Evaluate a NeXt Generation PortablE Diagnostic Platform for Determination and Immediate Triage of Emergency Large Vessel Stroke

EXPEDITE IIA

Date:	*01 NOV 2020*
Version:	*01*
Protocol No.:	*NA-01STR-03*
Sponsor:	NovaSignal Corp.
Funding Entity	National Institute of Health (NIH)

Confidentiality Statement

Protocol Signature Page- Principal Investigator

I have read the protocol entitled, **Evaluate a NeXt Generation PortablE Diagnostic Platform for Determination and Immediate Triage of Emergency Large Vessel Stroke (EXPEDITE IIA)** and agree that it contains all necessary details for carrying out the described study. I will conduct this study as outlined therein and will make reasonable effort to complete the study within the designed time frame. I will provide copies of the study plan and all information furnished by NovaSignal to all study personnel under my supervision. I will discuss this material with them to assure that they are fully informed about the device and the conduct of this study.

I will ensure that the study is conducted according to applicable regulations, to applicable laws and to hospital policy and Institutional Review Board (IRB) and/or Ethics Committee (EC) requirements.

_____	_____	_____/_____/_____
Principal Investigator's Printed Name	Principal Investigator's Signature	Date (dd/mmm/yyyy)

Protocol Signature Page- Sub-Investigator

I have read the Study entitled, **Evaluate a NeXt Generation PortablE Diagnostic Platform for Determination and Immediate Triage of Emergency Large Vessel Stroke (EXPEDITE IIA)** and agree that it contains all necessary details for carrying out the described study.

I will ensure that the study is conducted according to applicable regulations, to applicable laws and to hospital policy and Institutional Review Board (IRB) and/or Ethics Committee (EC) requirements.

_____	_____	_____/_____/_____
Sub- Investigator's Printed Name	Sub-Investigator's Signature	Date (dd/mmm/yyyy)

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1 PROTOCOL SYNOPSIS

<table>
<tr><th colspan="2">Protocol Synopsis:</th></tr>
<tr><td rowspan="4">Study Sponsor:
NovaSignal Corp.
2440 S. Sepulveda Blvd., Suite 115
Los Angeles, CA 90064
National Institute of Health (NIH)</td><td>Protocol No.: NA-01STR-03</td></tr>
<tr><td>Regulatory Class: II</td></tr>
<tr><td>Study Device(s): NovaGuide and/or Lucid TCD System</td></tr>
<tr><td>Development Phase:
Phase 1: Feasibility; Phase 2: Pivotal</td></tr>
<tr><td colspan="2">Study Title:
Evaluate a NeXt Generation PortablE Diagnostic Platform for Determination and Immediate Triage of Emergency Large Vessel Stroke (EXPEDITE IIA)</td></tr>
<tr><td colspan="2">Overall Study Design:
This study is a multi-center, multi-phase, multi-cohort, prospective, randomized, open, blinded endpoint (PROBE), non-significant risk (NSR) device study including up to 420 evaluable subjects measured with the study device(s).</td></tr>
<tr><td colspan="2">Objective:
The purpose of this study is to collect robust data from the robotic NovaGuide device or the Lucid TCD device to validate the Velocity Curvature Index (VCI) as a diagnostic biomarker tool to drive clinical decision making for assessing cerebral vascular occlusions confirmed by standard of care Computed Tomography Angiography (CTA) imaging.</td></tr>
<tr><td>Number of Subjects:
Phase 1: Up to 216
(54 Cohort A TCD, 54 Cohort A No TCD)
(54 Cohort B TCD, 54 Cohort B No TCD)
Phase 2: Up to 624
(156 Cohort A TCD, 156 Cohort A No TCD)
(156 Cohort B TCD, 156 Cohort B No TCD)</td><td>Number of Sites:
Phase 1: Up to 3 sites
Phase 2: Up to 5 sites</td></tr>
<tr><td colspan="2">Duration of Study Participation:
• Phase 1 Enrollment: 18 months
• Phase 2 Enrollment: 24 months
• Total Study Duration: 1 to 7 days</td></tr>
<tr><td colspan="2">Phase 1 Study Design</td></tr>
<tr><td colspan="2">Phase 1 will include up to 54 subjects enrolled in Cohort A and 54 subjects enrolled in Cohort B. An interim feasibility and safety assessment will be completed after Phase 1.</td></tr>
<tr><td colspan="2">Phase 1 and Phase 2 Entry Criteria:

Cohort A LVO

Inclusion Criteria
1. Subject aged 18 years and older
2. Large vessel occlusion of the intracranial ICA, MCA (M1, M2), or multiple areas of the aforementioned locations confirmed by computed tomography angiography (CTA)
3. Subject or Legally Authorized Representative has the ability to provide informed consent and comply with the protocol.

Exclusion Criteria
1. Head CT findings consistent with acute primary intracranial hemorrhage (SAH, ICH, etc.)
2. Hemodynamically unstable patients requiring pharmacological support for hypertension</td></tr>
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	Regulatory Class: II
	Study Device(s): NovaGuide and/or Lucid TCD System
	Development Phase: Phase 1: Feasibility; Phase 2: Pivotal

3. Subjects who underwent partial or full craniotomy
4. Additional intracranial pathologies present (tumor, hydrocephalus, etc.)
5. Anticipated insufficient time to acquire a complete initial TCD scan as described by the protocol
6. Subjects who have a physical limitation preventing placement of the system.

Cohort B Non-LVO

Inclusion Criteria

1. Subject aged 18 years and older
2. Non-large vessel occlusion confirmed by computed tomography angiography (CTA)
3. Subject or Legally Authorized Representative has the ability to provide informed consent and comply with the protocol.

Exclusion Criteria

1. CTA findings including:
    a. Occlusions in the common carotid artery, internal carotid artery, anterior carotid artery, middle cerebral artery (M1 and M2 segments), anterior communicating artery, basilar artery, posterior communicating artery and vertebral arteries.
2. Head CT findings consistent with acute primary intracranial hemorrhage (SAH, ICH, etc.)
3. Hemodynamically unstable patients requiring pharmacological support for hypertension
4. Subjects who underwent partial or full craniotomy
5. Anticipated insufficient time to acquire a complete set of scans as described by the protocol
6. Subjects who have a physical limitation preventing placement of the system.

Phase 2 Study Design

Phase 2 will include up to 312 subjects (156 cohort A and 156 in cohort B) presenting with stroke like symptoms for which diagnostic imaging has been ordered. Primary and secondary endpoints will be calculated after completion of Phase 2.

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Phase 1: Feasibility; Phase 2: Pivotal</td></tr>
<tr><td colspan="2">Imaging Core Lab Analysis:
All imaging data will be sent to a core laboratory which will provide independent quantitative and qualitative assessment of all study data. They will be blinded to the study and radiology report data and provide independent review.

TCD Data Analysis:
All TCD data acquired by the NovaGuide Robotic System or the Lucid M1 System (manual TCD) will be sent to NovaSignal which will provide independent quantitative and qualitative assessment of all study data. They will be blinded to the study and radiology report data and provide independent review.

