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CLINICAL INVESTIGATION PLAN (CIP)

Clinical Investigation Title:	Validation of 3D Synthetic MRI for neuroimaging – prospective, multicenter, multireader investigation
Clinical Investigation Code:	CIP-003
Code Name:	Curie
Investigational Device(s):	SyMRI 15 (3D)
Coordinating Investigator:	Dr. Jeffrey Miller Phoenix Children's Hospital 1919 East Thomas Road Phoenix, AZ 85016 USA
Sponsor:	SyntheticMR AB (publ) Storgatan 11 582 23 Linköping Sweden
Date:	21-December-2023

Revision	**Version History**
K	Investigational Device renamed
J	Update of intended purpose and claims of investigational device, handling of incidental findings, statistical design, method and analytical procedure
I	Recruitment of healthy adult controls added and update of pediatric total
H	Intended purpose of device updated, endpoints changed accordingly.
G	Internal version, never released.
F	Inclusion criterion number 5 updated (subject information can be given in English or Spanish). Table 6 with acquisition parameters updated.
E	Internal version, never released. Not used in CIP-003 study and not distributed to sites.
D	Pediatric population divided in two sub-groups (Anesthesia and No-Anesthesia)
C	Updated according to IRB request 27-May-2022

B	Updated according to IRB request 23-May-2022
A	First release

This clinical investigation will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Furthermore, the clinical investigation will be performed in compliance with ISO 14155:2020, Regulation (EU) 2017/745 and applicable regional or national US regulations.

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This Clinical Investigation Plan contains privileged or confidential information, which is the property of the Sponsor. Information may not be disclosed to a third party without written authorization from the Sponsor

1 SYNOPSIS

NAME OF THE SPONSOR:
SyntheticMR AB (publ)
Storgatan 11
582 23 Linköping
Sweden

CLINICAL INVESTIGATION TITLE:

Validation of 3D Synthetic MRI for neuroimaging – prospective, multicenter, multireader investigation

CLINICAL INVESTIGATION CODE:

CIP-003

INVESTIGATIONAL DEVICE(S):

SyMRI 15 (3D)

OVERALL CLINICAL INVESTIGATION DESIGN:
This is a pre-market, prospective, multicenter, reader clinical investigation in which multiple blinded readers will assess accuracy and image quality of synthetic and conventional 3D MR images to evaluate the performance of the SyMRI 15 (3D) software when used for visualization of the brain. The investigation consists of two parts, the image acquisition and the image review.

For the image acquisition part, subjects will be recruited at up to 6 sites in the US. Subjects will consist of patients aged 0-99 years, scheduled for MRI of the brain, and healthy controls. In total 180 evaluable subjects will be included. Approximately 120 will be patients, whereof 65 adult subjects (age 18-99 years) and 55 pediatric subjects (age 0-17 years). The pediatric population will consist of two groups, one with subjects receiving anesthesia (Sub-group Anesthesia) and one with subjects not receiving anesthesia (Sub-group No-anesthesia). In addition, a group of approximately 60 evaluable, healthy adult controls will be included. The aim is to include subjects covering a broad range of pathologies reflecting the intended use population.

All subjects will undergo an MRI scan of the brain, using a fixed set of scanning parameters on a 3T MRI scanner from Philips. From each subject, the following sequences will be acquired for the investigation:

- 3D T1w (conventional image)
- 3D T2w (conventional image)
- 3D T2w FLAIR (conventional image)
- 3D-QALAS (data for generation of synthetic images)

For the image review part of the investigation, the software SyMRI 15 (3D) will be used to post-process data from the 3D-QALAS acquisition to generate synthetic T1w and T2w images. For each subject, conventional and synthetic images will then be assessed by 5 blinded, experienced neuroradiologists who will assess the images with regards to image quality, legibility of anatomical structures, artifacts, and radiological findings. The readings will be separated into two reading sessions with a 4-week memory-washout period.

Results will be analyzed for the whole cohort, a pediatric sub-population (subjects aged 0-17 years) and an adult sub-population (subjects aged 18-99 years).

