Author: [redacted]
GEN: Clinical Development Scientist

Sponsor: Philips Medical Systems Nederland BV
Veenpluis 6,
5684 PC Best
The Netherlands

Department: Clinical Science & Medical Affairs

Clinical coordinating investigator [redacted]
Karolinska University Hospital
17176 Stockholm Sweden
Department of Neuroradiology

NCT number: **NCT04571099**

Approval

Name	Role	Date	Signature
[redacted]	GEN: Clinical Operations Lead	28 Feb 2020	[redacted]
	InCs:Study Leader	2020 Feb 28	
	Q&R: RA Officer	28 feb 2020	
	GEN: Biostatistician	28 FEB 2020	

Controlled Document is approved when all approvers have signed. Approval and effective date is the date of the latest signature.

Revision History

Revision	Revision Date	Author	Changes/Comments
00	2019 nov 05	[redacted]	Initial version
01	2020 Feb 27	[redacted]	Revision to incorporate changes in response to questions of MPA: - Summary & section 6.6.3: Removed exclusion criteria (eGFR prior to investigational scan lower than 45 or relevant risk factors excludes iodine contrast injection) because patients can still be included, but will not receive a contrast enhanced scan. - Section 3.4: added that before enrollment of subjects, the study will be registered in the ClinicalTrials.gov database. - Section 6.6.1: clarified which subject will be replaced: Subjects will be replaced if they or the investigator withdraws the patient for any reason described in 6.4.1 or if image quality is too low due to movement during exam. - Section 6.6.2.1: Clarified that patients that fail to return on day 2 for examination will not be replaced. - Section 7.2 & Appendix IV: Clarified the meaning of immediately based on MEDDEV 2.7 / 3 rev.3, which the sponsor is stated to follow (page 27): The Sponsor shall report immediately, but no later than 2 calender days after awareness by sponsor of a new reportable event or new information in relation with an already reported event - Section 8.1: In response to the comment that the procedure for evaluating image endpoints was not clearly described, we have rewritten this section to clarify that readers will not be involved in the study and will have no information regarding the acquisition type (e.g. CBCT, CT, DE-CBCT). - Section 14: Added extra information regarding the termination of the study: (1) After the last patient has been included and investigated with the investigational device the clinical investigator and Sponsor will inform the EC and regulatory authority about end of inclusion. (2) An early termination and/or study termination of the clinical investigation will be documented and shared with the EC and regulatory authority. - Section 15: added “This clinical investigation will be recorded on ClinicalTrials.gov.”

Open Issues

None

Table of Contents

1. Document Introduction

1.1. Purpose

This template shall be used as a basis of a clinical Research protocol for clinical Research. The document describes the minimum amount of information to be included in the clinical Research protocol based on the regulations to ensure safety and wellbeing of human subjects and users.

1.2. Scope

This clinical research protocol applies to study: Next Generation X-ray Imaging System (NEXIS)

1.3. References

Reference	Identification	Title / additional remarks
[REF-1]	XCY607-130522	Investigator Brochure - NEXIS
[REF-2]	XCY607-130561	Monitoring Plan - NEXIS

1.4. Definitions & Abbreviations

Term	Description
ADE	Adverse Device Effect
AE	Adverse Event
AICA	Anterior inferior cerebellar artery
AIS	Acute Ischemic Stroke
ASPECTS	Alberta Stroke Program Early CT Score (See Appendix V for details)
CBCT	Cone beam computed tomography
CE	Conformité Européenne (European Conformity)
CEC	Clinical Events Committee
CFR	Code of Federal Regulation
CRF	Case Report Form
CNR	Contrast-to-noise ratio
CT	Computed tomography
CTA	CT Angiography
CTP	CT Perfusion
DE-CBCT	Dual energy CBCT
DECT	Dual energy CT
DL	Dual Layer (detector)
e-CRF	Electronic Case Report Form
e-GFR	Estimated Global Filtration Rate
EPX	Examination, Patient, X-ray information
EU-MDD	Medical Device Directive (EEC) 93/42 of the European Council of 14 June 1993 as amended
EU-MDR	Medical Device Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017
FDA	Food Drug Administration
HE	High Energy layer of the detector, also known as the second layer
ICA	Internal carotid artery
ICF	Informed Consent Form
IFU	Instructions for Use
IRB	Institutional Review Board
ISO	International Organization for Standardization
IW	Interventional Workspot: Philips product that enables advanced applications
LE	Low Energy layer of the detector, also known as the first layer
LVO	Large vessel occlusion

Term	Description
MCA	Middle cerebral artery
mCTA	Multiphase CTA (See Appendix V for details)
MEC	Medical Ethic Committee
mTICI	modified thrombolysis in cerebral infarction (TICI) score (See appendix V for details)
neCT	Non-contrast enhanced CT
NEXIS	Next Generation X-ray Imaging System
PICA	Posterior inferior cerebellar artery
SAE	Serious Adverse Event
SCA	Superior cerebellar artery
SNR	Signal-to-noise ratio
USADE	Unanticipated Serious Adverse Device Effect

Summary

Identification of investigational device

[redacted]

Study design

The study is prospective, open label, single centre. This is a first in man study of a novel dual energy flat panel detector technique, which also entails new reconstruction and segmentation algorithms.

With this trial, we aim to evaluate the diagnostic capabilities of a novel flat panel detector capable of acquiring and processing multi energy photon information. The Allura NEXIS Investigational Device emplys a flat panel detector system having novel energy separation capabilities. Consequently, we see a need to study and assert the diagnostic capabilities of our new detector in a relevant patient population.

The study serves as a proof of concept and, given results are satisfactory, would have substantial impact on treatment time for patients eligible for thrombectomy. If patients are diagnosed and treated for ischemic stroke in the same room, we would expect a significant reduction in neuron loss due to ischemia and thus have a positive impact on patient outcome.

Objective

The objective of this study is to evaluate the capability of DE-CBCT to render an accurate diagnosis by defining the diagnostic performance of DE-CBCT compared to gold/reference standard.

Primary and secondary objectives

Primary objective

Ischemic stroke diagnostic accuracy
Accuracy of DE-CBCT to determine the extent and localization of ischemic stroke changes in brain tissue, using neCT as the reference standard.

Secondary objective

Vessel tree visibility
Proportion of contrast-enhanced DE-CBCT rated non-inferior (i.e. equal or superior) vessel visibility compared to CTA (reference standard).

Intracranial hemorrhage detection accuracy
Accuracy of DE-CBCT to determine the presence of intracranial hemorrhage, using neCT as the reference standard.

Additional objectives – 3D diagnostic imaging

- Ischemic stroke diagnostic accuracy, vessel tree visibility and hemorrhage detection accuracy compared to regular CBCT.
- Characterization of brain tissue as normally perfused, at risk (penumbra) or infarcted.
- Characterization of intracranial hemorrhage.
- Characterization of intracranial thrombus.
- Separation of grey and white matter, and iodine from blood and calcium.
- Assessment of novel segmentation and reconstruction techniques.

Additional objectives – 3D image quality parameters

- Objective image quality parameters.
- Subjective image quality parameters.
- Image artefacts, especially near bony structures.

Main inclusion criteria

1. The patient has signed and dated the Informed Consent Form (ICF)

2. Age ≥ 50 years old

3. Clinical and radiological signs consistent with acute stroke

    I. Patient diagnosed with ischemic stroke of the anterior circulation and not eligible for thrombectomy.
    II. Patient diagnosed with ischemic stroke of the anterior circulation and subjected to thrombectomy.
    III. Patient diagnosed with hemorrhagic stroke.

Main exclusion criteria

1. Pregnant or breastfeeding women.

2. Previous stroke or parenchymal damage/defects in anterior circulation territories (only applicable for subjects included by criterion 3.I or 3.II).

3. Subject participates in a potentially confounding drug or device trial during the course of the study.

4. Participation in the study exposes the subject to risk, as assessed at the discretion of the treating physician.

5. All subjects who meet an exclusion criteria according to national law.

6. Subject or subject family member is a known Philips employee.

No. of subjects

In total, the minimum sample size required is 20 subjects, of which two-thirds have ischemia, one-third have intracranial hemorrhage, and at least half must have done a contrast enhanced DE-CBCT. Our estimated necessary sample size is 29 subjects, taking algorithm optimization and potential invalid data into account.
Study procedures

Screening and procedures

Subjects will be screened regarding the study inclusion/exclusion criteria to determine their initial eligibility. A member of the research team (hospital/institution personnel assigned to the Study) should review their eligibility. All screened subjects will be documented in the Screening/Enrolment log, including the reason for non-participation for subjects who do not enrol. The only procedures imposed by the study is imaging without and if eligible, with iodine contrast agent.

Computed tomography (CT)

Computed tomography (CT), including DECT, obtained directly prior to and during the study will be used for comparison.

Procedural angiography

For patients undergoing thrombectomy (criterion 3.II). Post thrombectomy angiogram result will be determined according to the mTICI score as assessed by the treating interventional radiologist.

Iodine contrast agent eligibility test

Kidney function by means of aGFR and non-renal risk factors for CI-AKI will be determined day 1 (criteria 3.I and 3.III) and/or day 2 (3.I and 3.II), before imaging with the investigational device.

Sufficient renal clearance is determined as aGFR equal to or over 45 ml/min. Non-renal risk factors for CI-AKI are determined as diabetes, chronic heart failure (NYHA III/IV), dehydration, sepsis, hypoxia, liver cirrhosis and regular intake of NSAID or nephrotoxic substances such as antibiotics, chemotherapy and immunosuppressive agents.

A sufficient renal clearance and absence of multiple non-renal risk factors for CI-AKI will be required to perform contrast enhanced scans according the following dosage (32): Gram iodine / GFR ratio ≤ 1,0. This dosage ratio also applies for consecutive scans with iodine contrast agent, such as day 1 subjects included by criterion 3.I (already investigated with standard of care mCTA and CTP).

DE-CBCT without (w/o) and with (w) contrast agent

Depending on inclusion criterion 3.I, 3.II or 3.III, the research protocol differs as depicted in Figure 4.

Investigational device exposure and comparators

As per clinic standard, patients with suspected ischemic stroke are evaluated with neCT, mCTA and CTP upon admission. Patients arriving from another hospital with a confirmed LVO can optionally be imaged with only neCT and CTP. Also, as per clinic standard, ischemic stroke patients treated in any way (thrombolysis and/or thrombectomy) undergoes DECT 12-36 hours after treatment to assess the presence and extent of hemorrhage and ischemia. Patients diagnosed with hemorrhagic stroke will typically be evaluated with neCT and mCTA/CTA upon admission.

This study will investigate the performance of DE-CBCT in comparison to regular neCT/mCTA/CTA/CTP imaging at admission and subsequent DECT (DECT only for subjects in 3.I and 3.II). Table 1 provides an overview of the devices each subject is exposed to depending on inclusion criterion.

	Day 1				Day 2			
Inclusion criterion	*Standard imaging (CT-based)*	Iodine contrast eligibility test	DE-CBCT w/o contrast agent	DE-CBCT w contrast agent	Iodine contrast eligibility test	*Standard imaging (DECT)*	DE-CBCT w/o contrast agent	DE-CBCT w contrast agent
3.I	*X*	X	X	X [1]	X	*X* [2]	X	X [1]
3.II	*X*				X	*X*	X	X [1]

3.III	*X*	X	X	X [1]				

Table 1. Overview of the devices the subject is exposed to depending on inclusion criterion. Timeline: left to right.
[1] No iodine contrast agent will be administered if deemed ineligible
[2] Only if subject has been treated with thrombolysis
Italics depicts standard diagnostic protocol

Subjects presenting with acute stroke will be evaluated by the physician in accordance with the institutional practice, to establish an appropriate treatment plan based on the subject's medical condition and available diagnostic screening procedures prior to recruitment in the Study. The 3rd inclusion criterion will define the investigational device exposure for the subjects:

3.I subjects will be imaged with DE-CBCT without and with contrast agent day 1 after standard diagnostic CT imaging. If subject is still hospitalized at Karolinska on day 2, an additional DE-CBCT without and with contrast agent will be made.

3.II subjects will be imaged with DE-CBCT without and with contrast agent day 2 directly after their standard diagnostic DECT scan.

3.III subjects will be imaged with DE-CBCT without and with contrast agent day 1 after standard diagnostic CT imaging.