Data Analysis:
Evaluation of correlation between diagnostic imaging standard of care and VCI biomarker by an independent core laboratory masked to local radiology determination. Success criteria will include clinical validation of VCI biomarker for LVO detection threshold performance at or exceeding 90% ROC–AUC (targeting SEN & SPE greater than 90%) to standard of care imaging.</td></tr>
</table>

Phase 1 & 2 Schedule of Assessments				
Assessments	**Cohort A[1] LVO TCD**	**Cohort B[2] Non-LVO TCD**	**Cohort C[3] LVO NO TCD**	**Cohort D[3] Non-LVO NO TCD**
Informed Consent	**X**	**X**	**X**	**X**
Medical History	**X**	**X**	**X**	**X**
NIH Stroke Scale♦	**X**	**X**	**X**	**X**
Non-Contrast CT♦	**X**	**X**	**X**	**X**
CT Angiography♦	**X**	**X**	**X**	**X**
Cohort Assignment	**X**	**X**	**X**	**X**
Randomization TCD / No TCD	**X**	**X**	**X**	**X**
TCD Scan (NovaGuide or Lucid)	**X**	**X**		
Device-Related Adverse Events	**X**	**X**		
Concomitant Medications	**X**	**X**		

♦ Standard of Care

1. Cohort A LVO TCD subjects scans will be collected following CTA within a three (3) hour window, prior to treatment (e.g. mechanical thrombectomy).
2. Cohort B Non-LVO TCD subjects scans will be collected within a 24-hour period after enrollment.
3. If randomized to 'No TCD' group in either Cohort, TCD scan will not be conducted, but still followed through to discharge.

1.1 List of Abbreviations

Abbreviation/Term	Definition
AE	Adverse Event
CBF	Cerebral Blood Flow
CBFV	Cerebral Blood Flow Velocity
CFR	Code of Federal Regulations
CE	Conformité Européene
CS	Cerebrospinal
CSF	Cerebrospinal fluid
CT Scan	Computed Axial Tomography Scan
DM	Device Malfunction
DSMB	Data Safety and Monitoring Board
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EX	Exclusion Criterion
F	Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HOB	Head of Bed
ICF	Informed Consent Form
ICP	Intracranial Pressure
IRB	Institutional Review Board
MCA	Middle Cerebral Artery
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effects
TCD	Transcranial Doppler
TIC	Thermal Index for Cranial Bone

2 BACKGROUND AND RATIONALE OF STUDY

The incidence of Large Vessel Acute Ischemic Stroke (AIS) has been estimated to be approximately 250,000 patients per year in the United States and is the leading cause of disability and fifth leading cause of death. Although endovascular interventions (stentriever) and pharmaceutical (tPA) treatments exist for large vessel occlusion (LVO), their use is limited due to the short time window from symptom onset during which these treatments are indicated to be administered. Moreover, recent estimates suggest only approximately 10% of eligible patients receive interventional treatment which has shown to lead to better outcomes in several world-wide RCTs. Currently, the gold standard for stroke diagnosis is CT angiogram (CTA) which is limited to in-hospital use or a low number of mobile stroke ambulances, all costing multi-millions of dollars, requiring expert operators and IV injection of iodine-rich contrast material. Additionally, the clinical stroke assessment scales (RACE, LAMS, CPSS) used in the field, although low cost and non-invasive, have proven unreliable due to training requirements and low inherent accuracies, with SEN and SPE ranging in a recent study from 0.50-0.64 and 0.83-0.92, respectively[13,14]. In order for intervention to be successful, a standardized, quantitative, field based (prehospital and pre-CTA) diagnostic tool is needed to improve LVO identification and ensure rapid transfer to a capable medical facility.

Goals. Establish clinical viability of a fully automated, non-invasive transcranial Doppler (TCD) derived biomarker based on cerebral hemodynamics for prehospital LVO assessment.

Great strides have been made in AIS treatment over the last decade; however, lack of a quantitative, bedside/field-based diagnostic severely which is suitable for hospital/prehospital use limits access to treatment. We were able to show positive results in a feasibility study (EXPEDITE) of 66 subjects (33 LVOs) for LVO diagnosis in the ER setting using a newly developed TCD-derived digital biomarker termed Velocity Curvature Index (VCI) [15,16]. The VCI biomarker which leverages a machine learning platform which leverages data produced by the NovaGuide System (NovaGuide Robotic System – K180455, NovaSignal Corp., Los Angeles, CA USA). The NovaGuide, a combination of the Lucid M1 System (510k K160442) and the NovaBot accessory, utilized in both phases of the proposed research plan, is capable of TCD signal acquisition in the hospital setting without need of a trained TCD technician for operation or interpretation. Phase I will establish baseline performance characteristics of the hemodynamic biomarker (VCI) and define the study characteristics and context of use for FDA submission. Phase II will provide a comprehensive, multi-site data set for full analytic validation of the biomarker, with the goal of regulatory submission for an expanded indication. The availability of this biomarker will have several potential applications including, monitoring post-intervention patients and supplement triage and transfer protocols for patients suspected of LVOs, which will result in potentially faster and more widespread access to intervention, affording vastly improved outcomes for thousands of potential patients each year. The analogy to the use of EKG for myocardial infarction (MI) which supplements clinical evaluation and more invasive imaging.

TCD ultrasonography is a safe, non-invasive, and reproducible technique that allows the assessment of cerebral blood flow velocity (CBFV) in the large conducting arteries of the head and neck. TCD data collection relies on the level of experience of a TCD technologist to acquire an accurate and high-quality signal from the intracranial vessel(s) of interest, thus per user, the data quality is variable. NovaSignal has developed the NovaGuide System to assist in the TCD data collection such that consistent high-quality data may be obtained independent of the experience of the user.

NovaSignal will collect safety and technical feasibility data regarding the use of TCD ultrasound via the NovaGuide System device in humans. Data collected during this study is for research purposes only. No treatment or healthcare decisions will be made based on study measurements collected in this study.

3 DEVICE DESCRIPTION

3.1 Lucid M1 Transcranial Doppler System

The Lucid M1 System is an adjunctive, portable, non-invasive, non-ionizing radiation, point-of-care TCD diagnostic ultrasound system. It is designed to non-invasively measure and display CBFV over the head and neck with a reusable, non-sterile 2-MHz hand-held probe. It can also be used bilaterally to monitor the blood flow velocity of the vessels insonated via the temporal window of the head with a headset with two reusable, non-sterile 2-MHz monitoring transducers. Additionally, the Lucid M1 System measures the occurrence of transient emboli signals within the blood stream. The Lucid M1 System is an FDA cleared diagnostic medical device, Lucid M1 Transcranial Doppler Ultrasound System, 510k (K160442).

3.2 NovaGuide

The NovaGuide System moves two ultrasound probes around the two temporal regions (Right and Left) of the head to find the transtemporal window and then optimizes CBFV measurements. The system uses TCD data to systematically specify and evaluate probe positions. The NovaGuide System consists of a head-support structure that houses two probe positioning modules, a robotic controller unit and computer tablets. The NovaGuide System is non-invasive and does not deliver energy into a subject. The NovaGuide System is comprised of both The NovaSignal Lucid M1 System and the NovaBot accessory.

For this study, the FDA cleared NovaGuide (K180455) will have study specific modifications that are not FDA cleared.

3.3 Intended use of the device

The NovaSignal Lucid M1 System is a medical ultrasound system intended for use as an adjunct to the standard clinical practices for measuring and displaying cerebral blood flow velocity within the major conducting arteries and veins of the head and neck. Additionally, the Lucid M1 System measures the occurrence of transient emboli signals within the blood stream.