INCLUSION AND EXCLUSION CRITERIA:
Inclusion Criteria
The subjects have to meet all of the following criteria to be eligible to participate in the clinical investigation:

	INCLUSION CRITERIA
1	Any gender, aged 0-99 years
2	Subject scheduled for MRI of the brain **OR** Healthy control with passed screening form
3	Subject suitable for MRI as judged by investigator
4	Subject agrees to 5-20 min extra MRI scan time
5	Subject able to understand written and verbal information in English or Spanish
6	Provision of informed consent (and assent if applicable)

Exclusion Criteria
Subjects meeting any of the following criteria will not be permitted to participate in the clinical investigation:

	EXCLUSION CRITERIA
1	Have contraindication(s) to MRI scanning per the routine MR Safety Screening policy of the investigational site
2	Have severe trauma, disability or pre-existing pathology that is expected to interfere with normal conduct of MRI scanning or complete scanning of the brain
3	Have medical condition(s) such as those requiring urgent medical care that, in the opinion of a physician investigator, would prevent safe participation in the study
4	Adult subjects (aged 18-99 years) in need of anesthesia during MRI scanning
5	Pregnancy at time of enrollment determined according to the clinic's MR Safety Screening policy
6	Previous enrollment in this investigation

OBJECTIVES:
Primary Objective
The primary objective is to:

- demonstrate non-inferiority of synthetic 3D MR images compared to conventional MR images with respect to sensitivity and specificity of pathological findings.

Secondary Objective(s)
The secondary objectives are to demonstrate non-inferiority of synthetic 3D MR images compared to conventional MR images with respect to:

- classification of pathological findings,
- diagnostic accuracy in an adult population, and
- diagnostic accuracy in a pediatric population

Other exploratory objectives are to evaluate:

- legibility of anatomical structures.
- frequency and type of artifacts.
- inter-rater and inter-method agreement, and
- image quality for T1w and T2w images, synthetic 3D MR images compared to conventional MR images

PERFORMANCE AND SAFETY ENDPOINTS:
Primary Performance Endpoint

- Difference in sensitivity of pathological findings (pathological vs normal/no finding) between synthetic and conventional MR images on the full analysis set.
- Difference in specificity of pathological findings (pathological vs normal/no finding) between synthetic and conventional MR images on the full analysis set.

Secondary Performance Endpoints

- Difference in diagnostic accuracy of radiological findings (radiological finding class) between synthetic and conventional MR images on the subgroup of pathological patients. The ground truth is the site-determined diagnosis (radiological finding class).
- Primary and secondary endpoints (sensitivity, specificity, accuracy) in adults (18–99 years).
- Primary and secondary endpoints (sensitivity, specificity, accuracy) in pediatrics (0–17 years).

Exploratory Endpoints

- Legibility of anatomical structures, per structure.
- Presence and type of artifacts, per contrast weighting (T1w, T2w).
- Inter-rater agreement (agreement, kappa coefficient and Gwet's AC1 coefficient) with regards to radiological finding classes.
- Inter-method agreement (agreement, kappa coefficient and Gwet's AC1 coefficient) with regards to radiological finding classes.
- Image quality score per contrast weighting (T1w, T2w).

Safety Endpoints

- Incidence of Adverse Events (AE), Adverse Device Effects (ADE), Serious Adverse Events (SAE), Serious Adverse Device Effects (SADE), Unanticipated Adverse Device Effect (UADE), Unanticipated Serious Adverse Device Effect (USADE) and Device Deficiencies (DD).

STATISTICAL METHODS:

Performance Analysis

Descriptive statistics of subject demographics, characteristics of readers, and performance endpoints will be summarized descriptively at the patient, reader and image level. Continuous variables will be described with mean, standard deviation, median, minimum, and maximum value, and categorical variables with numbers and percentages.

Statistical analyses will be performed on the patient level. Comparisons between conventional and synthetic MR images will be conducted using non-inferiority testing procedures.