The figure below provides an overview of the study flow, consisting of a combination of standard of care scans and scans with the NEXIS investigational device.

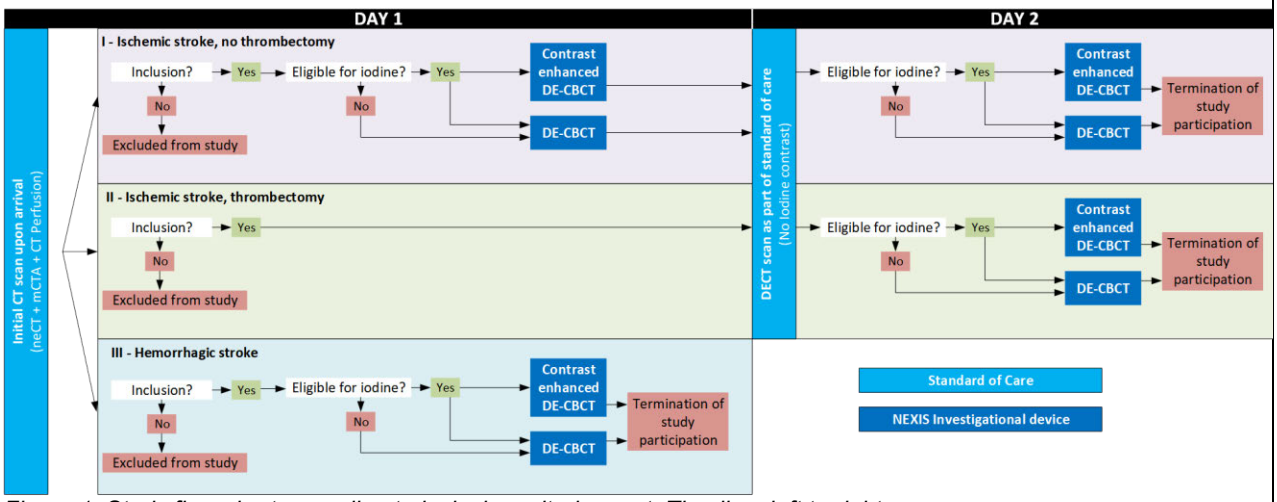

Figure 1: Study flow chart according to inclusion criterion met. Timeline: left to right.

Follow up

Patient departs from the investigation at end of investigation day 1 (group III) or day 2 (group I and II).

Duration of the study

The total duration of the study is expected to be 4-6 months for subject recruitment and investigation

2. State of the art in stroke treatment

2.1. Stroke prevalence and associated costs

Stroke is the third most common cause of death in the developed world and the leading cause of acquired neurological disability.
The World Health Organisation (WHO) estimates that cardiovascular diseases are the leading cause of death globally, causing 17.3 million deaths in 2008. Of these, stroke caused an estimated 6.2 million deaths in 2008 and was the second leading cause of global death. Cerebrovascular disease is the most common

cause of neurological disability in older adults (1) and contributes substantially to other late complications such as dementia and epilepsy. Stroke incidence rates are increasing rapidly in low-income and middle-income countries (2, 3). In high-income countries, substantial increases in the absolute numbers of individuals affected by stroke are projected due to increasing population life-expectancy, even if stroke incidence rates are reduced or maintained at current levels (2). Stroke is also a substantial contributor to healthcare costs. The American Heart Association estimates that annual total (direct and indirect) costs of stroke were $34 Billion in 2011. In Ireland, a collaboration between clinicians and the Economic and Social Research Institute estimated total stroke-related costs of 0.5-0.7 Billion Euro in 2007, with costs projected to exceed 1 Billion Euro by 2020 (4).

2.2. Current standard of care

Ischemic stroke is caused by acute occlusion of an artery leading to immediate reduction in blood flow within the corresponding cerebrovascular territory. The size and site of the occlusion, and the efficiency of compensatory collateral blood flow, determine the extent of impaired blood flow and resulting neurological symptoms from “at risk" (ischemic) and/or dead (infarcted) brain. Early spontaneous re-canalisation may occur from the endogenous release of tPA, a serine protease of the fibrinolytic system which converts the zymogen plasminogen into the active protease plasmin, leading to cleavage of fibrin and the dissolving of newly formed thrombin “clot". However, for most patients, and particularly in those with large occlusions (5), this natural physiological function is inadequate to avoid the outcome of infarcted cerebral tissue from the occluded vessel.

2.3. Stroke Imaging

Multiple imaging protocols are used together to diagnose patients presenting with symptoms consistent with acute stroke, such as focal disabling neurological deficit or loss of consciousness. A reliable diagnosis is essential to determine the most beneficial treatment strategy for the patient.
Studies that established the efficacy of modern endovascular recanalization (6) most commonly use non-contrast agent enhanced CT (neCT) and vessel tree visualization such as CT angiography (CTA) combined with dynamic information through a brain perfusion scan for patient selection.

2.4. Computed Tomography (CT)

Currently, Computed Tomography (CT) is the preferred diagnostic imaging technique because of high contrast resolution, good availability and quick scan time. A neCT scan is the first diagnostic investigation to be done in order to exclude the presence of intracranial hemorrhage (i.e. hemorrhagic stroke) and extensive infarction, as both are contraindications for intravenous thrombolytic therapy. Today, neCT provides sub-millimeter resolution in x, y as well as z direction (3D).

2.5. Computed Tomography Angiography (CTA)

CTA serves the purpose of mapping the cerebral vascular anatomy as well as identifying any present occlusion, stenosis or vessel anomaly which could have implications on treatment strategy. Computed tomography angiography (CTA) is performed with and synchronized to intravenous iodine contrast agent administration. With CTA, the radiologist can identify the thrombus in the case of an ischemic stroke. Currently, there is substantial evidence (6) that it is possible to access and extract large vessel occlusions (LVOs) located in proximal anterior circulation vessels such as the internal carotid artery (ICA) and middle cerebral artery (MCA) M1 and M2 section. Also, LVOs in the posterior circulation located in the vertebral artery, basilar artery and posterior cerebral artery (PCA) segment P1 are accessible. Approximately 80% of all ischemic strokes occur in the anterior circulation.

The majority of ischemic stroke patients presenting with severe focal neurological deficit have a LVO on CTA. At Karolinska, the CTA also includes the aortic arch and neck vessels and thus provide anatomical information and determines the presence of stenosis or dissection, which can have implications on catheter selection and treatment strategy.

2.6. Computed Tomography Perfusion (CTP)

Using dynamic information provided by CT Perfusion (CTP), early manifest infarctions not visible on neCT can be detected. This information is crucial as manifest ischemia increases risk and decreases potential

benefit from endovascular recanalization therapies. Equally important, dynamic imaging also visualizes tissue with decreased blood flow at risk of manifest ischemia (penumbra) that could potentially be salvaged by endovascular recanalization. Similar to CTA, CTP is performed with and synchronized to intravenous iodine contrast agent administration. However, CTP involves repeated scans over the head (usually 17-35 sweeps) over the course of 40-60 seconds. The assessment of CTP involves a “mismatch” concept where an intact cerebral blood volume in an area of decreased blood flow and/or blood transit time is thought to indicate a penumbra, and a corresponding area with decreased cerebral blood volume is thought to indicate manifest ischemia. Multiple software tools are available to assess CTP parameters, with some agreement differences (7).
The HERMES collaboration (6) indicated that dynamic imaging was beneficial in selecting patients for thrombectomy, and subsequent large studies such as DAWN and DEFUSE 3 (8, 9) both used dynamic imaging for patient selection in an extended time window (up to 24 hrs from symptom onset). Similarly, patient selection by perfusion imaging for thrombolysis in an extended time frame (4.5 - 9 hrs) has also been proven to correlate with beneficial outcome (10, 11).
Accordingly, CTP has rapidly become established practice at most comprehensive stroke centres worldwide when assessing patients with suspected acute ischemic stroke (AIS).

2.7. Multiphase CT Angiograpy (mCTA)

An alternative or complement to CTP to assess vessel perfusion dynamics is to use Multiphase CT Angiography (mCTA). This technique usually involves three consecutive CTA scans performed on the same patient, approximately 8 seconds apart. mCTA has been shown to correlate with functional outcome in patients better than a single-phase CTA (12) and determined a reliable tool for imaging selection in patients with AIS (13). Moreover, mCTA has been shown to predict tissue fate similar to CTP in patients with AIS (14). The assessment of mCTA does not necessarily involve additional software tool analysis (which is required for CTP), and thus makes mCTA easier to use and less dependent on advanced processing algorithms.

2.8. Flat panel detector imaging including Cone Beam CT (CBCT)

Endovascular recanalization is done with X-ray guidance in an interventional suite equipped with a flat panel detector C-arc system. The flat panel detector is predominantly used for 2D image guidance during interventional procedures. However, it can also be used for diagnostic 3D imaging by rotating the detector around the patient and reconstructing the resulting 3D volume. This imaging technique is known as Cone Beam CT (CBCT) and enables important diagnostic information, usually in conjunction with an interventional procedure. Most often, CBCT is used for anatomical assessment such as bone morphology and characterization of iodine contrast enhanced blood vessels, peri- and postprocedural information such as stent/graft placement, as well as detection of important procedure related complications such as intracranial hemorrhage. However, due to detector limitations, flat panel detector systems currently lack the possibility of detailed low contrast tissue discrimination, such as soft tissue and brain tissue characterization.

2.9. Spectral CT / Dual Energy Computed Tomography (DECT)

Photons (X-rays) interact with matter in different ways dependent on atomic number (AN) and electron density (ED) of the material. The main photon interactions in the energy range used for diagnostic imaging are through Compton Scattering (CS) and Photoelectric Effect (PE). Essentially, the composition of the tissue or material (AN and ED) determines the probability of a photon with a certain energy to interact by either CS or PE. Especially the PE interaction component shows great energy dependency. Photons that are not absorbed (by PE) or scattered away from the imaging detector (by CS) are registered and quantified. The differences in PE interaction can be used to separate different tissues and materials, as well as to improve image contrast resolution.
Imaging techniques to separate photon energy (spectral imaging) have emerged and gained much attention over the last decade due to great technical advances and an increasing number of clinical applications. The rationale for how diagnostic CT scans are performed and interpreted is changing with the availability of added spectral information. Today, the readily available technique is interchangeably referred to as Spectral CT or Dual Energy CT (DECT). Several spectral techniques exists and yet more promising ones are under development.
Spectral CT / DECT can add significant value to a diagnostic investigation, for example by offering the potential of improved tissue characterization through reconstruction of virtual monoenergetic images (VMI)

as well as material separation and iodine quantification (15-17). Today, DECT is widely used within neuroradiology, for example to separate blood from iodine contrast leakage after an interventional procedure (18). Recent studies show promising results using DECT for acute stroke imaging (19-21), indicating a possibility of higher diagnostic sensitivity and specificity to detect early ischemic changes.

2.10. Spectral Cone Beam CT / Dual Energy Cone Beam CT (DE-CBCT)

As of yet, photon energy separation is most commonly utilized in CT scanners to improve image quality and to extract additional image information. Applying this concept to flat panel detectors placed in interventional suites would theoretically render CBCT images with improved tissue and anatomical characterization, as well as an increased iodine detectability. This technique has been termed Spectral CBCT or Dual Energy CBCT (DE-CBCT).
A technically sophisticated approach to enable energy separation is to superimpose detector layers on each other. Using this technique, the first detector layer captures low energy photons, and the second detector layer captures photons of higher energy. This enables a separation of photon energy spectra, which is utilized to improve image information content. Improved detector properties could also make it feasible to lower the necessary radiation dose to the patient and health care personnel involved in a wide range of interventional procedures.
Preclinical studies have provided insights on the possibilities of energy separating flat panel detectors, and our trial aims to evaluate this technique in a diagnostic application. In order to assess the images, new reconstruction algorithms are developed.

2.11. Stroke treatment

Acute ischemic stroke (AIS) can be treated either by administering a thrombolytic drug (thrombolysis), or by thrombectomy where the blocking thrombus is retrieved from the occluded vessel with a endovascular device. Commonly, both treatment strategies are used together in the case of a LVO.