The NovaGuide System when used with the Lucid M1 System is a medical ultrasound device which assists the user in the setup and acquisition of cerebral blood flow velocity via the patient's temporal windows. It is intended for use as an adjunct to standard clinical practices for measuring and displaying cerebral blood flow velocity and the occurrence of transient emboli within the blood stream. The NovaGuide System is intended to be used by persons qualified by training in its safe and effective use.

The NovaGuide System is for use in this study only and is not cleared for use by the FDA. It is labelled with the following statement:

CAUTION: Investigational device. Limited by Federal (or United States) law to investigational use only.

The use of the Lucid M1 System with or without the NovaGuide Robotic System in this study is not for the purposes of diagnosis. This device is being used solely for research to develop technology for assisted TCD signal acquisition. As such, the device is considered a Nonsignificant Risk Device under 21 CFR 812.3(m).

3.4 Contraindications

The Lucid M1 System is not intended to be used in fetal applications or inside a sterile field. Use proposed in this study is consistent with the current FDA cleared and CE Mark approved labelling.

The NovaGuide System is not intended to be used when the following conditions are present:

- The NovaGuide System is not intended to be used in persons younger than 18 years of age.
- The NovaGuide System is not intended to be used in fetal applications.
- The NovaGuide System is not intended to be used inside the sterile field.

3.5 Velocity Curvature Index (VCI)

As part of the feasibility work performed in the initial EXPEDITE study (Expedite a NeXt Generation PortablE Diagnostic Platform for Determination and Immediate Triage of Emergency Large Vessel Stroke) between October 2016 and October 2017, advanced forms of CBFV morphology were investigated as potential biomarkers for LVO diagnosis in the ER. Termed Velocity Curvature Index (VCI; or simply “curvature” in the context of cerebral hemodynamics), it provides a quantitative metric which can be used to evaluate a single waveform in isolation, or incorporate information from both cerebral hemispheres. VCI requires only a brief recording of MCA flow to compute. Upon locating the TCD signal associated with flow in the MCA, 15 seconds of the CBFV waveforms are recorded (approximately 15 - 30 TCD “beats”; directly analogous to the EKG heartbeat waveform). The recorded beats are then extracted, smoothed, aligned, and averaged, resulting in a single representative beat waveform for each recording

Having obtained a representative averaged beat waveform, VCI is computed straightforwardly according to the following steps. First, local curvature is computed for each time point. For any time series (including TCD), curvature is a well-defined mathematical property which quantifies the degree to which a curve deviates from being “straight” at a given point. Since curvature is a nonlinear function sensitive to small inflections, we elect to consider only curvature associated with the beat systolic complex, where the signal-to-noise ratio is greatest. The systolic complex (or “beat canopy”) comprises the proportion of the beat with the highest velocities and richest morphological structure.

4 STUDY PLAN

4.1 Objectives

The purpose of this study is to collect robust data from the Lucid M1 Transcranial Doppler System and NovaGuide System (NovaGuide) devices to validate the Velocity Curvature Index (VCI) as a diagnostic biomarker tool to drive clinical decision making for assessing cerebral vascular occlusions confirmed by standard of care Computed Tomography Angiography (CTA) imaging.

4.1.1 Scope

This study will be conducted with FDA cleared and CE Mark approved product Lucid M1 System, and an investigational device (NovaGuide). The acoustic power delivered by the ultrasound to the patient is only controlled by an FDA / CE Mark cleared product (Lucid M1 System) and the Investigational NovaGuide Robotic System cannot alter the power of the system.

4.2 Study Endpoints

4.2.1 Phase 1 Study Endpoints

Phase 1 Primary Endpoint:
- Area Under the Curve (AUC), Sensitivity, and Specificity of VCI when compared against standard of care CTA imaging for large vessel occlusion assessment.

Phase 1 Secondary Technical Efficacy Endpoint:
- Area Under the Curve (AUC), Sensitivity, and Specificity of a novel machine learning (ML) algorithm when compared against standard of care CTA imaging for large vessel occlusion assessment.
- VCI and experimental ML algorithm compared to prehospital/neurological clinical scales for alternative diagnostic criteria.

Phase 1 Primary Safety Endpoint:
- Incidence of device-related serious adverse events
- Last Known Normal (LKN) to First Hospital Arrival (Initial Door-In) time
- Door to Initial CT imaging (non-contrast) time
- Door to IV-tPA time
- Door to Initial CTA Acquisition time
- Door to Groin Puncture time
- CTA Acquisition to Groin Puncture time

4.2.2 Phase 2 Study Endpoints

Phase 2 Primary Endpoint:
- Area Under the Curve (AUC), Sensitivity, and Specificity of VCI when compared against standard of care CTA imaging for large vessel occlusion assessment.

Phase 2 Secondary Technical Efficacy Endpoint:
- Area Under the Curve (AUC), Sensitivity, and Specificity of a novel machine learning (ML) algorithm when compared against standard of care CTA imaging for large vessel occlusion assessment.

- VCI and experimental ML algorithm compared to prehospital/neurological clinical scales for alternative diagnostic criteria.

Phase 2 Primary Safety Endpoint:
- Incidence of device-related serious adverse events
- Last Known Normal (LKN) to First Hospital Arrival (Initial Door-In) time
- Door to Initial CT imaging (non-contrast) time
- Door to IV-tPA time
- Door to Initial CTA Acquisition time
- Door to Groin Puncture time
- CTA Acquisition to Groin Puncture time

4.3 Study Design

This study is a multi-center, multi-Phase, multi-cohort, prospective, randomized, open, blinded endpoint (PROBE), non-significant risk (NSR) device study including up to 420 evaluable subjects measured with the study device(s).

4.4 Study Population Size

Phase 1: Approximately 108 subjects will be randomized to the TCD only group (54 subjects in Cohort A and 54 subjects in Cohort B). An additional 108 subjects will be randomized to the NO TCD group. An interim feasibility and safety assessment will be completed after Phase 1.

Phase 2: Approximately 312 subjects presenting with stroke like symptoms for which diagnostic imaging has been ordered will be enrolled (156 in Cohort A and 156 in Cohort B). Primary and secondary endpoints will be calculated after completion of Phase 2.

4.5 Study Duration

Phase 1: The enrollment period for Phase 1 will last up to 18 months. Subject's participation will last from 1 to 7 days depending on cohort and randomization assignment.

Phase 2: Enrollment period will last up to 24 months. Subject's participation will last from 1 to 7 days depending on cohort and randomization assignment.

The study will be complete when all subjects have been enrolled and all data collected. The study can be terminated at any time, for any reason, by NovaSignal. Should this occur, the study investigator will be notified as soon as possible. The Principle Investigators will be responsible for informing their IRBs of the termination of the trial.

4.6 Phase 1 and 2 Subject Inclusion/Exclusion Criteria

4.6.1 Cohort A LVO

4.6.1.1 Inclusion Criteria

A subject must meet all of the following inclusions criteria to be enrolled in the study:

1. *Subject aged 18 years and older
2. (*) Large vessel occlusion of the intracranial ICA, MCA (M1, M2), or multiple areas of the aforementioned locations confirmed by computed tomography angiography (CTA)

3. Subject or Legally Authorized Representative has the ability to provide informed consent and comply with the protocol.