The mean difference will be presented with corresponding two-sided 95% confidence interval. Non-inferiority will be established if the lower limit of the two-sided 95% confidence interval for the mean difference (i.e., intercept) is strictly greater than a pre-specified non-inferiority margin. The primary analyses will be performed on the full analysis set. Separate analyses on adult and pediatric sub-populations, and separate analyses by reader, will also be performed.

For the primary and secondary endpoints, a non-inferiority margin of -0.05 will be used. All tests will be one-sided and conducted at significance level α=0.025. In case of a successful non-inferiority test for the two primary performance endpoints, the entire probability mass α=0.025 will be transferred to the secondary performance endpoints in the order specified in Section 10.2.2 Secondary performance endpoints. Non-inferiority will then be declared for all secondary performance endpoints with a successful non-inferiority test until the first encounter of a non-successful non-inferiority test. Estimates and confidence intervals of remaining performance endpoints will be presented descriptively but not considered as confirmatory findings.

Safety Analysis

Safety variables will be summarized descriptively.

Power and sample size
A total of 180 evaluable subjects (90 pathological, 90 controls) and 5 readers will be included in the study to obtain 80% simultaneous power in both primary endpoints using one-sided test, significance level α=0.025, non-inferiority margin -0.05. The calculations are based on the following assumptions:

All tests will be one-sided and conducted at significance level α=0.025. The power for each of the primary endpoints is 90% and power for both primary endpoints simultaneously is 80%. No multiplicity adjustment is needed for the primary endpoints since non-inferiority in both primary endpoints is required to declare non-inferior diagnostic accuracy (sensitivity/specificity) with synthetic MR images compared to conventional MR images. Secondary performance endpoints will be evaluated using a hierarchical testing procedure only if the pass criteria for the primary endpoints is fulfilled.

2 SPONSOR CIP APPROVAL PAGE

The undersigned, hereby confirms that they have read and understood the content of this Clinical Investigation Plan (CIP) and further approves its content.

_____ _____

Ulrik Harrysson
CEO, SyntheticMR

Date (dd-Mmm-yyyy)

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4 ABBREVIATIONS AND ACRONYMS

ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CRO	Contract Research Organization
DMC	Data Monitoring Committee
DMP	Data Management Plan
DMR	Data Management Report
DVP	Data Validation Plan
eCRF	Electronic Case Report Form
EU	European Union
FDA	Food and Drug Administration
GDPR	General Data Protection Regulation
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
ISF	Investigator Site File
ISO	International Organization for Standardization
LAR	Legally Authorized Representative
MDR	Medical Device Regulation – Regulation (EU) 2017/745
MRI	Magnetic Resonance Imaging
PI	Principal Investigator
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SMF	Study Master File
SOP	Standard Operating Procedure
TBD	To Be Decided
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
WMA	World Medical Association

5 INTRODUCTION

This investigation is funded by SyntheticMR AB. A clinical trial agreement is set between the sponsor and each investigational site, detailing roles, and responsibilities.

5.1 Background

Magnetic Resonance Imaging (MRI) is a highly versatile, non-invasive, and widely used medical imaging technique intended for acquiring detailed anatomical information, thereby contributing to the study of the mechanistic underpinnings of both body function and dysfunction. The principle of MRI relies upon every tissue having its own intrinsic physical properties[1]. Briefly, MRI employs powerful magnets that generate a strong magnetic field forcing protons in the body to align with it. Pulsing thereupon a radiofrequency current through the patient triggers the stimulation of the protons, causing them to *spin* out of equilibrium. The MRI sensors can thereafter detect the resulting release of energy as the protons realign with the magnetic field, striving towards returning to their original position, in a phase called relaxation. This measurable energy imbalance differs depending on the physical and chemical properties of the tissue and/or lesion[2]. In general, one MRI acquisition is done for each contrast setting, implying that the patient often undergoes several imaging passes if several contrast settings are needed for the examination. A typical MRI exam takes about 30 to 45 minutes, depending on how many different contrast settings are required. The images are visually examined by the physician post-acquisition. Nowadays, MRI is the gold standard for investigating most affections of the central nervous system and its indications for use are therefore wide-ranging: stroke, epilepsy, brain tumors, infections and inflammation, multiple sclerosis (MS), dementia, metabolic disorders, post-trauma, nerve palsies, and vascular diseases, to name a few[3].

