1:1 through central randomization system.

- ① Experimental group: mechanical thrombectomy system manufactured by NeuroVasc Technologies Inc. (the product is not commercially available yet).
- ② Control group: intracranial stent retriever (trade name: Solitaire FR) approved by the National Medical Products Administration (NMPA).

### **2. Small sample study:**

Subjects who meet the inclusion criteria within 8-24 hours after symptom onset are enrolled. There is currently no appropriate thrombectomy device for the indications of such subjects, so no control group is established.

#### IV. Process and Period:

Subjects who are successfully enrolled after screening will receive intravascular thrombectomy, and related examinations and follow-ups 24±6 hours after surgery and 7±2 days after surgery (or before discharge). Further outpatient/telephone follow-up will be carried out 90±14 days after surgery. The doctors will ask about drug use and the subjects' general health condition. Specific contents are as follows:

##### **(I) Subject screening and preoperative routine examination**

If you are willing to participate in this study, your doctor will review your past and current treatment, including medicines you are taking, past medical history and history of present illness. In your participation in this study, the doctor will ask you to cooperate in related examinations. These examinations are part of routine medical examinations and they are also required even if you do not participate in the study. The examples include CT/CTA or MR, MRI-DWI or CTP-rCBF, physical examination, blood test, pregnancy test (if necessary) (if you are female patients, this test should be performed when pregnancy signs are suspected during screening).

1. Signature of the informed consent form by the subject or guardian.
2. Collection of medical history/demographics.
3. Vital sign examinations.
4. Laboratory examinations: blood routine, chemistry panel (only creatinine and random blood glucose), and pregnancy test if necessary.
5. ECG, brain CT (CTA) or MR (MRA), MRI-DWI or CTP-rCBF (small sample study).
6. NIHSS score and mRS score.
7. Review of inclusion/exclusion criteria.
8. Concomitant medication record: thrombolytic therapy (if any).

##### **(II) Inclusion/exclusion criteria**

###### **1. Inclusion criteria (you should meet all of the following conditions)**

###### **(1) Randomized controlled study:**

- ① Clinical symptoms and signs consistent with acute ischemic stroke;
- ② mRS score before this acute ischemic stroke  $\leq 1$ ;
- ③ 18 years  $\leq$  age  $\leq 85$  years;
- ④  $6 \leq$  NIHSS score  $\leq 30$ ;
- ⑤ Expected to complete arterial puncture within 8 hours of onset;
- ⑥ Patients whose imaging examination should meet MR/CT: infarction core volume  $< 70$  ml; or whose ASPECTS score is 6 to 10;
- ⑦ DSA radiography findings: ICA (intracranial segment), MCA (M1 or M2) or ACA (A1 or A2) occlusion;
- ⑧ Subjects who can receive IV-tPA treatment should receive IV-tPA and it is required that the investigators confirm that the subjects have received/are receiving the correct dose of IV-tPA within 4.5 hours of stroke onset;
- ⑨ Subjects or their Agents that are able to understand the purpose of the trial, voluntarily participate and sign written informed consent forms and receive follow-up.

(2) Small sample study:

- ① Clinical symptoms and signs consistent with acute ischemic stroke;
- ② mRS score before this acute ischemic stroke  $\leq 1$ ;
- ③ 18 years  $\leq$  age  $\leq 85$  years;
- ④  $6 \leq$  NIHSS score  $\leq 30$ ;
- ⑤ Expected to complete arterial puncture within 8-24 hours of onset;
- ⑥ Patients whose imaging should meet "clinical-image mismatch" (mismatch between baseline NIHSS score and core infarct volume on MRI-DWI/CTP-rCBF), defined as:
  - a: 80-85 years old (inclusive), NIHSS score  $\geq 10$ , core infarction volume  $< 21$  ml;
  - b:  $< 80$  years old, NIHSS score  $\geq 10$ , core infarction volume  $< 31$  ml;
  - c:  $< 80$  years old, NIHSS score  $\geq 20$ ,  $31 \text{ ml} \leq$  core infarction volume  $< 51$  ml.
- ⑦ DSA radiography findings: ICA (intracranial segment), MCA (M1 or M2) or ACA (A1 or A2) occlusion;
- ⑧ Subjects who can receive IV-tPA treatment should receive IV-tPA and it is required that the investigators confirm that the subjects have received/are receiving the correct dose of IV-tPA within 4.5 hours of stroke onset;
- ⑨ Subjects or their Agents that are able to understand the purpose of the trial, voluntarily participate and sign written informed consent forms and receive follow-up.