4.6.1.2 Exclusion Criteria

A subject cannot be enrolled in the study if any of the following exclusion criteria are met:

1. (*) Head CT findings consistent with acute primary intracranial hemorrhage (SAH, ICH, etc.)
2. * Hemodynamically unstable patients requiring pharmacological support for hypertension
3. * Subjects who underwent partial or full craniotomy
4. * Additional intracranial pathologies present (tumor, hydrocephalus, etc.)
5. (*) Anticipated insufficient time to acquire a complete initial scan as described by the protocol
6. * Subjects who have a physical limitation preventing placement of the system.

4.6.2 Cohort B Non-LVO

4.6.2.1 Inclusion Criteria

A subject must meet all of the following inclusions criteria to be enrolled in the study:

1. * Subject aged 18 years and older
2. (*) Non-large vessel occlusion confirmed by computed tomography angiography (CTA)
3. Subject or Legally Authorized Representative has the ability to provide informed consent and comply with the protocol.

4.6.2.2 Exclusion Criteria

A subject cannot be enrolled in the study if any of the following exclusion criteria are met:

1. (*) CTA findings including:
    a. Occlusions in the common carotid artery, internal carotid artery, anterior carotid artery, middle cerebral artery (M1 and M2 segments), anterior communicating artery, basilar artery, posterior communicating artery and vertebral arteries.
2. (*) Head CT findings consistent with acute primary intracranial hemorrhage (SAH, ICH, etc.)
3. * Hemodynamically unstable patients requiring pharmacological support for hypertension
4. * Subjects who underwent partial or full craniotomy
5. (*) Anticipated insufficient time to acquire a complete set of scans as described by the protocol
6. * Subjects who have a physical limitation preventing placement of the system.

4.7 Subject Pre-Screening

Subjects will be pre-screened to determine their initial eligibility and interest in a study. Pre-screening criteria indicated with an asterisk * in section 4.6 (Phase 1 & Phase 2) Inclusion/Exclusion imaging criteria are considered standard of care in stroke management. Asterisks in parentheses (*) indicate inclusion/exclusion criteria that can be evaluated at sites that routinely perform multimodal CT or MRI as they are considered standard of care in stroke management. Therefore, subject eligibility to pre-screening criteria can be evaluated without obtaining informed consent. Informed consent will be obtained once subject has satisfied pre-screening criteria. All subjects pre-screened and screened will be documented on the Screening/Enrollment log.

4.8 Informed Consent and Screening

Subject identification and eligibility will be determined by the PI or study team based on their clinical assessment of the potential subject while that patient is undergoing standard of care for their neurological condition.

Before participation in the study, candidates who may be eligible for the study will be provided with an informed consent according to 21 CFR 56 and 45 CFR 160-164 and guidelines of the Investigational Review Board of the institution at which the study is being conducted. Candidates will be given time to review the consent form and ask questions about the study. The investigator will obtain written informed consent from the candidate. The candidate or legal representative must sign the consent form prior to enrolment. Candidates will also be required to sign a Health Insurance Portability and Accountability Act (HIPAA) form which includes a Privacy Rule. This rule gives special safeguards to Protected Health Information (PHI) that is identifiable or can be directly linked to the subject (e.g., social security number, name, birth date). This authorization may be part of the informed consent form or separate. If applicable to the investigator site location, candidates will also be required to sign the California Experimental Subject Bill of Rights.

A subject will be considered enrolled at the time of Informed Consent signature.

Potential subjects and/or their legal authorized representative / surrogate will be guided through the informed consent process by a member of the research team. This process includes informing the subject of the study procedures (in simple language), answering all questions, and obtaining written consent (Consent Form). The investigator or delegated study staff is responsible for obtaining written informed consent from each potential study participant. Informed consent should be obtained, when required, in written format and using a form approved by the local IRB. The subject must receive a copy of the signed and dated informed consent. Waivers of consent will not be utilized in this study.

A subject will be considered enrolled at the time of Informed Consent signature.

4.9 Randomization

Randomization will occur once subject has satisfied all inclusion/exclusion criteria and informed consent has been obtained. Subjects will be randomly assigned in equal number (1:1) to one of two procedure arms within each cohort: 1) TCD Exam or 2) No TCD Exam. The number of procedures and controls will be balanced within investigational sites, by baseline NIHSS severity (<= 17 versus >17), age (<70 years versus >=70 years at the time of randomization) occlusion location (M1 versus all other), and time of day of initial CT scan (0900-1700 and 1701-0859). Subject allocation to procedure will be accomplished by using an interactive web response (IWRS) or interactive voice response system (IVRS).

At the time of randomization, the site will access IVRS/IWRS and enter subject's screening NIHSS, age, occlusion location, and time of CT scan. Based on the information provided, the system will automatically generate the assigned treatment. If the site is unable to access website for randomization, an interactive voice response randomization is also available by phone.

4.10 Numbering of Study Subjects

Each site will be assigned a site number at the beginning of the study and each enrolled subject will be assigned a subject number. Subjects will be considered enrolled in the screening phase

when the informed consent has been signed and enrolled in the randomized phase when the randomization system (IVRS/IWRS) provides a treatment assignment. Site study coordinators will assign/obtain the subject number from the IVRS/IWRS and document the subject number on the screening/enrollment log once the subject has signed the informed consent. The subject number will consist of the study number and the site number followed by a sequential number that begins with “001”. Site will also need to access the IVRS/IWRS to register the subject in the screening phase (detailed instructions on accessing the IVRS/IWRS will be provided in the user manual developed by the IVRS/IWRS vendor).

4.11 Screen Failures

Subject eligibility will be determined by the PI or study team based on their clinical assessment of the potential subject while that patient is undergoing standard of care CTA in the hospital.

For this protocol, a single measurement is defined as a collection of data at a single depth on a single side of the head. A scan is defined as a set of measurements which occur during a single data collection session and can include multiple measurements. A bilateral scan refers to measurements which are collected on each side of the head.

Subjects will be measured with TCD and the de-identified data will be reviewed to determine the quality of the data for analysis. Subjects will be considered screen failures if participant does not meet inclusion and exclusion criteria and if the device is unable to pass the registration process. At any point, the PI or research personnel can end the study.

4.12 Study Discontinuation

4.12.1 Study Discontinuation by IRB

The IRB may choose to discontinue the study at any center(s) for which they granted approval if the:

- The research study is not conducted in accordance with the IRB requirements.
- The research study indicates unexpected serious harm to Subjects.

4.12.2 Study Discontinuation by Sponsor

The Sponsor may choose to discontinue the study should the Sponsor discover additional information during the study that may cause harm to subject safety.

If the study is terminated prematurely or suspended, the Sponsor will promptly inform all clinical Investigators of the termination or suspension and the reason(s) for this. The IRB/EC will also be informed, either by the Sponsor or Investigator if a local IRB/EC is utilized, promptly and provided with the reasons(s) for the termination. If applicable, regulatory authorities will be informed.

4.13 Study Procedures

4.14 Imaging

Given the importance of imaging and quality of imaging to subject assessment, before and during the Study, the Sponsor will collaborate with participating centers to evaluate and optimize the quality of imaging and image transfer associated with the study.