2.11.1. Thrombolysis (IVT)

Clot-dissolving drugs such as intravenous recombinant tissue plasminogen activator (IV rtPA) can significantly improve the prognosis for a patient with AIS by restoring blood flow to a region of the brain blocked by an arterial clot/thrombus. Until 2015, this was the only scientifically proven treatment for any type of AIS. However important, it has been shown that IVT has a very small likelihood of successful recanalization when the thrombus measures 8 mm or more (5). Large thrombi commonly occlude the proximal intracranial arteries, usually termed large vessel occlusions (LVO). The proximal location of a LVO typically leads to substantial neurological deficits and a poor prognosis without successful treatment.

2.11.2. Endovascular treatment

A blood clot/thrombus in a proximal intracranial artery can be removed by an endovascular procedure termed thrombectomy. The thrombectomy aims to achieve arterial recanalization and thus restoration of blood flow and oxygen delivery to brain tissue. Typically, the femoral artery is punctured with a needle and the intracranial arterial vasculature is subsequently accessed using a catheter system under X-ray guidance. Endovascular treatment for patients with AIS and LVO using second-generation devices (primarily stent retrievers (SRs)) have demonstrated to be beneficial across five large randomized clinical trials (RCTs) (6). The addition of endovascular thrombectomy to standard medical care also resulted in better 24-h recanalization rates (71% of successful recanalization rate)(6). In these five RCTs, mechanical thrombectomy was performed in more than 80% of cases with a SR, a self-expanding stent used to retrieve thrombi (6). These studies provided compelling evidence for the beneficial results of mechanical thrombectomy in patients with LVO of the anterior circulation presenting within 6 hours of symptom onset and has since 2015 been established practice world wide.
Furthermore, RCTs DAWN and DEFUSE 3 published in 2018 provided insights that thrombectomy can be a beneficial treatment option up to 24 hours after symptom onset, thus making endovascular recanalization a possible treatment option for an even larger patient group (8, 9). These studies both used “mismatch” concepts separating irreversible ischemic tissue from potentially salvageable tissue to select patients for thrombectomy.

2.12. Patient outcome

Treatment impact on patient functional outcome is of paramount importance. Selecting the most beneficial treatment for a patient can be challenging. Determination of tissue with irreversible damage (infarct) and regions with impaired oxygenation at risk of irreversible damage (penumbra) in relation to unaffected brain tissue gives important insight of brain integrity in the acute stroke phase. Infarct core volume assessed on neCT alone does not seem to predict patient outcome (22), however it has been shown that information from dynamic imaging (such as CTP), about ischemia and penumbra extent and localization, correlates to patient outcome (23). This confirms the rationale for diagnostic perfusion imaging performed before decision on treatment strategy in most of the large thrombectomy studies (6, 8, 9).

Although perfusion imaging is important, the necessity of it for patient outcome prediction has been discussed and possible alternatives have been addressed. As mentioned above, it has been shown that mCTA predicts tissue fate similarly to CTP (14) and even that single phase CTA collateral scoring may suffice for patient outcome predicition (24), obviating the need for mCTA and CTP for certain patients.

The proposed study is a first in man approach to provide information of brain tissue viability with a spectral flat detector and does not gather information about patient outcome as the selection criteria and sample size is only sufficient to evaluate image and diagnostic quality. The correlation between imaging results and patient functional outcome will be very important to assess in a future study, given our results are satisfactory.

3. Device description

3.1. Summary description of the investigational device and comparator

The following medical devices will be used in this clinical study (see Table 2).

Table 2: Medical devices involved in this clinical study

#	Device description	Manufacture	Regulatory status
[redacted]			

As part of the study, we will also use commercially CE marked IW and XperCT Dual.

3.2. Detailed description of the investigational device

[redacted]

The described modification is only present during the clinical investigation, i.e. the time reserved for the clinical study of the NEXIS dual layer detector. After the clinical investigation period the Allura system will be brought back to its original product status.

[redacted]

3.2.1. Intended Purpose

The intended medical purpose of the Allura NEXIS Investigational Device is to perform neurovascular imaging applications, including diagnostic, interventional and minimally invasive procedures on human patients. It is intended to support cerebral angiography, as well as PTAs, stent placements, embolization and thrombolysis.

It can be used for all human patients, subject to the inclusion criteria, for the goal described in this research protocol. Patient weight is limited to the specification of the patient table.

3.2.2. Necessary training and experience needed to use the research device

The Allura NEXIS Investigational Device is intended to be used and operated by: adequately trained, qualified, and authorized health care professionals who have understanding of the safety information and emergency procedures as defined by local laws and regulations for radiation workers and staff.

To facilitate safe and efficacious operation of the system by a trained healthcare professional, instructions for use are provided as part of the device labelling, as well as a basic training at system handover The Instruction for Use (IFU) contains safety precautions and handling of the investigational device.

3.2.3. Materials that will be in contact with tissues or body fluids

No materials of the Allura NEXIS Investigational Device will be in contact with tissue or body fluids.

3.2.4. Device Traceability

Records shall be kept to document when the device is received, installed or returned/uninstalled/disposed at the hospital.

3.2.5. The Allura NEXIS Investigational Device

[redacted]

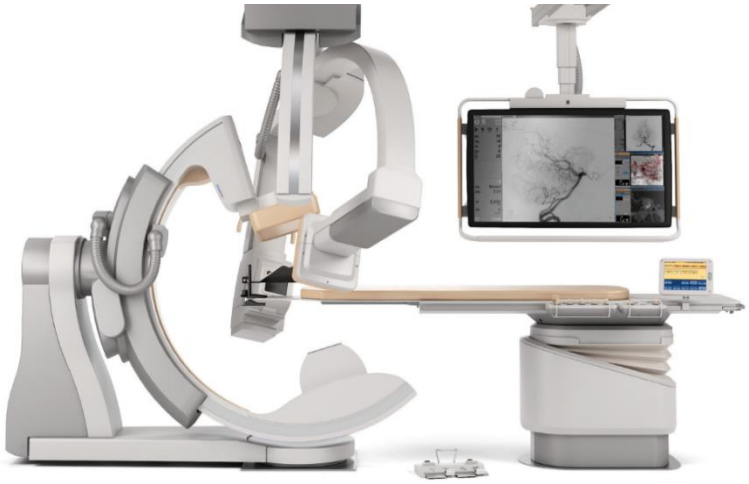

Figure 2 Allura FD20/15 biplane product

[redacted]

[redacted]

3.2.6. Limitations of the investigational device

[redacted]

3.3. Evaluation of preclinical testing

[redacted]

[redacted]

3.4. Evaluation of clinical testing

As no commercially available flat panel detector system has energy separation capabilities today, the investigation NEXIS devices has not been tested clinically. This study will collect the first clinical data. Before enrollment of subjects, the study will be registered in the ClinicalTrials.gov database.

4. Risks and benefits of the investigational device and clinical research

The NEXIS system is not CE marked and is referred to as an investigational device that needs approval from both the Swedish Medical Products Agency (MPA, Läkemedelsverket) and the Ethics committee (Etikprövningsmyndigheten) before it can be used in this clinical trial.

Clinical benefits
No direct benefit will be added for the patients. However, their participartion in this study will provide valuable scientific information and guidance towards an improved diagnostic and treatment approach for future patients with the same diagnosis. Our strategy of diagnosing and treating stroke in the same room has the potential to lower the time elapsed before treatment and thus give patients a better chance of successful reperfusion of brain tissue (25).

Risk assessment
The risk assessment process that Philips follows is in accordance with ISO 14971.This will ensure that the level of risk is acceptable prior to the start of the study. A detailed overview of the risk assessment can be found in the Investigator Brochure section 5 [REF-1].

The Overall Conclusion of the risks vs benefits analysis is that:

- Both device related risks and the study related risks have been considered and mitigation controls in place are effective
    - All device related risks have been reduced as far as possible and individual residual risks after mitigation are classified as acceptable.
    - Risks to the subject associated with the clinical procedure required by the study plan are limited to additional X-ray dose and iodine contrast and can be justified.
- The overall residual risk is acceptable;
- Based on the overall safety profile, AlluraNEXIS Investigational Device can be safely used in clinical practice.

5. Objectives

This study aims to assess the diagnostic imaging properties as well as image quality properties in subjects presenting with suspected ischemic stroke. Infarcted stroke tissue, white and grey matter discrimination, thrombus characteristics, separation of blood, iodine and calcium as well as artifacts near the skull base and posterior fossa will be evaluated, among others. As initial stroke imaging must be able to identify or exclude intracranial bleeding, subjects with hemorrhagic stroke will be included. For detailed information about evaluation of endpoints and statistics, please see chapter 8.

5.1. Primary objective

Ischemic stroke diagnostic accuracy
Accuracy of DE-CBCT to determine the extent and localization of ischemic stroke changes in brain tissue, using neCT as the reference standard.

5.2. Secondary objective

Vessel tree visibility
Proportion of contrast-enhanced DE-CBCT rated non-inferior (i.e. equal or superior) vessel visibility compared to CTA (reference standard).

Intracranial hemorrhage detection accuracy
Accuracy of DE-CBCT to determine the presence of intracranial hemorrhage, using neCT as the reference standard.

5.3. Additional objectives – 3D diagnostic imaging

- Ischemic stroke diagnostic accuracy, vessel tree visibility and hemorrhage detection accuracy compared to regular CBCT.
- Characterization of brain tissue as normally perfused, at risk (penumbra) or infarcted.
- Characterization of intracranial hemorrhage.
- Characterization of intracranial thrombus.
- Separation of grey and white matter, and iodine from blood and calcium.
- Assessment of novel segmentation and reconstruction techniques.

5.4. Additional objectives – 3D image quality parameters

- Objective image quality parameters.
- Subjective image quality parameters.
- Image artefacts, especially near bony structures.

5.5. Justification for the design of the study

Despite recent advancements in the treatment of ischemic stroke, time management for patients potentially eligible for thrombectomy remains far from ideal. When the patient arrives at the hospital, he/she must first be transported to the CT scanner for diagnosis and then further to the interventional suite for thrombectomy. This consumes a substantial amount of time and resources, and any delay to proper treatment may lead to additional manifest brain ischemia. It is estimated that about 2 million neurons are lost per minute during an acute ischemic stroke caused by a large vessel occlusion (26). Earlier diagnosis of the stroke cause followed by immediate treatment is quintessential to save brain tissue. The concept of diagnosing and treating ischemic stroke in the same room would be revolutionary, with similarities to modern management of acute coronary syndrome. In recent years, this concept of stroke diagnosis and treatment in the same room has been proven feasible in small studies, minimizing time to recanalization of occluded intracranial arteries (27, 28)

With this study, we aim to evaluate the diagnostic capabilities of a novel flat panel detector capable of acquiring and processing multi energy photon information. The Allura NEXIS Investigational Device employs a flat panel detector system having novel energy separation capabilities. Consequently, there is a need to study and evaluate the diagnostic capabilities of our new detector in a relevant patient population. All subjects included in the study will receive standard protocol healthcare. The only intervention imposed on study participants is additional imaging and intravenous iodine contrast agent administration.

The study is designed to provide a proof of concept and, given results are satisfactory, could have substantial impact on time to treatment for patients eligible for thrombectomy. If patients are diagnosed and treated for ischemic stroke in the same room, we would expect a significant reduction in neuron loss due to ischemia and thus have a positive impact on patient outcome.

In order to evaluate relevant diagnostic quality and image quality in the acute stroke setting, we will include subjects with ischemic stroke of the anterior circulation coming to the comprehensive stroke center at Karolinska University Hospital (inclusion criteria 3.I and 3.II). As initial imaging must be able to identify or exclude intracranial hemorrhage, subjects determined to have a hemorrhagic stroke will also be included in the study (3.III). For stroke patients, an additional contrast enhanced scan is relevant to delineate the intracranial vessels in order to identify relevant pathology.

Even though no additional radiation dose compared to a standard CBCT is anticipated, subjects will receive an additional radiation dose compared to standard diagnostic protocol due to the additional image acquisition. However, the brain is quite insensitive to radiation exposure (weighting factor of 0.01

when calculating effective organ doses (29), and sensitivity to stochastic radiation effects decreases with age (30). The great majority of stroke patients in Sweden are 65 years or older (31). To ensure that the risks of additional radiation is minimized, no subject under the age of 50 will be included in the study. No gender specific safety considerations have been identified for subjects aged 50 and over. However unlikely, women included in the study will be asked about current pregnancy.