**2. Exclusion criteria (randomized controlled study and small sample study)**

- (1) Life expectancy possibly less than 90 days;
- (2) Pregnant or lactating women, or those who are planned to be pregnant in the next 90 days;
- (3) Allergy to contrast agent, nickel-titanium metal or alloy; and other materials;
- (4) Renal failure suspected. Renal failure is defined as serum creatinine  $> 3.0$  mg/dL ( $264 \mu\text{mol/L}$ ) or glomerular filtration rate (GFR)  $< 30$  ml/min;
- (5) Severe sustained hypertension (systolic blood pressure  $> 185$  mmHg or diastolic blood pressure  $> 110$  mmHg) that cannot be controlled by medication;
- (6) Patients with active bleeding or known bleeding tendency;
- (7) Platelet count  $< 50 \times 10^9/\text{L}$ ;
- (8) RBG  $< 50$  mg/dL ( $2.78 \text{ mmol/L}$ ) or  $> 400$  mg/dL ( $22.20 \text{ mmol/L}$ );
- (9) Subjects with occlusion in multiple vascular areas (e.g. bilateral anterior circulation or anterior/posterior circulation);
- (10) Intracranial hemorrhage or massive cerebral infarction suggested by CT or MR (infarct volume  $\geq 70$  ml or infarct volume  $> 1/3$  MCA blood supply area);
- (11) Failure to obtain accurate results of NIHSS assessment at the onset of stroke;

ICF version No.: V1.1

NeuroVasc Technologies Inc.

- (12) Radiography suggesting occlusion of intracranial artery due to arterial dissection or arteritis;
- (13) DSA angiography suggesting tortuous vessel path, making investigational/control device difficult to reach the target location or be recovered;
- (14) Presuming as embolism due to septic emboli or bacterial endocarditis;
- (15) CT or MR suggesting intracranial tumor (except for tentorial meningiomas);
- (16) Treatment with any thrombectomy device or other intra-arterial (neurovascular) therapy within the last three months;
- (17) Unable to complete 90±14 days of follow-up;
- (18) Stroke within the past 3 months;
- (19) Previous clinical manifestations of AVM rupture or aneurysm rupture;
- (20) Serious organic diseases in heart, lung, kidney, etc.;
- (21) Patients participating in other drug or medical device clinical trials but failing to complete the primary study endpoint;
- (22) Other conditions not suitable for inclusion judged by investigators.

**You cannot participate in the study if meeting any of the following exclusion criteria.**

**(III) Post-operation examination and clinical follow-up**

**1. Post-operation to 24±6 hours**

- (1) Vital signs;
- (2) Brain CT (CTA) or MR (MRA);
- (3) NIHSS score
- (4) Adverse event record;
- (5) Concomitant medication record (antiplatelet, anticoagulant and statin drugs).

**2. 7±2 days after operation or before discharge (whichever is earlier)**

- (1) Laboratory examination: blood routine, chemistry panel and coagulation profile;
- (2) NIHSS score;
- (3) Adverse event record;
- (4) Concomitant medication record (antiplatelet, anticoagulant and statin drugs).

**3. 90 days after operation (± 14 days)**

- (1) mRS score;
- (2) Adverse event record;
- (3) Concomitant medication record (antiplatelet, anticoagulant and statin drugs).

## **V. Source of Funds and Potential Conflict of Interest**

Neurovasc (Weihai) Medical Device, Ltd. is the organizer and agent of the clinical study. The Company shall pay the relevant costs of the clinical study, without any conflict of interest with other institutions or organization.

## **VI. Possible Benefits, Risks and Discomforts of Subjects**

### **(I) Possible benefits to subjects**

You may be benefited from the study, but we cannot guarantee improvement in your health condition, and we hope future subjects with the same medical conditions as you may be benefited from the information obtained from your participation in the study. Whether participating in the study or not, you will receive reasonable examination and treatment.

### **(II) Possible risks and discomfort**

When feeling any discomfort during the study, please immediately report to your physician. This is very important. The study physician may arrange for you relevant examination, adjust the drug dosage, or add other drugs for treatment or controlling the medical condition. If you think or your study physician thinks you are not suitable to participate in the study, you may withdraw from the study.