4.15 Schedule of Assessments

Phase 1 & 2 Schedule of Assessments				
Assessments	**Cohort A[1] LVO TCD**	**Cohort B[2] Non-LVO TCD**	**Cohort C[3] LVO NO TCD**	**Cohort D[3] Non-LVO NO TCD**
Informed Consent	**X**	**X**	**X**	**X**
Medical History	**X**	**X**	**X**	**X**
NIH Stroke Scale♦	**X**	**X**	**X**	**X**
Non-Contrast CT♦	**X**	**X**	**X**	**X**
CT Angiography♦	**X**	**X**	**X**	**X**
Cohort Assignment	**X**	**X**	**X**	**X**
Randomization TCD / No TCD	**X**	**X**	**X**	**X**
TCD Scan (NovaGuide or Lucid)	**X**	**X**		
Device-Related Adverse Events	**X**	**X**		
Concomitant Medications	**X**	**X**		

♦ Standard of Care

4. Cohort A LVO TCD subjects scans will be collected following CTA within a three (3) hour window, prior to treatment (e.g. mechanical thrombectomy).
5. Cohort B Non-LVO TCD subjects scans will be collected within a 24-hour period after enrollment.
6. If randomized to 'No TCD' group in either Cohort, TCD scan will not be conducted, but still followed through to discharge.

4.16 Scanning/Data Acquisition

The User Manual provided for the device details, in specific steps, the actions to be executed with the device for scanning/data acquisition. A general overview is provided below.

4.16.1 NovaGuide System Scanning Technique

The scanning session will consist of an initial set-up and signal search (up to 20 minutes). During this time, the system will search for CBFV signals at depths between 45-65 mm. Once the signal is acquired, the system will monitor the signal for up to 20 minutes or until the PI or research teams end study.

The head cradle of the NovaGuide System is positioned underneath the subject's head and secured to a fixed location (bed, chair, or gurney). The user will affix two registration dots on each side of subject's temples. The subject's head is then positioned into the head cradle. The TCD modules are aligned to the head such that the probes are in contact with the subject's temples (temporal window). The user will register the Headmount to the subject's specific head shape and size. The user will apply gel to improve signal quality. The NovaGuide System will collect data and indicate to the user the scan status. The TCD operator will record the scan up to 20 minutes. Study measurements will not delay nor interfere with the patients' standard of care treatment as the PI or research team can end the study at any point.

Subjects will be evaluated during the scanning period per ALARA ("As Low As Reasonably Achievable") criteria. Scanning may not violate ALARA levels and will be immediately terminated if ALARA criteria reached during a scanning session.

4.16.2 Lucid M1 System Scanning Technique (Traditional TCD)

If traditional TCD is conducted using the Lucid M1 System alone, measurements will be collected in the MCA at multiple depths ranges between 45 to 65 mm. The MCA scans will be collected from the trans-temporal window by positioning the probe superior to the zygomatic arch. Once cerebral blood flow velocity (CBFV) of the target vessel is found, the TCD operator will hold this position to record 30 seconds of data.

Cohort A TCD will be subjects identified per CTA findings in the Emergency Room (ER), Stroke Care Unit or Imaging Unit as having a large vessel occlusion. A single TCD scan will be collected by a designated TCD operator using the NovaGuide System or the Lucid M1 System alone (manual TCD). The TCD scan will be collected following CTA within a three (3) hour window and prior to standard of care stroke treatment (e.g., mechanical thrombectomy). Note, tPA can be administered prior to TCD measurements. Study measurements will not delay nor interfere with the patients' standard of care treatment. No follow-up scans will be collected.

Cohort B TCD will be subjects identified per CTA findings in the Emergency Room (ER), Stroke Care Unit or Imaging Unit as having a **non**-large vessel occlusion. A single TCD scan will be collected by a designated TCD operator using the NovaGuide Robotic System or the Lucid M1 System alone (manual TCD). These scans will be collected within a 24-hour period after enrolment and no follow-up scans will be collected.

Cohort C NO TCD will be subjects identified per CTA findings in the Emergency Room (ER), Stroke Care Unit or Imaging Unit as having a large vessel occlusion. No TCD scans will be conducted and subjects followed through to discharge.

Cohort D NO TCD will be subjects identified per CTA findings in the Emergency Room (ER), Stroke Care Unit or Imaging Unit as having a **non**-large vessel occlusion. No TCD scans will be conducted and subjects followed through to discharge.

4.17 ALARA Considerations

ALARA Considerations: "As Low As Reasonably Achievable – ALARA" principle for ultrasound to reduce the amount of total exposure to the subject without compromising exam quality.

Diagnostic ultrasound, including TCD, has been used clinically and in research for decades. In addition to the FDA guidance, there are several groups including the American Institute of Ultrasound in Medicine (AIUM), British Medical Ultrasound Society (BMUS), and the World Federation for Ultrasound in Medicine and Biology (WFUMB) that make recommendations on ultrasound safety for both fetal and non-fetal applications. These groups have focused on several areas of ultrasound safety including Thermal Index (TIC).

The FDA specifically references the AIUM for the ALARA recommendations for TIC and corresponding scan durations in the new guidance released in October 2017. Table 1 shows the recommended scan duration for a given TIC range. The ALARA recommendations are based on the TIC output by the device (which is displayed on the Lucid M1 System device at all times). TIC is defined as:

TIC – the thermal index for applications in which the ultrasound beam passes through bone near beam entrance into the body.

Thermal Index (TIC)	Recommended Duration (minutes)
>6.0	0
5.0-6.0	0.25
4.0-5.0	<1
3.0-4.0	<4
2.5-3.0	<15
2.0-2.5	<60
1.5-2.0	<120
<1.5	No Limit

Table 1 Recommended maximum exposure duration and TIC ranges (except the eyes which are not evaluated in this protocol)

If a subject meets ALARA criteria at any time during a scanning session, the scan will be discontinued.