Usage of iodine contrast agents poses a small risk of contrast-induced acute kidney injury (CI-AKI). We will follow Swedish national guidelines, recommending that the total amount of iodine (in grams) administered for a contrast enhanced scan should not exceed the calculated aGFR in mL/min (32), given that the patient has a sufficient renal clearance and does not have multiple risk factors. For more information, see section 6.2.3.

Subjects not eligible for thrombectomy (criterion 3.I) receive less iodine contrast agent and radiation exposure compared to patients undergoing thrombectomy, where iodine is used to navigate during the procedure under X-ray image guidance. Investigational DE-CBCT of these subjects on day 1 imposes varying extent of residual iodine intracranially (from previous standard of care imaging). However, these subjects typically show very relevant imaging features, as hyperacute ischemic changes are challenging yet crucial to visualize. Moreover, DE-CBCT imaging potentially enables iodine removal/suppression. If still hospitalized day 2, an additional DE-CBCT enables diagnostic information about stroke progression.

Subjects that have undergone thrombectomy (inclusion criteria 3.II) will be included one day after admission (day 2), when most of the iodine typically has been filtered out by the kidneys. An absolute GFR (aGFR) and non-renal risk factors for CI-AKI will be assessed before administering iodine contrast agent. These measures will ensure that the risks associated with iodine contrast agents will be minimized.

Similar to above, subjects with a verified intracranial hemorrhage (inclusion criteria 3.III) will be imaged without and with iodine contrast agent day one after assessment of aGFR and non-renal risk factors.

If the subject is deemed inappropriate to receive iodine contrast agent, only imaging without iodine contrast agent will be done. In addition to above, other individual or healthcare aspects may select subjects to undergo only imaging without injection of iodine contrast agent.

6. Study Design

6.1. General

The study is prospective, open label, single centre. This is a first in man study of a novel dual energy flat panel detector technique, which also entails new reconstruction and segmentation algorithms. The study will be run in Karolinska University Hospital, Solna. Radiographers and selected physicians will be trained in the use of the Allura NEXIS Investigational Device protocols before any subject investigation.

6.2. Screening and procedures

Subjects will be screened regarding the study inclusion/exclusion criteria to determine their initial eligibility. A member of the research team (hospital/institution personnel assigned to the Study) should review their eligibility. All screened subjects will be documented in the Screening/Enrolment log, including the reason for non-participation for subjects who do not enrol. The only procedures imposed by the study is imaging without and if eligible, with iodine contrast agent.

6.2.1. Computed tomography (CT)

Computed tomography (CT), including DECT, obtained directly prior to and during the study will be used for comparison.

6.2.2. Procedural angiography

For patients undergoing thrombectomy (criterion 3.II). Post thrombectomy angiogram result will be determined according to the mTICI score as assessed by the treating interventional radiologist.

6.2.3. Iodine contrast agent eligibility test

Kidney function by means of aGFR and non-renal risk factors for CI-AKI will be determined day 1 (criteria 3.I and 3.III) and/or day 2 (3.I and 3.II), before imaging with the investigational device.

Sufficient renal clearance is determined as aGFR equal to or over 45 ml/min. Non-renal risk factors for CI-AKI are determined as diabetes, chronic heart failure (NYHA III/IV), dehydration, sepsis, hypoxia, liver cirrhosis and regular intake of NSAID or nephrotoxic substances such as antibiotics, chemotherapy and immunosuppressive agents.

A sufficient renal clearance and absence of multiple non-renal risk factors for CI-AKI will be required to perform contrast enhanced scans according the following dosage (32): Gram iodine / GFR ratio ≤ 1,0. This dosage ratio also applies for consecutive scans with iodine contrast agent, such as day 1 subjects included by criterion 3.I (already investigated with standard of care mCTA and CTP).

6.2.4. DE-CBCT without (w/o) and with (w) contrast agent

Depending on inclusion criterion 3.I, 3.II or 3.III, the research protocol differs as depicted in Figure 4.

6.3. Enrollment and duration

Subjects are considered to be enrolled in the Research after they have signed the informed consent form. No study procedures will be performed before this moment.

We will enrol adults admitted with suspected acute stroke that have undergone standard diagnostic imaging upon admission. The study process will not affect the standard of care, only provide additional imaging data. Images will be processed retrospectively. All consecutive patients who meet the inclusion criteria and not the exclusion criteria will be enrolled, in accordance with investigational device availability.

The total duration of the study is expected to be 4-6 months for subject recruitment and investigation. The subject will only be actively involved in the study when acquiring images, other parameters will be documented as regular standard of care and accessed retrospectively. Thus, that part of the study is purely observational.

6.4. Informed consent process

Informed consent will be obtained from every subject in writing by the Investigator or his authorized designee before the clinical Research is started. The subject will be informed both orally and in writing about all aspects that are relevant to the subject's decision to participate in the trial, including the trial procedures and risks and benefits of participation in the clinical Research. The informed consent will include an explanation of the study, duration, explanation of medical record access and patient anonymity, and how their coded data may be transferred, used for publications or in submissions for reimbursement support. The informed consent form will contain language that is non-technical and understandable to the patient.

Ample time should be provided for the subject to read and understand the informed consent form and to consider participation. The informed consent will include personally dated signatures of the subject and the principal investigator or an authorized designee responsible for conducting the informed consent process. The investigator or an appropriately designated member of the study staff shall co-sign the consent form, indicating they believe the subject has understood the nature and risks of the study and, in their estimation, the subject clearly understands the scope of the consent. The investigator must inform subjects that they are in a clinical trial, apprise them of their rights as set forth in the informed consent document, and make written documentation that such a discussion took place. The subject will receive a copy of the signed informed consent and any other written information.

If new information becomes available that might significantly affect the subject's future health and medical care, it shall be provided to the subjects in written form. If relevant, subject shall be asked to reconfirm their continuing informed consent in writing. In this trial only patients that can give informed consent themselves will be included.

The procedure around how the informed consent is collected will be recorded in each subjects' medical record. The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor on request.

The Investigation site will maintain a log of all screened patients detailing the reasons for any subsequent patient exclusions or non-participation in the study.

6.4.1. Subject withdrawal or discontinuation

Participation in this investigation is voluntary, and the subject may withdraw at any time. All enrolled subjects will be included in data analysis, unless they withdraw permission for their data to be used. The Sponsor will retain and continue to use any data collected prior to the withdrawal of consent, unless specified by the Subject.
In the event the subject chooses to withdraw, he/she will be instructed to contact the Investigator immediately. Withdrawal from the investigation will not affect the subject's standard of care. The subject will be informed of any significant information regarding new findings that may develop during the course of the research study that may relate to his or her willingness to continue participation as a study subject.
Subjects will participate in their routine follow-up (day 2, when applicable) and allow this data to be gathered. If their participation is terminated, any of their data which has been already gathered will continue to be included. The completion of a subject's participation in the study or early departure from the study must be fully documented in the subject's study progress notes.

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

- Subject voluntarily withdraws from the study: A subject may withdraw consent from study participation at any time.
- Subject withdrawn from the study by the investigator. An investigator may withdraw an enrolled subject from the study for the following reason:

If participation in the study is life threatening for the subject or at the investigators own discretion.

6.5. Investigational device exposure and comparators

As per clinic standard, patients with suspected ischemic stroke are evaluated with neCT, mCTA and CTP upon admission. Patients arriving from another hospital with a confirmed LVO can optionally be imaged with only neCT and CTP. Also, as per clinic standard, ischemic stroke patients treated in any way (thrombolysis and/or thrombectomy) undergoes DECT 12-36 hours after treatment to assess the presence and extent of hemorrhage and ischemia. Patients diagnosed with hemorrhagic stroke will typically be evaluated with neCT and mCTA/CTA upon admission.

This study will investigate the performance of DE-CBCT in comparison to regular neCT/mCTA/CTA/CTP imaging at admission and subsequent DECT (DECT only for subjects in 3.I and 3.II). Table 3 provides an overview of the devices each subject is exposed to depending on inclusion criterion.

	Day 1				Day 2			
Inclusion criterion	*Standard imaging (CT-based)*	Iodine contrast eligibility test	DE-CBCT w/o contrast agent	DE-CBCT w contrast agent	Iodine contrast eligibility test	*Standard imaging (DECT)*	DE-CBCT w/o contrast agent	DE-CBCT w contrast agent
3.I	*X*	X	X	X [1]	X	*X* [2]	X	X [1]
3.II	*X*				X	*X*	X	X [1]
3.III	*X*	X	X	X [1]				

Table 3. Overview of the devices the subject is exposed to depending on inclusion criterion. Timeline: left to right.
[1] No iodine contrast agent will be administered if deemed ineligible
[2] Only if subject has been treated with thrombolysis
Italics depicts standard diagnostic protocol

Subjects presenting with acute stroke will be evaluated by the physician in accordance with the institutional practice, to establish an appropriate treatment plan based on the subject's medical condition and available diagnostic screening procedures prior to recruitment in the Study. The 3rd inclusion criterion will define the investigational device exposure for the subjects:

3.I subjects will be imaged with DE-CBCT without and with contrast agent day 1 after standard diagnostic CT imaging. If subject is still hospitalized at Karolinska on day 2, an additional DE-CBCT without and with contrast agent will be made.

3.II subjects will be imaged with DE-CBCT without and with contrast agent day 2 directly after their standard diagnostic DECT scan.

3.III subjects will be imaged with DE-CBCT without and with contrast agent day 1 after standard diagnostic CT imaging.

Figure 4 provides an overview of the study flow, consisting of a combination of standard of care scans and scans with the NEXIS investigational device.

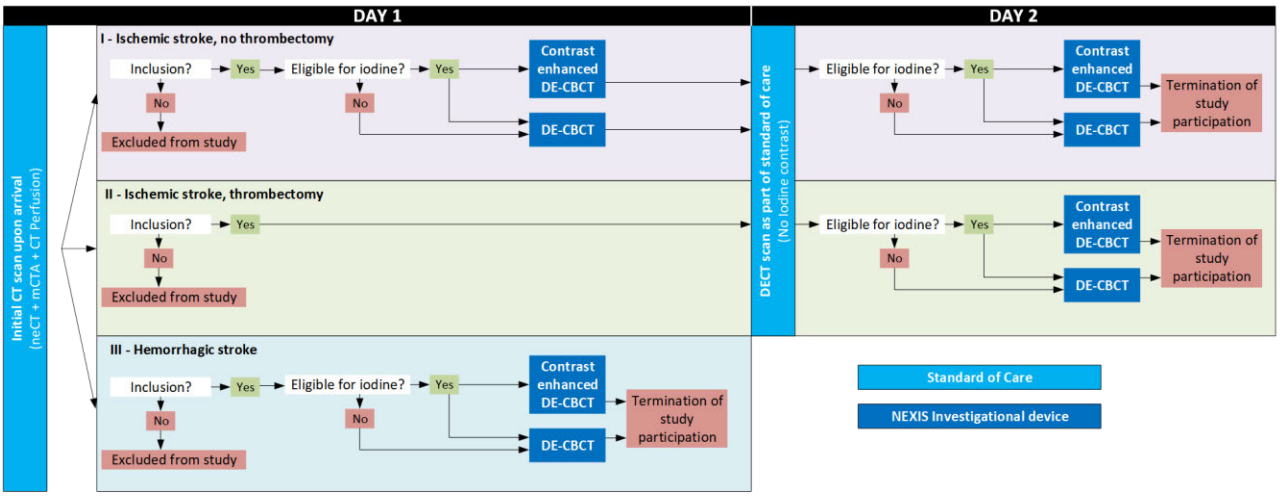

Figure 4. Study flow chart according to inclusion criterion met. Timeline: left to right.

6.6. Subjects

6.6.1. Number of subjects

In total, the minimum sample size required is 20 subjects, of which two-thirds have ischemia, one-third have intracranial hemorrhage, and at least half must have done a contrast enhanced DE-CBCT. Our estimated necessary sample size is 29 subjects, taking algorithm optimization and potential invalid data into account.

The number of subjects are necessary to collect sufficient data for the evaluation of the primary and secondary endpoints, taking algorithm optimization and potential invalid data into account. Subjects will be replaced if they or the investigator withdraws the patient for any reason described in 6.4.1 or if image quality is too low due to movement during exam. The enrollment period is expected to last for 4-6 months.

See Section 8 (Statistical considerations) for more details on the subject sample size.