#### **1. Potential risks from investigational product and/or surgery:**

The Sponsor shall ensure any risk related to the product is within the acceptable range, according to Medical device - Application of risk management to medical devices. The potential risks for this clinical trial are basically the same as those for receiving normal intracranial artery thrombectomy, including but not limited to the following symptoms:

- Adverse reactions to antiplatelet/anticoagulant drugs or contrast agent
- Air embolus
- Arterio-venous fistula
- Change of mental state
- Death
- Device deformation, folding, rupture or malfunctions
- Distal embolism not covered before
- Hematoma and hemorrhage of puncture position
- Infection
- Intracranial hemorrhage
- Focal ischemia

- Neurological dysfunction
- Neurological deterioration including stroke and death
- Vessel perforation and dissection
- Postoperative hemorrhage
- Pseudoaneurysm formation
- Thrombus
- Vascular occlusion
- Vasospasm

## **2. Risks and discomfort related to blood sampling**

The risks from blood sampling from arms include transient discomfort and/or cyanosis. With low possibility, though, infection, excessive bleeding, blood coagulation or syncope may occur.

## **3. Reproductive risk:**

For female subjects: If necessary, pregnancy test may be conducted for females of childbearing age during screening, so if you are in lactation, pregnancy or you think you may be pregnant or are preparing for pregnancy, you cannot participate in the study. If you are in pregnancy or lactation, potential risks that are uncertain now may be caused to you and your child.

For male subjects: Currently no data is available to demonstrate the impact on reproduction from the study, while it cannot be excluded potential damage may be caused to your child conceived during the study. With low possibility, though, such damage is beyond estimation now.

Therefore, we strongly recommend you not to prepare conception during the study. If you are/your wife is pregnant or might be pregnant during your participation in the study, please immediately inform the study physician. This is very important. The study physician may therefore adjust your drug administration, and if necessary, terminate your participation, discuss with you on what you should do, and ask you about pregnancy and the child after the end of the study.

## **4. Other risks**

Administration of aspirin, cilostazol, clopidogrel, ticagrelor and other antiplatelet drugs may cause the risks of gastro-intestinal discomfort, blood coagulation disorder, allergy, and thrombopenia. In addition, there may be some unpredictable risks, discomforts, drug interaction or adverse reactions.

## **VII. Alternative Diagnostic and Treatment Approaches:**

You may choose not to participate in the study, and it will not cause any adverse impact on your conventional treatment. Considering your health condition, the following conventional diagnostic and treatment approaches are now available, apart from the study:

ICF version No.: V1.1

NeuroVasc Technologies Inc.

- (1) Arterial thrombolysis;
- (2) Emergency angioplasty;
- (3) Other marketed mechanical thrombectomy devices and other medical products.

#### **VIII. Diagnostic and Treatment Items and Other Subsidies Available During Trial:**

When participating in the trial, you need not pay any additional cost for examination. According to the requirements of the study, the costs for the thrombectomy devices (mechanical thrombectomy system or Solitaire FR intracranial stent retriever) and related laboratory examination (once) in the study shall be paid by the Agent Neurovasc (Weihai) Medical Device, Ltd.

#### **Laboratory examination after operation to 7±2 days after operation/before discharge, including:**

- (1) Vital signs (after operation to 24±6 hours after operation): Blood pressure, pulse (heart rate), respiration and temperature.
- (2) Blood routine: White blood cell count, red blood cell count, platelet count and hemoglobin.
- (3) Chemistry panel: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, creatinine, random blood glucose (including blood glucose testing in any case).
- (4) Cruor examination: Activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), and international normalized ratio of prothrombin (INR).

To better protect your rights and interest, we will provide you with RMB200 as the blood sampling subsidy for this examination. Furthermore, we will arrange a phone call or outpatient clinical follow-up 90 days (±14 days) after operation, and you shall come to the hospital for the follow-up, for which we shall provide additionally RMB200 as the traffic subsidy.

#### **IX. Treatment and Economic Compensation for Damage Related to Trial:**

The Agent of the study Neurovasc (Weihai) Medical Device, Ltd. has covered the insurance for subjects participating in the study, and you will receive the timely treatment and compensation in case of any damage related to the clinical trial, even if you withdraw from the study during the follow-up. Upon any damage related to the investigational product, the insurance company is required to provide relevant compensation according to legal requirements, and when the compensation is lower than the deductibles or exceeds the indemnity limit, the shortage shall be on account of Neurovasc (Weihai) Medical Device, Ltd.

#### **X. Confidentiality of Medical Records:**

Your medical records shall be kept at the clinical trial institution. The Investigator, competent authorities and the ethics committee are allowed to access your medical records.

Any open report related to the study results shall not disclose your personal identity. We shall use all reasonable efforts to protect the privacy of your personal medical information to the extent permitted by law.