4.18 Data Collection

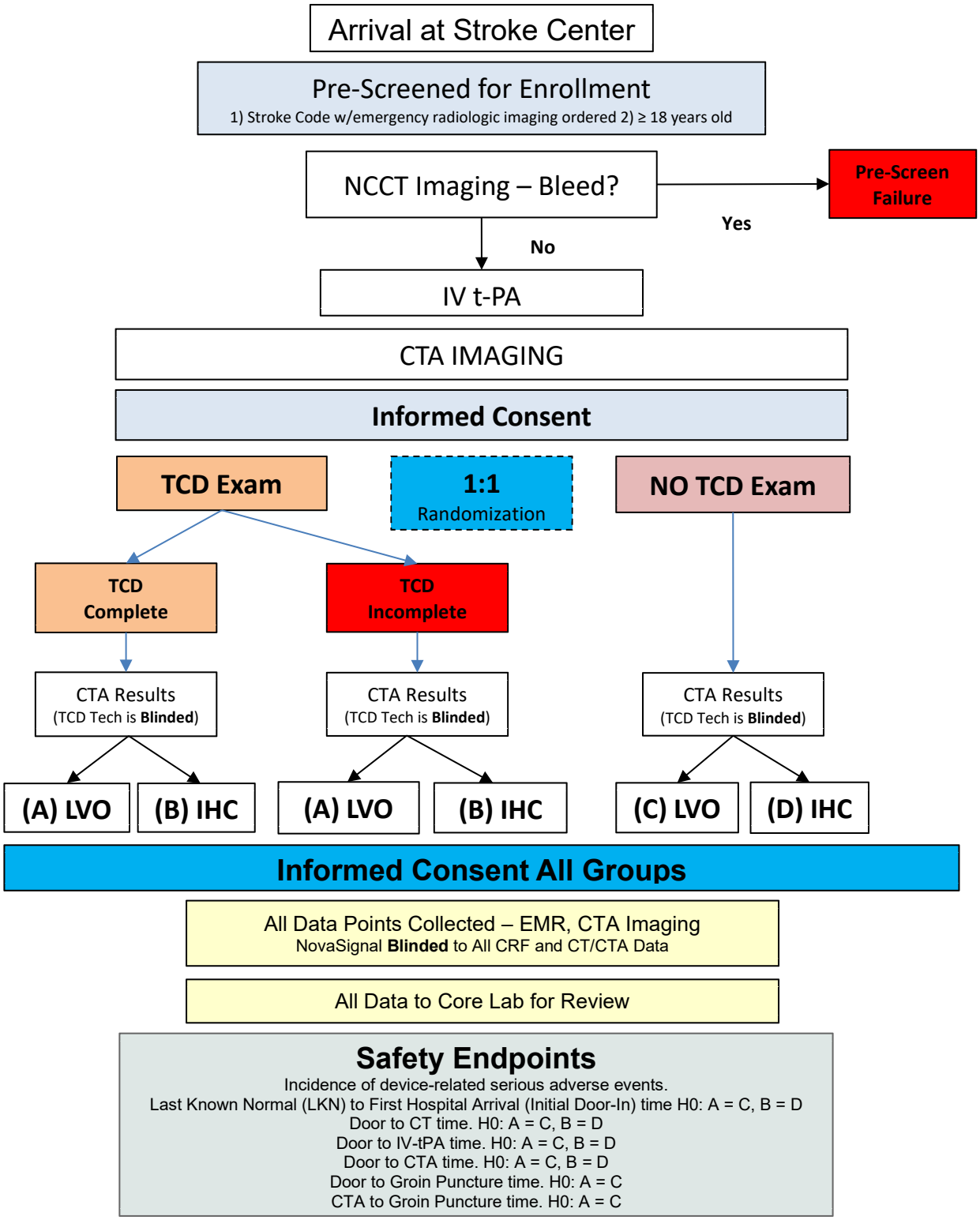
Subjects will have the following data collected:

- *Informed Consent*
- *Subject Demographics*
- *Clinical assessment metrics*
- *Cohort Assignment*
- *Randomization Assignment*
- *Relevant Medical History*
- *Stroke Workflow times (as specified with 'Get with the Guidelines')*
- *NovaGuide System or Lucid M1 System use information*
- *Head inclination (degree)/subject positioning/location of the exam*
- *User (name)*
- *Start/stop time- scan duration*
- *Relevant Concomitant Medications*
- *Device-Related Adverse Events*
- *Device Deficiencies / Technical Observations*

4.19 TCD data collection and data transfer

TCD data will be collected and stored on the NovaGuide System. The details of the data collection and transfer can be found in the User Manual and Data Transfer Instructions.

4.20 Study Workflow



5 MEASURES TO AVOID AND MINIMIZE BIAS

5.1 Imaging Core Laboratory

The objectives of the Core Lab are to provide an unbiased assessment of computed tomography angiography (CTA) to determine presence of large vessel occlusion.

For each subject that received a CTA, the Investigational Site will be instructed to follow a standard procedure developed by the Core Lab for obtaining catheter angiographic images pre-procedure.

Images will be sent directly from the site to the Core Lab. Core Lab definitions and procedures will adhere to specifications documented in the Core Lab Manual of Operations.

5.2 Imaging Core Lab Blinding

The Core Lab will assess all CT/CTA/MRA imaging blinded to cohort assignment. The Investigational Site will ensure subject identifying information is blinded prior to imaging data submission to the Core Lab. Should it not be possible for a site to blind the information without also deleting/omitting information required for evaluation of the angiography or CT/MRI images, NovaSignal shall have the option to contract with the Core Lab to blind the images. Subject's date of birth will be required in order to identify images provided from the study sites.

5.3 TCD Waveform Blinding

There are several methods used to blind both the site clinical team and NovaSignal. First, the clinical team will be blinded to the results of the VCI and therefore will not have the ability to influence specific groups. Additionally, the use of the fully automated system (NovaGuide) will further reduce the influence and variability of an individual clinical researcher. Core Lab will make the assessment of the CTA and NovaSignal will be blinded to the comparison of the VCI and CTA results.

6 RISKS AND BENEFITS

There is minimal potential clinical risk associated with the scans described in the study. The risks associated with the use of the NovaGuide System in humans have not been determined as this study is one of the initial uses of the device. *An ongoing study utilizing the device in subjects experiencing neurological symptoms of stroke has not reported any unexpected or serious device related adverse events (Protocol No.: NA-01STR-01).* The NovaGuide System is designed to be physically and electro-mechanically safe according to manufacturing standards. At any time, for any reason, the use of the device can be discontinued. Additionally, the FDA cleared version of the NovaGuide System is in commercial deployment in the US and Europe and no unexpected or serious device related events have been reported.

There is no direct benefit to the subject participating in the study.

7 DEVICE-RELATED ADVERSE EVENTS

Collection of device-related adverse events will start after the time that informed consent form is obtained. Device-related adverse events will be monitored throughout the study.

All suspected device related adverse events shall be recorded on the Adverse Event page of the CRF, if they are suspected to be related to the use of the NovaGuide System. If appropriate, the event shall subsequently be reported to the relevant IRB. The event shall be thoroughly investigated and a causal relation as to whether the event is related or not to the use of the NovaGuide System shall be established.

Events which are required to be reported and/or considered to be serious are categorized into either Serious Adverse Events (SAE), Unanticipated Serious Adverse Device Effect (UADE/USADE) or all Serious Adverse Device Effects (SADE) and include the following:
Adverse event that:

a) Led to a death
b) Led to a serious deterioration in the health of the subject that:
    1) resulted in a life-threatening illness or injury
    2) resulted in a permanent impairment of a body structure or a body function
    3) required in-patient or prolongation hospitalisation
    4) resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function
c) Led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, without serious deterioration in health, is not considered a serious adverse event.

Device deficiencies are also reportable if they did not lead to an adverse event but could have led to a SADE:

a) if either suitable action had not been taken,
b) if intervention had not been made, or
c) if circumstances had been less fortunate

NOTE: Device deficiencies include inadequacies of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

The Investigator will record the nature, severity, relatedness, treatment and outcome of the AE. This classification of the event determines the reporting procedures to be followed. NovaSignal may upgrade the classification as required for reporting purposes.

At the initiation of device use through end of use of the device, all subjects with adequate quality NovaGuide System data shall be assessed for any potentially device related complications or adverse events. All events shall be followed until resolution or through the end of a subject's study participation.

7.1 Potential or Anticipated Device Related Adverse Events/Complications

The following device related adverse events have been identified as possible (anticipated) with the use of the NovaGuide System:

- Physical discomfort of the head and neck due to pressure from the probe, or probe accidentally coming in contact with ears, eyes or hair.
- Psychological feeling of claustrophobia- the fear of being enclosed in a small space.

7.2 Unanticipated Adverse Device Effect (UADE)

An Unanticipated ADE (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.3 Reporting Adverse Events

Device-related adverse events information will be collected throughout the study. From the initiation of and end of device use, all subjects scanned with the NovaGuide System shall be assessed for any potentially device related complications or adverse events. All events shall be followed until resolution or through the end of a subject's study participation.