6.6.2. Procedure for the replacement of subjects

Subjects in the study will be replaced in case of withdrawal of consent or if subject is found ineligible for the study after signing of the informed consent and before the measurement. Subject will also be replaced if patient movement during image acquisition significantly affect assessment of the image material, as judged by the investigator. If only the second scan for subjects included according to 3.I is invalid, they will not be replaced.

6.6.2.1. Lost to follow-up

If a subject enrolled by inclusion criterion 3.I fails to return for their day 2 examination, their first study examination will still be included in the study. Thus, these subjects will not be replaced.

6.6.3. Inclusion and exclusion criteria

Subjects participating in the study will be carefully selected based on the next inclusion and exclusion criteria.

6.6.3.1. Inclusion criteria

1. The patient has signed and dated the Informed Consent Form (ICF)

2. Age ≥ 50 years old

3. Clinical and radiological signs consistent with acute stroke

    I. Patient diagnosed with ischemic stroke of the anterior circulation and not eligible for thrombectomy.
    II. Patient diagnosed with ischemic stroke of the anterior circulation and subjected to thrombectomy.
    III. Patient diagnosed with hemorrhagic stroke.

6.6.3.2. Exclusion criteria

1. Pregnant or breastfeeding women.

2. Previous stroke or parenchymal damage/defects in anterior circulation territories (only applicable for subjects included by criterion 3.I or 3.II).

3. Subject participates in a potentially confounding drug or device trial during the course of the study.

4. Participation in the study exposes the subject to risk, as assessed at the discretion of the treating physician.

5. All subjects who meet an exclusion criteria according to national law.

6. Subject or subject family member is a known Philips employee.

6.7. Follow Up

Subject participation is terminated at the end of investigation day 1 (criterion 3.III) or day 2 (criterion 3.I and 3.II).

6.8. Adverse Events

Any adverse events that occur during the investigation (day 1 or day 2) will be recorded.

7. Adverse event reporting

The proposed study will be started under the MDD, however as of 26 May 2020, the reporting of serious adverse events and device deficiencies shall be carried out in accordance with the Medical Device Regulation.
Adverse event reporting under MDD is done according to ISO14155:2011 and MEDDEV 2.7/3 revison 3.

7.1. Definitions

Adverse Event (AE)
ISO14155: Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device
NOTE 1 This definition includes events related to the investigational medical device or the comparator.
NOTE 2 This definition includes events related to the procedures involved.
NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.

EU-MDR: An Adverse Event (AE) is defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical research, whether or not related to the investigational device.

Serious Adverse Event (SAE)
ISO14155: Adverse event that led to any of the following:
a) death
b) serious deterioration in the health of the subject, that resulted in any of the following:
1) a life-threatening illness or injury, or
2) a permanent impairment of a body structure or a body function, or
3) hospitalisation or prolongation of patient hospitalization, or
4) in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure of a body function.
5) a chronic disease
c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect

EU-MDR: Any adverse event that led to any of the following:
(a) death,
(b) serious deterioration in the health of the subject, that resulted in any of the following:
(i) life-threatening illness or injury,
(ii) permanent impairment of a body structure or a body function,
(iii) hospitalisation or prolongation of patient hospitalisation,
(iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
(v) chronic disease,
(c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect

Device Deficiency
ISO14155: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance
NOTE Device deficiencies include malfunctions, use errors, and inadequate labelling.

EU-MDR: Any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

Adverse Device Effect (ADE)
ISO14155: Adverse event related to the use of an investigational medical device. Note This includes any adverse event resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device, and any event resulting from use error or from intentional misuse of the investigational medical device.

Serious Adverse Device Effect (SADE)
MEDDEV 2.7/3 rev 3: Adverse device effect that has resulted in any of the consequences characteristic of a serous adverse event.

Unanticipated Serious Adverse Device Effect (USADE)
ISO14155: Unanticipated Serious Adverse Device Effect is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report
NOTE Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

7.2. Reporting

It is the responsibility of the Investigator to comply with 1) his/her Ethical Committee requirements for reporting safety event, and 2) any country specific regulatory/CA Investigator requiremnts for safety events.

All adverse events shall be recorded. The safety assessments will consist of Adverse Events (AE) from the time the ICF is signed through departure from study for those patients enrolled, and to discharge or 24 hours for those patients identified as screening failures by inclusion/exclusion criteria.
The AEs will be categorized using MedDRA Coding of Adverse Events Nomenclature Standardized nomenclature.

The investigator shall report to Sponsor any related or unrelated serious adverse (device) event and device deficiencies that could have led to a Serious Adverse Device Effect (SADE) if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate via the adverse event form or device deficiency form in the e-CRF. The investigator shall supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event.
The investigator should report to the MEC and/or competent authority these serious adverse events and device deficiencies that might have led to a serious adverse device effect, if required by MEC or competent authority, as further detailed in Appendix IV.

The reporting requirement from investigational site to the sponsor is:

Type of Adverse Event	Reporting Requirements
• SAE • SADE • USADE • Death • Any study device deficiency that could have led to an SADE	Report to Sponsor immediately upon awareness of event but no later than 24 hours (In written within 5 days).
• All other Adverse Events • All other study device deficiencies	Report to Sponsor immediately upon awereness of event, but no later than 14 calender days.

Non-serious adverse (device) events shall be recorded on the adverse event forms. Device Deficiencies shall be recorded on the device deficiency form. The Sponsor and Monitor can request access to this information at any time. The event reporting is done via the electroic data capture system (EDC). If the electroic data capture system (EDC) is unavaible the AE can be notified via email to the study mailbox: [redacted]

The study site personnel must seek information on Adverse Events by specific questioning and, as appropriate, by examination. Information on each Adverse Event should be recorded immediately in relevant source documents, and also on the appropriate eCRF (in the EDC). The following attributes must be assigned by the Investigator for adverse events:

- Description of the event
- Actions taken
- Date of onset and resolution
- Determination if event is serious
- Determination if the event is anticipated – in the even of an SADE
- Determination of event severity
- Determination of the causal relationship to study device and study procedure

Information collected for device deficiencies are:

- Date of device deficiency
- Whether this could have led to a Serious Adverse Device Effect (SADE) if
  - a) suitable action had not been taken or
  - b) intervention had not been made or
  - c) if circumstances had been less fortunate.

The clinical course of each event will be followed until resolution or stabilization.

The investigator shall supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event.

The investigator should report to the MEC and/or competent authority these serious adverse events and device deficiencies that might have led to a serious adverse device effect, if required by MEC or competent authority, as described below and summarized in Appendix IV: Reporting requirements to MEC and Competent Authority.

Adverse Events (AE) and Adverse Device Effects (ADE)

All adverse events shall be recorded. The safety assessments will consist of Adverse Events (AE) from the time the ICF is signed through departure from study for those patients enrolled, and to discharge or 24 hours for those patients identified as screening failures by inclusion/exclusion criteria.
The AEs will be categorized using MedDRA Coding of Adverse Events Nomenclature Standardized nomenclature.

The sponsor is:

- Responsible for the classification of adverse events and ongoing safety evaluation of the clinical research and shall review the investigator's assessment (done by the CEC) of all adverse events and determine and document in writing their seriousness and relationship to the investigational device; in case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to MEC and Competent authorities
- Review all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect; in case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to MEC and competent authority.
- Report or ensure the reporting, to the MEC by the principal investigator(s), of all serious adverse events and device deficiencies that could have led to a serious adverse device effect,

- In case of serious adverse device effects and device deficiencies that could have led to serious adverse device effects, determine whether the risk analysis needs to be updated and assess whether corrective or preventive action is required.

Competent Authorities:
The Sponsor shall report immediately, but no later than 2 calender days after awareness by sponsor of a new reportable event or new information in relation with an already reported event to the competent authorities the following Serious Adverse events and device deficiency that occur at any of the involved trial sites:

- Serious Adverse Events and
- Device Deficiencies that could have led to a Serious Adverse Device Effect (SADE) if
  a) suitable action had not been taken or
  b) intervention had not been made or
  c) if circumstances had been less fortunate

A causal relationship between the SAE and the investigational device(s), or procedures performed as part of the clinical trial or other conditions of the trial conduct cannot be excluded.

7.2.1 Adverse Event Severity

The intensity or severity of each Adverse event must be assessed according to the following classifications:

Mild	Awareness of signs, symptoms, or events that are otherwise easily tolerated that may result in minimal transient impairment of body function or damage to a body structure, but do not require intervention other than monitoring.
Moderate	Any event that results in moderate transient impairment of body function or damage to a body structure that causes interference with usual activities, or that warrants possible intervention, such as the administration of medication, to prevent permanent impairment of body function or damage to body structure.
Severe	Any event that is incapacitating (an inability to do usual activities) or is life-threatening and results in permant impairment of body function or damage to a body structure, or requires intervention, such as major surgery, to prevent permanent impairment of body function or damage to a body structure.

7.2.2 Adverse Event Causality Assessment

The clinician who examines and evaluates the enrolled subject will determine the AE's causality based on temporal relationshil and his/her clinical judgment . The degree of certainty about causality will be graded using the categories below.

Causality	**Defintion of causality**
Causal relationship	The event is associated with the investigational device beyond reasonable doubt.
Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.
Possible	The relationship with the use of the investigational device is week but cannot be ruled out completely.
Unlikely	The relationship with the use of the investigational device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Not related	Relationship to the investigational device can be excluded.

7.2.3 Adverse Event Outcome

The outcome of each Adverse Event must be assessed according to the following classification.

Outcome classification	Definition
Recovered/Resolved	Subject fully recovered with no observable residual effects
Recovered/Resolved with sequelae	Subject recovered with observable residual effect
Recovering/Resolving	Subject's condition improving, but residual effects remain
Not Recoverering/Not Resolved	AE is ongoing without improvement in the overall condition
Fatal	Subject died as a result of the AE (whether or not the AE is related to the investigational device)
Unknown	AE outcome is unknown (e.g., subject is lost to follw-up)

7.3. Anticipated adverse device effects

Anticipated adverse device effects are described below in Table 4

Anticipated adverse device effects	**Likely incidence**	**Mitigation or treatment**
Side effects of additional X-ray dose	PoH 1	The brain is quite insensitive to radiation exposure: weighting factor of 0.01 when calculating effective organ doses (29), and sensitivity to stochastic radiation effects decreases with age (30). To ensure that the risks of additional radiation is minimized, no subject under the age of 50 will be included in the study.
Side effects of additional Iodine contrast	PoH 1	An absolute GFR (aGFR) and non-renal risk factors for CI-AKI will be assessed before administering iodine contrast agent. These measures will ensure that the risks associated with iodine contrast agents will be minimized.
Dose control functionality fails, causing more radiation than expected	PoH 2	Tests are implemented
Poor scan quality if slower XperCT scan results in motion artifacts	PoH 2	Add guidance in the IFU to guide scan selection in case a fast scan is required. The Allura product also has a 20s neuro scan and the user can use a faster non-spectral scan when needed.

Table 4 Aniticipated adverse device effects.

7.3 Clinical Event Committee (CEC)

Clinical Events Committee (CEC) & Event notification
An independent board consisting of radiologists, hospital physicists and stroke physicians who are not participating in the study will adjudicate serious adverse events in the trial.
The role of the CEC will be to:

- Adjudicate any SAE that could be attributable to ionizing radiation.

- Adjudicate whether an SAE is deemed attributable to the procedure or is from the natural course of the standard research protocol or stroke illness.
- Continuous evaluation of available external data and/or knowledge, as presented at major congresses and /or published in peer-reviewed journals, which may have an impact on the study or be considered a protocol violation.
- The CEC role does not interfer with the sponsor's responsibility to classify and report adverse events to competent authorities.

7.4. Unavoidable adverse events

Not applicable since only a scan will be acquired.

8. Statistical considerations

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

8.1. Image data management

The raw image data with added dual energy properties (DE-CBCT) will be processed using novel reconstruction and segmentation techniques. During the intervention only the product reconstruction algorithm is available for raw image data acquired by the first layer of the detector and images reconstructed in this fashion will be identical to current CBCT.

After the intervention the DE-CBCT raw image data will be reconstructed with the novel spectral reconstruction software and then evaluated by three independent neuroradiologists (not involved in the clinical investigation) for subjective outcome variables. The first cases will also be used to iterate and optimize reconstruction algorithms. Images will be processed on-site and off-site. For ordinal outcome variables comparing the subjective performance of DE-CBCT and CBCT to CT, CTA and CTP (such as the first secondary objective), neuroradiologists will have access to both DE-CBCT and reference image data concurrently. For the primary and second secondary objective DE-CBCT and reference image, data will be cleaned from any information regarding acquisition technique and evaluated randomly and separated in time, in order to limit the possibility of bias.