The technology surrounding MRI is developing steadily, and newer quantitative techniques are now available to complement qualitative imaging, altogether resulting in more specific anatomical information[4]. Recent progress in quantitative MRI makes it possible to measure physical properties of the human soft tissue, such as R1 and R2 relaxation rates and proton density (PD), on an absolute scale, altogether in a reasonable acquisition time[1]. In other words, contrast varying synthetic MR images can be produced upon a single acquisition by calculating the expected image intensity with virtual contrast settings[1]. Therefore, this technique may contribute to shortening the duration of the MRI exam[5]. In addition, quantitative MRI approaches allow for a more objective and reproducible evaluation of the tissue than does conventional MRI, the assessment of which is based on the arbitrary signal contrast between tissues[6, 7]. However, the extensive acquisition time deployed to quantify these tissue parameters[1], and the potential emergence of motion artifacts[8] are limitations that deserve to be considered. In this regard, motion artifacts could arise owing to the fact that the quality of synthetic MR images hinges on that of a single acquisition[8] and that the patient's comfort may be impacted by long MR acquisition times[9].

The generation of synthetic MR images using SyMRI, which is most commonly based on the two-dimensional (2D) multi-dynamic multi-echo (MDME) sequence[6, 10], has been previously validated for the brain and proven to be non-inferior to conventional MR images[8]. For example, the MDME sequence has been used for the assessment of different brain diseases, including MS[6, 11], brain infarctions[12], and meningitis[13], among others. However, this sequence, owing to its 2D properties, has a relatively low resolution in the slice direction compared to three-dimensional (3D) acquisition, fact that has likely hampered its use in routine clinical examination.

More recently, efforts have been made to improve the spatial resolution of existing mapping techniques by acquiring the whole-brain data in 3D instead. Compared with a 2D approach, 3D acquisitions enable thinner slices, which are contiguous and easier to interpolate in the slice direction. Furthermore, a 3D acquisition allows visualization of the subject from any orientation, thus enhancing depiction of structures and subsequent more refined characterization of the pathologies[14]. One of these techniques, the so-called 3D-quantification using an interleaved Look-Locker acquisition sequence with a T2 preparation pulse (3D-QALAS) sequence, has been successfully applied to both the heart[15-17] and brain[7, 10, 14, 18, 19] structures, with high-level accuracy, precision, repeatability and reproducibility. In

their study, Fujita et al[7] assessed the reliability of 3D-QALAS sequence-derived parameters values and compared them with those obtained using the MDME sequence. The authors concluded that the method's reliability was high, and was likewise accompanied by high spatial resolution, which enabled the collection of detailed morphological information of the whole brain. In another study by the same authors[18], 3D-QALAS was shown to be reliable for measuring cortical thickness and subcortical volumes in most brain regions. Despite the potential of the 3D-QALAS relaxometry method, current 3D quantitative imaging techniques require long acquisition times, thereby limiting its clinical use. The studies by Fujita et al[14] and Murata et al[10] investigated the addition of the compressed sensing (CS) reduction factor to the process and assessed whether it impacted the 3D-QALAS output quality in the brain. In both studies, the use of CS accelerated the 3D-QALAS scan while preserving tissue quantitative values and the quality of the resulting synthetic images.

SyMRI is a post-processing software medical device intended for use in visualization of soft tissue in the head. The device analyzes input data from MRI systems and utilizes data from supported MR sequences to generate synthetic MR images with multiple contrasts, which can be subsequently adjusted by the user post-acquisition. A 3D version of SyMRI has been developed under research agreement since 2013 when the first feedback related a 3D version of SyMRI was received from the market.