Event, onset date, severity, relatedness, device relationship, treatment and outcome of the AE will be recorded on the appropriate case report form. Any device-related AEs will be monitored until they are adequately resolved or explained. This classification of the event determines the reporting procedures to be followed. For purposes of this protocol, the following definitions will apply.

7.3.1 Adverse Event Severity Rating

The following categories of adverse event severity are to be used:

Mild	Awareness of sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment and with no sequelae.
Moderate	Interferes, but does not hinder, the subject's usual activity and/or may require treatment.
Severe	Symptom(s) causing severe discomfort and significant impact on the subject's usual activity and requires treatment or intervention.

7.3.2 Causality Rating

The causal relationship to study device will be evaluated as follows:

Definitely Related	The adverse event is clearly related to the test product.
Probably Related	The adverse event is temporally associated and plausibly related to the product/procedure but there are also potential alternative explanations, though the alternatives are not likely.
Possibly Related	The adverse event may be related, scientifically plausible, but there are also alternative explanations.

8 REPORTING OF DEVICE DEFICIENCIES / TECHNICAL OBSERVATIONS

In case device malfunctions occur, they will be reported to NovaSignal within 10 business days. The report should include at a minimum, a description of event, date of occurrence, lot or serial number of the device.

A study device has malfunctioned if it meets the following definition: The failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made on the labelling for the device. The intended performance of a device refers to the intended use for which the device is labelled.

Classification	Reporting time	Type of report
Unanticipated Adverse Device Effects (UADE)	Notify NovaSignal within 1 business day of learning of event. Notify IRB as required.	Device Related Serious Adverse Event Report Form
Serious Device Related Adverse Events (related to the performance of the study device)	Notify NovaSignal within 1 business day of learning of event. Notify IRB as required.	Device Related Serious Adverse Event Report Form
Study Device Deficiency/Malfunction – NOVAGUIDE with or without Adverse Event	Notify NovaSignal within 10 business days of learning of event. Notify IRB as required.	Device Deficiency/Malfunction Form

9 PROTOCOL DEVIATIONS

A protocol deviation is defined as a study related activity that is not in compliance with the protocol. Examples of deviations include but are not limited to a required test not being done or not being done within the specified timeframe, a subject enrolled who did not meet the inclusion/exclusion criteria, or enrolment of a subject without appropriate consent.

Deviations from the protocol must be reported to NovaSignal.

Protocol deviations can be classified into one of the three categories:

- Class I: Was intended to protect the life and physical well-being of the subject in an emergency.
- Class II: Was a non-emergency situation but the deviation was beyond the investigator's control.
- Class III: Was a non-emergency situation and was within the investigator's control. This deviation must be reported to NovaSignal in a timely manner.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Organizational Preparations

A site evaluation via personnel and facility documentation will be performed by NovaSignal or their designee during the study to ensure the availability of appropriately trained personnel to conduct the study according to the FDA Code of Federal Regulations and ICH Guidelines on Good Clinical Practices (ICH-E6). This study will be conducted under the principles described in the Declaration of Helsinki.

10.2 Training

NovaSignal will provide training for the use of the NovaGuide System, in adherence to the Instructions for Use/ User Manual. Documentation of training should be maintained by the Principal Investigator throughout the study.

10.3 Data Quality Assurance

Training of appropriate site personnel will be the responsibility of NovaSignal or designee. To ensure uniform data collection and protocol compliance, site personnel will utilize source documentation worksheets to document protocol procedures.

10.4 Subject Privacy

All data will be maintained under highly secure and fully HIPAA-compliant dedicated servers under the direction supervision of the Principal Investigator. Primary data that is obtained will have identifying information and will be stored securely onsite. Access to identifiable subject data is limited to project staff who have direct data management and/or statistical responsibilities, under the direct supervision of the Principal Investigator.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB.

Data de-identification will be performed manually using the "safe-harbor" approach under the supervision of the Principal Investigator. At this point, a unique ID is generated for each subject, and each exam. These will populate two databases using the "safe-harbor" approach under the supervision of the Principal Investigator. The database that is devoid of all PHI will be used for data analysis in this research.

10.5 Case Report Forms

All required data for this study will be collected on standardized Case Report Forms (CRF). The forms may be paper based or electronic. The forms will only include the subject study number assigned once the subject is screened. The investigator is responsible for the accuracy, completeness and legibility of the data reported to NovaSignal in the CRFs and in all required reports. The CRFs are to be dated and signed by an investigator on appropriate pages to verify that he/she has reviewed the recorded data.

10.6 Investigational Device Accountability

The NovaGuide System specific serial numbers must be documented at a study site by a designated person, handled and stored properly in a secured location in which only the study staff have access. The Principal Investigator must maintain an accurate record of the status of the products throughout the study. Investigators are responsible for appropriate logging of the devices used, verification of packing slip information (i.e. lot numbers and quantity shipped), date and identity that each device was used in the study, disposition information regarding disposal or return to the Sponsor.

10.7 Selection of Investigators

The study will be conducted at multiple centers. Study staff for each center will meet the following criteria:

- A user trained by NovaSignal in the use of the Lucid M1 System and NovaGuide System.
- Commitment from the participating investigator to pursue details of any potentially device related adverse event outcomes
- Commitment from the participating investigator to enroll only subjects meeting the local approved protocol
- Dedicated staff members who can collect data and be willing to perform necessary documentation (e.g. CRF)

10.8 Close-out Document Review

The purpose of the final document review is to collect all outstanding study data documents, ensure that the principal investigator's files are accurate and complete, review record retention requirements with the principal investigator and ensure that all applicable requirements are met for the study.

The investigator agrees to allow the monitoring of study data, the completion of all data clarification or audits even after study close-out visit has been performed at NovaSignal' request.

11 STATISTICAL ANALYSIS

11.1 Phase 1 Statistical Analysis:

Primary Endpoint Analysis: Demonstration of VCI diagnostic performance at or exceeding 85% ROC–AUC (targeting SEN greater than 90%) to standard of care imaging.

Biomarker Validation and Analysis: VCI will be computed for each subject according to the procedure outlined in section 3.5, and group differences will be assessed using appropriate statistical methods. ROC-AUC will be computed detailing separability between groups for comparison to standard of care imaging (CTA) and prehospital/neurological clinical scales, along with SEN, SPE, and accuracy at various levels of diagnostic threshold, including that corresponding to Youden's maximal J-statistic.

Sample size calculation: From the results of our feasibility study, we estimate that expected effect size between VCI distributions for LVO (cohort A) and IHC groups (cohort B) will be large (Cohen's D > 1.25), such that only a small number of subjects in each group (N = 11) will be sufficient to detect significant differences (alpha of 0.05) with standard statistical power of 80%. However, in Phase 1 we seek to demonstrate the stronger aim of biomarker diagnostic performance in excess of 85% ROC-AUC. Assuming this target AUC is met, then sample size determines the confidence bounds on that estimate. In Phase 1 we require a sample of sufficient size to power confidence in the superiority of VCI diagnostic performance relative to current clinical prehospital stroke assessment scales. As existing preclinical scales top out at 78% AUC, this can be accomplished with a sample of roughly 50 subjects in each patient group, which gives a one-tailed 95% confidence bound on the target 85% AUC of less than 7%. The specification of 54 subjects per group is a target number intended to guarantee acquisition of a sufficient sample assuming at least 90% of target enrollment.