A secure image data repository will be set up at Karolinska University Hospital, the access to which will be provided through IntelliSpace Discovery (ISD) that will serve as the interfacing client for managing and logging the access of data by authorized personnel involved in this study. No additional software will be required by the user to access the data as the ISD client runs in chrome web browser with a zero footprint i.e., no data will be stored on user's computer while using the ISD interface.

8.2. Sample size justification

Statistical analyses will be performed by Karolinska University Hospital. This is a prospective, open label single centre study. A diagnostic study using DE-CBCT on confirmed acute ischemic or hemorrhagic stroke has not been done before. The sample size estimations aims to prove diagnostic quality non-inferiority compared to CT according to performance goals below.

The sample size for the primary endpoint is trait-based, using ten [10] ASPECTS regions for each subject. To evaluate the diagnostic accuracy of DE-CBCT compared to CT, it is estimated that a sample size of 137 is required to render a power of 90% (target accuracy of 0.90, performance goal lower boundary of 0.80, one-sided alpha of 0.025). For this endpoint, a minimum sample size of 14 subjects is required.

The first secondary endpoint (vessel tree visibility) is also trait-based, using eleven [11] arterial regions for each subject. To evaluate the proportion of regions rated equal or superior to CT, it is estimated that a sample size of 126 is required to render a power of 80% (target proportion of 0.90, performance goal lower boundary of 0.80, one-sided alpha of 0.0125, adjusted for multiple secondary endpoints). For this endpoint, a minimum sample size of 12 subjects is required.

The second secondary endpoint is defined as diagnostic accuracy to determine the presence of intracranial hemorrhage, comparing DE-CBCT to CT (reference). The endpoint is subject-based and it is estimated that a sample size of 20 is required to render a power greater than 95% (target accuracy of 0.9999, performance goal lower boundary of 0.80, one-sided alpha of 0.0125, adjusted for multiple secondary endpoints). The sample size includes both subjects with hemorrhage and negative controls, preferably with 0.5 hemorrhage prevalence, with a threshold of at least a third of our subjects to have an intracranial hemorrhage. For this endpoint, a minimum sample size of 20 is required.

In total, the minimum sample size required is 20 subjects, of which two-thirds have ischemia, one-third have intracranial hemorrhage, and at least half must have done a contrast enhanced DE-CBCT. Our estimated necessary sample size is 29 subjects, taking algorithm optimization and potential invalid data into account.

8.3. Statistical methods

All variables will be summarized by descriptive statistics The statistics for continuous variables includes mean, median, standard deviation, 95% confidence interval for the means, and the number of observations. For categorical variables, number of events, event rate, and 95% confidence interval for the event rate will be presented.

For categorical variables, the Fisher's Exact or chi-squared test will be used. For numerical variables, Student's t-test will be applied for image quality parameters such as signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR). For ordinal rank variables concerning radiologist interpretation, the Wilcoxon test will be used. The decision to use non-parametric or parametric tests will be based on the result from Shapiro-Wilk test as well as the distribution of the data on a P-P plot.

Receiver operating characteristic (ROC) curves will be constructed and accuracy as well as area under the curve (AUC) will be used to assess image diagnostic performance, where applicable. Sensitivity, specificity, negative and positive predictive value will be assessed with optimal cut off, where applicable. The DeLong test will be applied when comparing ROC curves. The Kappa coefficient will be used to evaluate interrater and within-observer agreement, where applicable. Additional statistical methods may be used in accordance with relevant literature (33). A biostatistician is involved in planning and executing the statistical analyses.

8.4. Subject Disposition

A subject disposition chart will be presented.

8.5. Demographics and Baseline Characteristics

Basic subject characteristics such as age, gender, height and weight etc., will be collected and described descriptively in a publication format.

8.5.1. Study characteristics

Subject characteristics

- Sex
- Age
- Iodine contrast agent dose received before investigation (during the previous 72 hrs)
- Treatment and diagnostic characteristics
- Time stamps for admission CT, follow-up DECT and study investigation
- Time of symptom onset, if available
- Thrombolysis yes/no (at least bolus)

- Thrombectomy yes/no
- mTICI score at the end of thrombectomy procedure rated by treating neurointerventionalist
- Time from symptom onset to start of thrombolysis
- Time from symptom onset to end result of endovascular therapy (thrombectomy)

Any deviation from the planned analysis described below will be documented with justification in the final clinical report.

8.6. Primary objective

8.6.1. Ischemic stroke diagnostic accuracy

Endpoint
Accuracy of DE-CBCT ASPECTS to determine the extent and localization of ischemic stroke changes in brain tissue, using neCT ASPECTS as the reference standard.

Applicable subjects
Subjects diagnosed with ischemic stroke on CT.

Data
- ASPECTS
  - Left / Right
  - 1 to 10
  - Location - L, C, IC, I, M1, M2, M3, M4, M5, M6

Analysis
Images are evaluated by radiologists using neCT as reference standard and the ASPECTS diagnostic accuracy is defined.

Hypothesis:

H_0: $\pi_1 \leq 0.80$
H_1: $\pi_1 > 0.80$

Where π_1 is the observed ASPECTS accuracy and 0.80 is the performance goal.

8.7. Secondary objectives

8.7.1. Vessel tree visibility

Endpoint (1st Secondary endpoint)
Proportion of contrast-enhanced DE-CBCT rated non-inferior (i.e. equal or superior) vessel visibility compared to CTA (reference standard).

Applicable subjects
All subjects with a contrast enhanced DE-CBCT scan and diagnostic CT angiography.

Data
- Radiologist rating
  - Inferior/Equal/Superior
    - Distal ICA (dICA)
    - A1-A2
    - Lenticulostriate arteries

- M1
- M2
- M3-M4
- Distal Vertebrals
- Basilar
- Basilar perforating branches
- AICA-PICA-SCA
- P1-P2

Analysis
Images are evaluated by radiologists using CT angiography as reference standard and the proportion of equal or superior vessel visibility rating in abovementioned vessel territories is defined.

Hypothesis:

H_0: $\pi_2 \leq 0.80$
H_1: $\pi_2 > 0.80$

Where π_2 is the observed proportion of equal or superior vessel visibility and 0.80 is the performance goal.

8.7.2. Intracranial hemorrhage detection accuracy

Endpoint (2nd Secondary endpoint)
Accuracy of DE-CBCT to determine the presence of intracranial hemorrhage using neCT as the reference standard.

Applicable subjects
All subjects in the study.

Data
- Intracranial hemorrhage
  - Yes / No

Analysis
Images are evaluated by radiologists using neCT as reference standard and the hemorrhage detection accuracy is defined.

Hypothesis:

H_0: $\pi_3 \leq 0.80$
H_1: $\pi_3 > 0.80$

Where π_3 is the observed intracranial hemorhage accuracy and 0.80 is the performance goal.

8.8. Additional Objectives – 3D diagnostic imaging

8.8.1. Ischemic stroke diagnostic accuracy, vessel tree visibility and hemorrhage detection accuracy compared to regular CBCT

Applicable subjects, data and analysis same to that of primary and secondary endpoints, but using conventional CBCT image data (acquired from the top layer of the investigational device) as reference.

8.8.2. Characterization of brain tissue as normally perfused, at risk (penumbra) or infarcted

Applicable subjects
Subjects diagnosed with ischemic stroke.

Data
- mCTA collateral score
  - Side: Left / Right
  - Score: 1 to 5
- ASPECTS score - CBV, MTT, CBF, TTP, Tmax or exploratory measurements
  - Side: Left / Right
  - Score: 1 to 10
  - Location - L, C, IC, I, M1, M2, M3, M4, M5, M6
- Infarct, penumbra and normally perfused tissue
  - Volume segmentation in ml

Analysis
Images are evaluated by radiologists using mCTA or CTP as reference standard. This is an exploratory objective.

8.8.3. Characterization of intracranial hemorrhage

Applicable subjects
Subjects diagnosed with intracranial hemorrhage.

Data
Extraaxial or Intraaxial
- Extraaxial: SAH / SDH / EDH
  - Small, medium or extensive (SAH)
  - Maximum width (SDH/EDH)
- Intraaxial: Contusion/deep/lobar/cerebellum/brainstem/intraventricular
  - Volume segmentation in ml

Hemorrhagic transformation of ischemic stroke
- HI – HI1 or HI2
- PH – PH1 or PH2
- Iodine vs blood – Majority/Minority or Equal

Analysis
Images are evaluated by radiologists using CT and/or DECT as reference standard.

8.8.4. Characterization of intracranial thrombus

Applicable subjects
Subjects with an intracranial thrombus on CT.

Data
Localisation
- Side: Left / Right
- Localisation of thrombus: dICA, M1-M2, M3-M4, A1-A2
- Attenuation of thrombus (HU)
- Homogenous/heterogenous attenuation

- Size: In mm as seen in maximum intensity projection (MIP)
  - Non contrast scan
  - Contrast enhanced scan (perceived filling defect)

Inferior, Equal or Superior

- Perceived ability to identify thrombus

Analysis
Images are evaluated by radiologists using CT and/or DECT as reference standard.

8.8.5. Separation of grey and white matter, and iodine from blood and calcium

Applicable subjects
All subjects.

Data
Possible / Not possible
Inferior, equal or superior

- Grey vs white matter (insula, basal ganglia, cortex, cerebellum)
- Blood vs iodine
- Calcium vs iodine
- Blood vs calcium

Analysis
Images are evaluated by radiologists using CT and/or DECT as reference standard. Proportion rated "possible" as well as equal or superior compared to reference standard is defined.

8.8.6. Assessment of novel segmentation and reconstruction techniques

Applicable subjects
All subjects.

Data

- Separate, delineate infarcted and viable brain tissue
- Identify thrombus location
- Separate, delineate infarcted tissue from tissue at risk and normally perfused tissue

Analysis
This is an exploratory objective. Reference standards include commercially available CT segmentation software from concurrent CT.

8.9. Additional Objectives – 3D image quality parameters

8.9.1. Objective image quality parameters

Applicable subjects
All subjects.

Data
HU (or equivalent), standard deviations, CNR and SNR

- Central vs peripheral location in the image
- Water

- Fat
- Grey matter
- White matter
- Blood
- Iodine
- Calcium (bone)

Analysis
Absolute numerical variables, mean and standard deviations of image quality indexes will be compared to reference standards (CT, DECT, CBCT).

8.9.2. Subjective image quality parameters

Applicable subjects
All subjects.

Data
Yes / No: Visualization of
- Whole cerebrum
- Whole cerebellum
- Whole skull base
- Vessels after intravenous contrast media

Inferior, equal or superior
- Sharp reproduction of the border between white and grey matter
  - Supratentorial
  - Infratentorial
- Sharp reproduction of the basal ganglia
- Sharp reproduction of the ventricular system
- Sharp reproduction of the cerebrospinal fluid space around the mesencephalon
- Sharp reproduction of the cerebrospinal space over the brain (subcalvarial space)
- Sharp reproduction of the great vessels and choroid plexuses after iv contrast media
  - Sharpness of large arteries (smoothness of vessel wall)
  - Visibility of small arteries (side branches)
  - Discrimination of crossing arteries/perforators
  - Venous filling

Analysis
This assessment is based on the European Guidelines on Quality Criteria for Computed Tomography (34). Images are evaluated by radiologists using CT, CBCT and/or DECT as reference standard.

8.9.3. Image artefacts, especially near bony structures

Applicable subjects
All subjects.

Data
More, equal or less
- Near skull base
- Near convexity
- Posterior fossa
- Artifacts from metal devices, coils, clips, embolization material

Analysis
Images are evaluated by radiologists and compared to reference standards (CT, DECT, CBCT).

8.10. Additional objectives - Safety

8.10.1. Radiation exposure and iodine contrast agent dose

Endpoint
Reported radiation exposure and iodine contrast agent dose compared to reference standards.

Applicable subjects
All subjects.