## **XI. Voluntary and Privacy Principles**

### **1. Voluntary principles**

Whether you are fully voluntary to participate in the study? If so, we hope you can hold on and complete the study; but, you may choose to withdraw from the study at any time without any loss of your benefits. You may choose not to participate in or withdraw from the study midway at any time without giving any reason, and you will not meet with any discrimination or retaliation, or any impact on your medical benefits, rights and interests.

If you decide to withdraw from this study during the study, we encourage you to consult with your study physician first. Considering your safety, our study staff shall provide you with a health evaluation upon your withdrawal from the study, and possibly another relevant examination after withdrawal.

### **2. Privacy principles**

With the understanding and assistance of you and other subjects, the results of this study may be published in medical journals, but we will keep your study records confidential pursuant to relevant laws. The personal information of you as a study subject will be kept strictly confidential, and will not be disclosed as required by laws. If necessary, the medical administration authorities, the ethics committee of the hospital and other relevant staff may get access to your data as required.

## **XII. Responsibilities of Subject**

**If you choose to participate in this study, you need to:**

1. Provide true information of accurate past medical history and current physical condition;
2. Tell the study physician any discomfort and health problem of you during the study;
3. During the study, follow the medical advice and requirements to receive examination and administer relevant drugs;
4. Disclose whether you are participating in other trials or studies (on drugs and medical devices) and relevant information;
5. Follow the instruction of the study staff and study physician, and ask them about the same when you have any question;
6. Assist the study physician to receive the phone call or outpatient follow-up visit 90±14 days after operation according to the required window time.
7. Upon follow-up, inform the study personnel what drugs you actually administered during the study (including discontinuing and adding drugs).

ICF version No.: V1.1

NeuroVasc Technologies Inc.

**XIII. Criteria for Termination of Study**

For your safety, you may need to withdraw from the study under any of the following circumstances:

1. If it finds that your rights and interests cannot be guaranteed, the ethics committee may suspend or terminate the clinical trial at any time in writing;
2. The clinical trial institution and investigators may propose to suspend or terminate the clinical trial when they find that the risks exceed the possible benefits, or the results sufficient to determine the safety and efficacy of the investigational medical device have been obtained;
3. When finding any matter that may affect the safety of the subjects, or if implementation of the trial may change the Ethics Committee's approval for continuing such trial, the sponsor shall immediately notify the investigator to terminated the study.

**XIV.Relevant Consultation**

You can learn about the progress related to the study at any time, and if you have any questions related to the study (e.g. rights and interests of the participant), or you have any discomfort or injury during the study, please contact (Investigator) \_\_\_\_\_ at \_\_\_\_\_ (Tel or mobile No.); and if you have any questions related to your rights and interests,

contact the ethics committee of the Site at: \_\_\_\_\_.

ICF version No.: V1.1

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**Subject Informed Consent Statement**

I have carefully read through the Informed Consent Form, and been given the opportunity to ask questions, and all the questions have been answered. I understand participating in the trial is subject to one's own choice, and I may choose not to participate in this study, or withdraw from this study at any time after notifying the investigator without discrimination or retaliation, and my medical benefits, rights and interests will not be affected.

If I need other diagnosis/treatment, or if I failed to comply with the study plan, or if I have any other sound reason, the Investigator can terminate my participation in the clinical trial.

I am willing to participate in the clinical trial "A prospective, multicenter, randomized controlled clinical study to evaluate the safety and efficacy of mechanical thrombectomy system for endovascular treatment of acute ischemic stroke", sponsored by NeuroVasc Technologies Inc. I will receive a signed copy of the "Informed Consent Form".

**Signature of the subject:** \_\_\_\_\_ **Date:** \_\_\_\_\_

**Tel:** \_\_\_\_\_

**Note: If the subject cannot sign the informed consent due to incapacity and other reasons, it will be signed by the guardian.**

**Signature of guardian:** \_\_\_\_\_ **Date:** \_\_\_\_\_

**Relationship with subject:** \_\_\_\_\_ **Tel:** \_\_\_\_\_

**Reason why the subject cannot sign:** \_\_\_\_\_

**Statement of Investigator**

I confirm that I have accurately informed the subject of the contents of the Informed Consent Form and answered the questions raised by the subject, and the subject is willing to participate in this clinical trial.

**Signature of the Investigator:** \_\_\_\_\_ **Date:** \_\_\_\_\_

**Tel:** \_\_\_\_\_