Initial safety endpoint analysis: Throughout the study we will collect adverse events, which will be used to determine the safety of the device within the acute stroke environment. In our EXPEDITE study which is also run in the ER for stroke assessment, the device has been designated minimal risk by the IRB and we have not had any serious adverse events in over 80 subjects. We will continue to closely monitor this metric.

In this work, we will also measure "Get with the Guidelines, Stroke" metrics from each site and compare them to literature, national and site metrics. This will enable us to demonstrate that the system does not adversely affect standard of care for subjects suspected of stroke. The reason we believe it will not affect standard of care is because the device will be used after initial CT and IV-tPA is administered, while the subject is waiting for CTA or intervention. The time window, although short, is available to allow us to measure both the TCD waveform and CTA to confirm VCI is an effective biomarker. Additionally, the times will be compared against the randomized groups (Cohort C and D).

Door to diagnostic imaging. (Statistical demonstration that show we will not delay anything when adding our NovaGuide workflow to), e.g. "Get with the Guidelines, Stroke": We will calculate the following for subjects that have NovaGuide measurements:

- IV rt-PA arrive by 2 hour, treat by 3 hour: Percent of acute ischemic stroke patients who arrive at the hospital within 120 minutes (2 hours) of time last known well and for whom IV t-PA was initiated at this hospital within 180 minutes (3 hours) of time last known well.
- % Door to CT ≤ 25 minutes: Percent of patients who receive brain imaging within 25 minutes of arrival.
- Door to Puncture (DTP) Time within 90 minutes: (Percentage of patients with acute ischemic stroke who receive mechanical endovascular reperfusion)

11.2 Phase 2 Statistical Analysis

Primary Endpoint Analysis: Demonstration of VCI biomarker performance at or exceeding 90% ROC–AUC (targeting SEN & SPE greater than 90%) to standard of care imaging across multiple centers.

Here, we will determine the final biomarker performance using the dataset collected and reviewed by the core lab. Similar analyses will be run on the VCI biomarker distributions for the Phase 2 subject group as was done in Phase 1. Additionally, subgroup analyses comparing biomarker results across research sites, and age groups, will be conducted to determine if any age or NovaGuide inter-operator variability effects are present in the data (two-way ANOVA with post-hoc comparisons).

Sample size calculation: In Phase 2, we seek to demonstrate stricter confidence bounds on biomarker diagnostic performance in excess of 90% ROC-AUC. Assuming the biomarker is observed to meet that performance threshold, then a sample of approximately 150 LVO subjects in each patient group is required to attain a one-tailed 95% confidence bound on the observed AUC of 3%. That is, the target AUC and sample size would afford 95% confidence that the underlying general population AUC is greater than 87%. Moreover, across five sites, this results in approximately 30 LVO subjects per site, affording sufficient power for detection of moderate potential inter-site effects in the range of Cohen's D >= 0.75.

Calculate study and site specific stroke workflow times: Stroke workflow parameters and times are well characterized in literature, including “Get with the Guidelines, Stroke” published by the American Heart Association, Inc. and will be utilized as a historical control comparator for data collected in Phase 2. We will use these published stroke guidelines which have mean times for the stroke workflow parameters to show that we are non-inferior to these when using the NovaGuide device. Additionally, the data will be compared to the corresponding randomized group (Cohort C and D)

11.3 Imaging Core Lab Analysis

All imaging data will be sent to a core laboratory which will provide independent quantitative and qualitative assessment of all study data. They will be blinded to the study and radiology report data and provide independent review.

11.4 TCD Data Analysis

All TCD data acquired by the NovaGuide System will be sent to NovaSignal which will provide independent quantitative assessment of all TCD study data. They will be blinded to the study and radiology report data and provide independent review.

11.5 Data Analysis

Evaluation of correlation between diagnostic imaging standard of care and VCI biomarker by an independent core laboratory masked to local radiology determination. Success criteria will include clinical validation of VCI biomarker for LVO detection threshold performance at or exceeding 90% ROC–AUC (targeting SEN & SPE greater than 90%) to standard of care imaging.

12 ETHICAL CONSIDERATIONS

12.1 Investigational Review Board (IRB) Approval

This study will be conducted using an FDA cleared product called the Lucid M1 System, 510k K160442 and CE Mark 32518. The study will also utilize an investigational device, called the NovaGuide System, comprised of a NovaGuide System and a research use only software program (that does not alter the FDA cleared/CE Mark approved Lucid M1 System). The study scans are non-invasive. A local Investigational Review Board (IRB) or ethics committee review and approval is required prior to commencement of the study.

This protocol and the informed consent must be reviewed and approved by the appropriate IRB where the study is to be conducted before enrolment of subjects. NovaSignal and the IRB must approve in writing any changes to the protocol that affect the rights, safety, and/or welfare of the subjects, or may adversely affect the validity of the study.

It is the responsibility of the investigator to submit the final version of the protocol with the Informed Consent Form (ICF), if required, to an appropriately constituted IRB prior to commencement of the study. The Investigator will submit the appropriate documentation if any extension, renewal or amendment of the IRB approval must be obtained. In particular, study plan amendments, ICF changes or other written information provided to the subject must be approved by the IRB in writing, when required.

12.2 Role of NovaSignal

As the study Sponsor of this clinical study, NovaSignal has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the Food and Drug Administration. NovaSignal will ensure adherence to the regulations as outlined in the Sponsor general duties, selection of investigators, monitoring, maintaining records, and submitting reports.

12.3 Investigator Responsibilities

The Principal Investigator (PI) shall be responsible for the day-to-day conduct of the study as well as for the safety and well-being of the human subjects involved in the study. The PI also assumes overall responsibility and accountability for the study team and for data obtained from each subject participating in the study.

The PI shall be responsible for:

1. Obtaining a written IRB approval for the study and subject ICF prior to including any subject in this study, as required by local rules and laws.
2. Ensuring that the study is conducted in compliance with IRB requirements including conditions which may be imposed by a reviewing IRB.
3. Ensuring compliance with the study plan, applicable laws, and applicable regulations.
4. Obtaining informed consent and privacy authorization for all study subjects prior to subject participation (the informed consent and privacy authorization processes may be combined, as per usual procedure of the IRB).
5. Collecting all required study data on the Case Report Forms provided.
6. Reviewing and signing CRF pages indicating documents are accurate and complete.

The PI will agree to provide access to the records of all subjects entered into this study, as well as all other study documentation. In addition, all records may be subject to inspection by officials of US FDA and other regulatory authorities according to local rules and laws.

The PI should make accurate and adequate progress reports to the IRB at appropriate intervals, according to the IRB requirements, when applicable. The PI will inform the IRB of study completion or termination within the time period specified by the IRB, when applicable.

The PI is responsible for informing the IRB of any safety issues related to the study as required.

The PI/site must maintain adequate records on all aspects of the study.

The PI/site must maintain the study records for at least two years after cessation of the study.

12.3.1 Records Custody

An investigator may withdraw from the study. If the PI withdraws from the study, the responsibility of conducting follow-up and maintaining records must be transferred to another responsible party within institution (i.e. Sub-I). Notice of transfer must be provided in writing by the PI to NovaSignal and the IRB when applicable, not later than 10 working days after transfer occurs.

12.4 Sub-Investigator (Sub-I) – Responsibilities

Sub-Investigators will be responsible for study activities in coordination with the PI and in accordance to the study plan. A Sub-Investigator may assume the responsibility of the PI should the PI resign from the study.