Data
- Radiation dose in relevant exposure measures
  - Patient radiation exposure – radiation exposure index (e.g. air kerma and CTDI)
  - Dose-related data (e.g. tube kilovoltage) will be collected.
- Iodine dose in ml

Analysis
The patient radiation dose exposure (absorbed organ dose and effective dose) is estimated based on the radiation-dose related data registered by the x-ray machine during the performed clinical procedures. Values are compared with reference standards.

8.10.2. Adverse events

Objective
Report all adverse events.

Endpoint
Adverse events, including information of the seriousness, treatment needed, resolution and relevant judgment concerning the causal relationship with the investigational devices, comparator or procedure will be summarized for safety information.

Analysis
The objective is descriptive with no performance requirements and no sample size has been calculated.
All subjects will be included in this analysis.

All adverse events will be presented in a tabular format.

8.10.3. Adverse Device Effects

Objective
Adverse device effects, including information of the seriousness, treatment needed, resolution and relevant judgment concerning the causal relationship with the investigational devices or procedure will be summarized for safety information.

Endpoint
Adverse device effects, including information of the seriousness, treatment needed, resolution and relevant judgment concerning the causal relationship with the investigational devices or procedure will be summarized for safety information.

Analysis
The objective is descriptive with no performance requirements and no sample size has been calculated. All subjects will be included in this analysis.

All adverse device effects will be presented in a tabular format.

8.10.4. Device Deficiencies that could have led to Serious Adverse Event

Objective
Device deficiencies that could have led to Serious Adverse Events, including any corrective actions taken during the study, if any, will be summarized for safety information.

Endpoint
Device deficiencies that could have led to Serious Adverse Events, including any corrective actions taken during the study, if any, will be summarized for safety information.

Analysis
The objective is descriptive with no performance requirements and no sample size has been calculated. All subjects will be included in this analysis.

All device deficiency that could have led to a serious adverse device effect will be presented in tabular format.

9. Data management

The handling of data, including data quality assurance, will comply with regulatory guidelines (for example GCP and ISO 14155) and the sponsor's SOPs and work instructions. All steps and actions taken regarding data management and quality assurance will be documented in the sponsor's SOPs and data handling guidelines.

A secure image data repository will be set up at Karolinska University Hospital, the access to which will be provided through IntelliSpace Discovery (ISD) that will serve as the interfacing client for managing and logging the access of data by authorized personnel involved in this study. No additional software will be required by the user to access the data as the ISD client runs in chrome web browser with a zero footprint i.e., no data will be stored on user's computer while using the ISD interface.

Electronic Case Report Form (e-CRF) will be used to collect medical history, subjects demographics, procedure related informaton, protocol deviations, adverse events and device deficiencies. The e-CRF will be used for data review, data cleaning and issuing and resolving queries. This e-CRF is a web-based e-CRF which is password protected and is CFR part 11 compliant. At the end of the study the data will be stored as a frozen dataset and will be retained.

The e-CRF data from the subjects will be key-coded (pseudo anonymized). The information related to the subjects (like name) is kept separately in the enrollment log at the hospital. Date and time of the procedure and date of discharge will be collected. Patient dose data will not contain any patient names or numbers. Procedure date and time will be used to link the dose data to the corresponding CRF data.
Exported (image) data will be de-identified. The remaining data will be de-identified.
The data will be collected and stored in a secure location.

Completed report forms will be verified against source data and visually checked by the study monitor for completeness, consistency, and legibility.

All adverse event terms recorded on the report forms will be entered into the safety database. All data on the adverse events will be entered into a validated database. Edit checks will be implemented to ensure data quality and accuracy. Responses to requests for further clarification of data recorded in the reports will be answered, dated, and electronically signed by the investigator. Changes will be implemented in the database and the data review and validation procedures will be repeated as needed.

At the end of the study, the database will be locked and the data will be released for reporting and statistical analysis.

9.1.1. Confidentiality

The investigator and institution involved in this study will only provide direct access to source data and documents to the steering committee, and to appropriate authorities for the purposes of monitoring, audit, ethics committee review or regulatory inspection. Each subject taking part in the study will have agreed explicitly to such access in writing.

All subject data will always be treated with strict adherence to professional standards of confidentiality. All reports and communications relating to subjects in the study will identify the subjects by their subject ID number only.

9.1.2. Source Documentation

Investigators are required to prepare and maintain adequate and accurate case histories, recording all observations and other data pertinent to the research on each subject.

9.2. Monitoring Plan

Monitoring will be performed by a trained person appointed by Philips to ensure compliance with the Clinical Research protocol, applicable national regulations and international standards, patient safety and data validity. Details of the Monitoring Plan can be found in the Monitoring Plan [REF-2]. The Sponsor may designate one or more individuals to monitor the progress of a clinical study. The Sponsor may also delegate the monitoring responsibilities to a third party. However, the Sponsor remains ultimately responsible for the conduct of the study. The Institution is responsible for the appropriate de-identification of subject data. The Investigation site should provide access to the source data of the subjects.

The first visit will occur as soon as possible after the first subject is enrolled at the study site. The monitoring schedule is based on the following considerations: enrollment rate, study compliance at the center, magnitude of data corrections required, complexity of the Research, IRB/MEC request, audit/inspection.

The monitor activities include:

- Check that the study is conducted, recorded and reported in compliance with this research protocol, , the good clinical practice, and applicable regulations. Acts to oversee the progress of the study.
- Check signed and dated informed consent of the subjects and check that this is signed before any study-related procedures are undertaken.
- Ensure that essential documents (e.g. contract, MEC/IRB approval) are maintained in the Site Regulatory File.
- Ensure recording of deviations from protocol and store in Site Regulatory File or CRF.
- Ensure that all adverse events and device deficiencies are reported to the sponsor, and all serious adverse events and device deficiencies that could have led to a serious adverse device effect are reported to the sponsor without unjustified delay.
- Ensure that adverse event and device deficiency are reported to the MEC/IRB and Competent Authority within the required timeframe, if required.
- Ensure that the principal investigator is informed and knowledgeable of all relevant document updates concerning the clinical research (e.g. research protocol and Investigator Brochure). Ensure that amendments to the protocol and/or Investigators Brochure are provided to the MEC/IRB and/or Competent Authority by the principal investigator.
- Ensure device accountability.
- No structural source data verification is anticipated.

Names of the monitor(s) can be found inAppendix II of this protocol. An update of this list can be provided to the site under separate cover.

9.3. Retention period

The investigator shall maintain the records related to this study during the investigation and for a period according to the national regulation.
Philips will maintain the records for a period of device End of Life (EoL) plus 15 years.

The sponsor and principal investigator shall take measures to prevent accidental or premature destruction of these documents.

9.4. AUDITS/INSPECTIONS

An independent audit by external regulatory agencies from the investigator's own country or from abroad may take place at any time during or after the study. This may include on- site inspections and source data verification at the investigator's hospital.

10. Amendments to the Clinical Research Protocol

Non-significant changes of the Clinical Reasearch protocol may be included (minor logistical or administrative changes not effecting the rights, safety and well being of human subjects or not related to the clinical Research objectives or endpoints), without prior approval. A simple notification to the MEC and where appropriate regulatory authorities will be made by the Sponsor. Significant changes (such as device modifications, study procedures) shall be discussed with the principal investigator and steering committee prior approval. All changes will be documented with a justification and described in the latest version of the Clinical Research Protocol. Significant changes shall be authorized by the MEC and the Competent Authority before implementation. Exempt from this requirement are measures which have to be taken immediately in order to protect the participants. In such circumstances, the investigator must notify the EC or IRB and steering committee and must describe the conditions necessitating the departure from the protocol and the outcome of the emergency intervention in a written report. The steering committee will determine whether the subject is to continue in the study or be considered a protocol violation.

11. Deviations from the clinical Research protocol

The Investigator is not allowed to deviate from the Clinical Research Protocol or to enroll subjects that do not comply with all inclusion and exclusion criteria.

Under emergency circumstances, deviations from the Clinical Research Protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the MEC. Such deviations shall be documented and reported to the sponsor and the MEC as soon as possible
Reporting requirements are further specified in section 14.2.

All deviations from the Clinical Research Protocol will be documented with date, subject, reason, actions taken and if the deviation affects subject's rights, safety and well being or the scientific integrity of the clinical Research. The deviation shall be notified to the Sponsor as soon as possible via the e-CRF. Deviations will be reviewed by the sponsor and in case of serious or repetitive deviations a corrective action plan may represent a need to initiate a corrective action plan with the principal investigator. In some cases, necessitate suspension of enrollment at the site or ultimately the principal investigator will be disqualified.

12. Device accountability

Access to the investigational device shall be controlled and the investigational devices shall be used only in the clinical Research and according to the Clinical Research Protocol.

The sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational device to the Investigation sites until return or disposal.

The principal investigator shall keep records documenting the receipt, installation, use, return and disposal of the investigational device, including date of receipt, identification of each investigational device and date on which the investigational device was returned.

13. Statements of compliance

This clinical Research shall be conducted in accordance with the clinical Research protocol, and with the ethical principles that have their origin in the Declaration of Helsinki and all applicable regional and/or national regulations. Furthermore, clinical research conducted in the European Union shall be conducted in accordance with the International Standards SS- EN ISO 14155: 2011 Clinical research of medical devices for human subjects – Good clinical practice and the Medical Device Directive (MDD). As of 26 May 2020 the reporting of serious adverse events and device deficiencies shall be carried out in accordance with the Medical Device Regulation (MDR).

This clinical Research shall not be started prior to obtaining a favorable opinion from a Medical Ethics Committee (MEC)/Institutional Review Board (IRB) and Regulatory authority, if required. Any additional requirements imposed by the MEC/IRB and/or regulatory authority shall be followed.

.

Insurance shall be provided for the subjects participating in this clinical trial according to local law.

14. (Early) termination and Study termination

There are no provisions or interim analyses planned that can result in an early termination of the trial. The principal investigator, EC, or regulatory authority may suspend or prematurely terminate participation in the clinical research at the Investigation sites for which they are responsible.
Any signs of unknown or increased risks for the subjects will be discussed by the sponsor and investigator to assess the impact on the subjects and clinical research. If suspicion of an unacceptable risk to subjects arises during the clinical research, or when so instructed by the EC or regulatory authorities, the sponsor shall suspend the clinical research while the risk is assessed.

The sponsor shall terminate the clinical research if an unacceptable risk is confirmed.
If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The principal investigator and sponsor shall keep each other informed of any communication received from either the EC or the regulatory authority.

Serious or repetitive occurrence of deviations from study protocol or non-compliance with regulations may also be reason for early termination or suspension of a study site.

After the last patient has been included and investigated with the investigational device the clinical investigator and Sponsor will inform the EC and regulatory authority about end of inclusion.

An early termination and/or study termination of the clinical investigation will be documented and shared with the EC and regulatory authority.

15. Publication policy

It is the joint responsibility of the investigator and sponsor to submit the clinical Research data for publication. Approximately two publications in peer reviewed journals such as Stroke, Radiology or AJNR. Each investigator is allowed to publish their results. All investigators that contributed to the content of the publication should be included in the author list.

This clinical investigation will be recorded on ClinicalTrials.gov.

16. STUDY FINANCES

The NEXIS project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 780026. The funding covers salary for involved personnel during planning and conduction of the clinical trial. This is defined for all participating members in the grant agreement No 780026.

17. STUDY REPORT

Study report will be written by the sponsor according to ISO 14155: 2011.

After completion of the investigation, the sponsor will provide a study report approved and signed by the principal investigator.

18. Literature

1. WHO. Preventing chronic diseases: a vital investment Geneva, Switzerland: World Health Organization; 2005 [
2. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol. 2009;8(4):355-69.
3. Johnston SC, Mendis S, Mathers CD. Global variation in stroke burden and mortality: estimates from monitoring, surveillance, and modelling. Lancet Neurol. 2009;8(4):345-54.
4. Smith S, Horgan F, Sexton E, Cowman S, Hickey A, Kelly P, et al. The cost of stroke and transient ischaemic attack in Ireland: a prevalence-based estimate. Age Ageing. 2012;41(3):332-8.
5. Riedel CH, Zimmermann P, Jensen-Kondering U, Stingele R, Deuschl G, Jansen O. The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. Stroke. 2011;42(6):1775-7.
6. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet (London, England). 2016;387(10029):1723-31.
7. Koopman MS, Berkhemer OA, Geuskens R, Emmer BJ, van Walderveen MAA, Jenniskens SFM, et al. Comparison of three commonly used CT perfusion software packages in patients with acute ischemic stroke. Journal of neurointerventional surgery. 2019.
8. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. N Engl J Med. 2018;378(1):11-21.
9. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. N Engl J Med. 2018;378(8):708-18.
10. Campbell BCV, Ma H, Ringleb PA, Parsons MW, Churilov L, Bendszus M, et al. Extending thrombolysis to 4.5-9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. Lancet (London, England). 2019;394(10193):139-47.
11. Ma H, Campbell BCV, Parsons MW, Churilov L, Levi CR, Hsu C, et al. Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke. N Engl J Med. 2019;380(19):1795-803.
12. Garcia-Tornel A, Carvalho V, Boned S, Flores A, Rodriguez-Luna D, Pagola J, et al. Improving the Evaluation of Collateral Circulation by Multiphase Computed Tomography Angiography in Acute Stroke Patients Treated with Endovascular Reperfusion Therapies. Interv Neurol. 2016;5(3-4):209-17.
13. Menon BK, d'Esterre CD, Qazi EM, Almekhlafi M, Hahn L, Demchuk AM, et al. Multiphase CT Angiography: A New Tool for the Imaging Triage of Patients with Acute Ischemic Stroke. Radiology. 2015;275(2):510-20.
14. d'Esterre CD, Trivedi A, Pordeli P, Boesen M, Patil S, Hwan Ahn S, et al. Regional Comparison of Multiphase Computed Tomographic Angiography and Computed Tomographic Perfusion for Prediction of Tissue Fate in Ischemic Stroke. Stroke. 2017;48(4):939-45.

15. Pomerantz SR, Kamalian S, Zhang D, Gupta R, Rapalino O, Sahani DV, et al. Virtual monochromatic reconstruction of dual-energy unenhanced head CT at 65-75 keV maximizes image quality compared with conventional polychromatic CT. Radiology. 2013;266(1):318-25.
16. Neuhaus V, Abdullayev N, Grosse Hokamp N, Pahn G, Kabbasch C, Mpotsaris A, et al. Improvement of Image Quality in Unenhanced Dual-Layer CT of the Head Using Virtual Monoenergetic Images Compared With Polyenergetic Single-Energy CT. Investigative radiology. 2017;52(8):470-6.
17. Lennartz S, Laukamp KR, Neuhaus V, Grosse Hokamp N, Le Blanc M, Maus V, et al. Dual-layer detector CT of the head: Initial experience in visualization of intracranial hemorrhage and hypodense brain lesions using virtual monoenergetic images. European journal of radiology. 2018;108:177-83.
18. Postma AA, Das M, Stadler AA, Wildberger JE. Dual-Energy CT: What the Neuroradiologist Should Know. Curr Radiol Rep. 2015;3(5):16.
19. Grams AE, Djurdjevic T, Rehwald R, Schiestl T, Dazinger F, Steiger R, et al. Improved visualisation of early cerebral infarctions after endovascular stroke therapy using dual-energy computed tomography oedema maps. European radiology. 2018;28(11):4534-41.
20. Noguchi K, Itoh T, Naruto N, Takashima S, Tanaka K, Kuroda S. A Novel Imaging Technique (X-Map) to Identify Acute Ischemic Lesions Using Noncontrast Dual-Energy Computed Tomography. J Stroke Cerebrovasc Dis. 2017;26(1):34-41.
21. Taguchi K, Itoh T, Fuld MK, Fournie E, Lee O, Noguchi K. "X-Map 2.0" for Edema Signal Enhancement for Acute Ischemic Stroke Using Non-Contrast-Enhanced Dual-Energy Computed Tomography. Investigative radiology. 2018;53(7):432-9.
22. Demeestere J, Scheldeman L, Cornelissen SA, Heye S, Wouters A, Dupont P, et al. Alberta Stroke Program Early CT Score Versus Computed Tomographic Perfusion to Predict Functional Outcome After Successful Reperfusion in Acute Ischemic Stroke. Stroke. 2018;49(10):2361-7.
23. Haranhalli N, Mbabuike N, Grewal SS, Hasan TF, Heckman MG, Freeman WD, et al. Topographic correlation of infarct area on CT perfusion with functional outcome in acute ischemic stroke. J Neurosurg. 2019:1-9.
24. Schregel K, Tsogkas I, Peter C, Zapf A, Behme D, Schnieder M, et al. Outcome Prediction Using Perfusion Parameters and Collateral Scores of Multi-Phase and Single-Phase CT Angiography in Acute Stroke: Need for One, Two, Three, or Thirty Scans? J Stroke. 2018;20(3):362-72.
25. Bourcier R, Goyal M, Liebeskind DS, Muir KW, Desal H, Siddiqui AH, et al. Association of Time From Stroke Onset to Groin Puncture With Quality of Reperfusion After Mechanical Thrombectomy: A Meta-analysis of Individual Patient Data From 7 Randomized Clinical Trials. JAMA Neurol. 2019;76(4):405-11.
26. Saver JL. Time is brain--quantified. Stroke. 2006;37(1):263-6.
27. Psychogios MN, Behme D, Schregel K, Tsogkas I, Maier IL, Leyhe JR, et al. One-Stop Management of Acute Stroke Patients: Minimizing Door-to-Reperfusion Times. Stroke. 2017;48(11):3152-5.
28. Brehm A, Tsogkas I, Maier IL, Eisenberger HJ, Yang P, Liu JM, et al. One-Stop Management with Perfusion for Transfer Patients with Stroke due to a Large-Vessel Occlusion: Feasibility and Effects on In-Hospital Times. AJNR American journal of neuroradiology. 2019;40(8):1330-4.
29. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP publication 103. Ann ICRP. 2007;37(2-4):1-332.
30. 1990 Recommendations of the International Commission on Radiological Protection. Ann ICRP. 1991;21(1-3):1-201.
31. Folkhälsomyndigheten. Folkhälsan i Sverige 2016 2016 [Available from: https://www.folkhalsomyndigheten.se/publicerat-material/publikationsarkiv/f/folkhalsan-i-sverige-2016/.
32. SURF. Nationella Rekommendationer för Jodkontrastmedel: Svensk Förening för Medicinsk Radiologi; 2017 [Available from: http://www.sfbfm.se/sidor/kontrastmedelsrekommendationer/.
33. MJ Campbell SS. Parametric and Non-parametric tests for comparing two or more groups. Public Health Action Support Team (PHAST), HealthKnowledge. 2016.

34. Bongartz G GS, Jurik AG, et al. European Guidelines on Quality Criteria for Computed Tomography. EUR (Luxembourg). 1999.
35. Pexman JH, Barber PA, Hill MD, Sevick RJ, Demchuk AM, Hudon ME, et al. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. AJNR American journal of neuroradiology. 2001;22(8):1534-42.
36. Tan IY, Demchuk AM, Hopyan J, Zhang L, Gladstone D, Wong K, et al. CT angiography clot burden score and collateral score: correlation with clinical and radiologic outcomes in acute middle cerebral artery infarct. AJNR American journal of neuroradiology. 2009;30(3):525-31.
37. Berkhemer OA, Jansen IG, Beumer D, Fransen PS, van den Berg LA, Yoo AJ, et al. Collateral Status on Baseline Computed Tomographic Angiography and Intra-Arterial Treatment Effect in Patients With Proximal Anterior Circulation Stroke. Stroke. 2016;47(3):768-76.
38. Zaidat OO, Yoo AJ, Khatri P, Tomsick TA, von Kummer R, Saver JL, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. Stroke. 2013;44(9):2650-63.
39. Gerber JC, Miaux YJ, von Kummer R. Scoring flow restoration in cerebral angiograms after endovascular revascularization in acute ischemic stroke patients. Neuroradiology. 2015;57(3):227-40.

Appendix I: List of Investigators and sites

Update of this list can be provided to the Investigation site under separate cover.

Table 1: List of principle Investigators

Name Principal Investigator(s)	Name and address investigation site(s)
[redacted]	

Table 2: List of Clinical coordinating investigator

Name Principal Investigator(s)	Name and address investigation site(s)
[redacted]	

Table 3: CRO and partners involved in the clinical Research

Name and address other Institution(s)
[redacted]

Appendix II: List of monitor(s)/Clinical Study Manager

Update of this list can be provided to the Investigational sites under separate cover.

Table 2: List of monitor(s)/clinical study manager

Name Monitor(s)/Clinical study manager	Contact Information of Monitor(s)
[redacted] Clinical study manager/Monitor Emergency contact	[redacted]

Appendix III: DECLARATION OF HELSINKI

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, South Africa, October 1996 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification on paragraph 29 added) 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification on Paragraph 30 added) 59th WMA General Assembly, Seoul, Korea, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection.

These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. The committee may make no change to the protocol without consideration and approval.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison

with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions

about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of

research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made.

Appendix IV: Reporting requirements to MEC and Competent Authority

1. ***Reporting requirements in Sweden***

Investigators have to report all SAEs to the Sponsor immediately.

Investigator shall report to the MEC:

Condition for reporting to MEC	Country of occurrence	Timeline for reporting to MEC
Adverse Events (AE) and Adverse Device Effects (ADE) If the Investigator is made aware of any SAEs after departure from study, these should also be reported provided the SAE is considered related to the investigational system. The site would then provide a completed SAE form within 1 business day and the event will be followed until resolution, or until adequate stabilization is met.	Sweden	1 day
Serious Adverse Events (SAE) and Serious Adverse Device Effects (SADE) The investigator must notify all serious adverse events immediately after becoming aware of the event (no later than 24 hours from being notified of the event). Any Serious Adverse Event (SAE) or Serious Adverse Device Effect (SADE) must be reported "in writing" within 5 days.	Sweden	1 day (notify) 5 days (in writing)
Should potential SAEs or SADEs be discovered during the study of which the investigator was not aware, the appointed representative/ study monitor will provide relevant documentation within 10 days from becoming aware of the event for the investigator's review and submission to the ethics committee, if applicable	Sweden	10 days
All device failures, malfunctions, misuse and near incidents (as defined below) will be documented on the electronic case report form and reported to within 1 working day after the investigator becomes aware of the event and reported to the IRB as required.	Sweden	1 day

Sponsor shall report to Competent Authority:

- all serious (assured or suspected) adverse events, known as SAE (see MEDDEV 2.7/3)
- substantial changes to the investigation plan
- changes regarding the coordinating investigator or principal investigator
- changes regarding participating investigation sites
- interruptions for reasons of safety in the investigation with an explanation
- restart of interrupted investigation with a justification
- if the investigation was terminated prematurely with a justification
- when the clinical investigation was completed

All serious adverse events must be fully recorded and immediately reported, but no later than 2 calender days after awareness by sponsor of a new reportable event or new information in relation with an already reported event to all the competent authorities in the Member States where the clinical investigation is being conducted. The sponsor and the principal investigator must notify each other on an ongoing basis in accordance with SS-EN ISO 14155:2011 and the applicable investigation plan.
All reports of serious adverse events (SAE/SADE) for medical devices should be submitted to the MPA in electronic format by using the online e-service (see link to the right).

- In the e-service drop down menu for Recipient, please choose the “SAE Report Clinical Investigation of Medical Device”option
- Add your name and e-mail address in the mandatory fields
- Attach the file with the report
- Please indicate both the MPA reference number and CIV ID of the clinical investigation in the message field.

The notification of amendments made to the investigation plan and the participating investigator(s) must be dated and signed by the sponsor and the relevant principal /coordinating investigator.
Use online e-service (see Notification of clinical investigations) to also electronically submit notifications of amendments. When using the e-service it is required that the notification form is resubmitted, specify in a cover letter if the form is updated to a new version.

Appendix V: Study Scales

The following measurement scales will be used in this clinical study:

ASPECTS - Alberta Stroke Program Early CT Score (35). This is a 10-point quantitative ordinal score used to assess early ischemic changed on non-contrast enhanced CT. It is used as a reproducible grading system in patients with suspected large vessel occlusion as part of the assessment of patients that might be eligible for thrombectomy.

mCTA Collateral Score (13, 36, 37) - Scoring system used for evaluation of collateral circulation in the case of a large vessel occlusion, which correlates with functional outcome and is used in combination with other markers to select patients that could benefit from thrombectomy.

mTICI - modified thrombolysis in cerebral infarction (TICI) score. This parameter will be reported using the mTICI (inclusive of the 2C rating) scale (38, 39).