The aim of this prospective, multicenter, multireader clinical investigation is to evaluate the performance of the SyMRI 15 (3D) software compared to conventional 3D MRI when used for visualization of the brain. The objectives are to compare image quality, legibility of anatomical structures, artifact prevalence and inter method agreement of synthetic 3D MR images with conventional 3D images.

The clinical investigation will be conducted in compliance with Declaration of Helsinki, the most current version of ISO 14155 and applicable regional or national regulations. The clinical data retrieved from this clinical investigation will be evaluated and incorporated in the product Clinical Evaluation Report (CER).

6 IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

SyMRI allows the user to generate multiple image contrasts from a single acquisition. This is accomplished by post-processing a multi-delay, multi-echo acquisition (M2D-MDME or 3D-QALAS) into parametric maps. The parametric maps are R1, R2 relaxation rates, and proton density (PD). The inverse relaxation parameters, T1 relaxation time (1/R1), and T2 relaxation time (1/R2) are also provided as parametric maps. The parametric maps can be visualized as contrast weighted MR images, such as T1, T2, PD, and Inversion Recovery (IR) weighted images (including T1-FLAIR, T2-FLAIR, STIR, Double IR, and PSIR weighted images). SyMRI calculates the pixel signal intensity as a function of R1, R2, PD, and desired MR scanner settings, such as echo time (TE), repetition time (TR), and inversion delay time (TI). A number of default settings for TE, TR, and TI are provided, but the user has the ability to change the contrast of the images. SyMRI generates all the different image contrasts from the same parametric maps, derived from the same acquisition. This leads to enhanced image slice registration, owing to the absence of inter-acquisition patient movement. SyMRI provides the user the ability to change the contrast of the images after the acquisition. This is performed by adjusting the TE, TR, and/or TI parameters post-acquisition, to generate the specific contrast desired.

SyMRI also enables the users to obtain volumetric information in the head, including white matter (WM), grey matter (GM), cerebrospinal fluid (CSF), Myelin correlated (MyC) partial volume, brain parenchyma (BP) and intracranial cavity (IC). This is accomplished by using tissue definitions based on the parametric maps. The tissue definitions provide tissue partial volume, or tissue fraction, per voxel. SyMRI also provides image processing tools to extract the values of the parametric maps, and tissue partial volume, per individual pixel, per region of interest, or the entire imaging volume.

SyMRI is intended to be used on data produced by any of the following acquisition sequences:

- M2D-MDME sequence data from GE MAGiC
- M2D-MDME sequence data from Philips SyntAc
- M2D-MDME sequence data from Siemens TSE_MDME
- 3D-QALAS sequence data from Philips 3D-QALAS

In this investigation, the 3D-QALAS sequence created by Philips Healthcare will be used. The 3D-QALAS technique is based on a 3D spoiled Turbo Field Echo sequence that contains multiple dynamics which are preceded by pre-pulses, T2-prep and inversion RF pulses. The signal amplitude per pixel in the raw data generated by the 3D-QALAS sequence is then used to calculate the PD, T1 and T2 values by SyMRI and can subsequently be transformed into routine imaging contrasts.

6.1 Manufacturer

SyntheticMR AB (publ)
Storgatan 11
SE-582 23 Linköping, Sweden

6.2 Identification of Investigational Medical Device

SyMRI 15 (3D)

6.3 Device Traceability

Device traceability is maintained in the clinical investigation by creating a new version of SyMRI that is used specifically in the clinical investigation. All contrast weighted images that will be used in the investigation are generated by SyntheticMR with this version after all subjects has been recruited and before the image reading can start. When the contrast weighted images are exported from SyMRI to DICOM format, the SyMRI software store relevant version information in DICOM tag *SyntheticMR private group* (3005), thus ensuring full traceability on the contrast weighted images back to the

investigational device. The SyMRI software is not sent to the readers or sites for the purpose of the investigation.

6.4 Intended Purpose

SyMRI is a post-processing software medical device intended for use in visualization of soft tissue. SyMRI analyzes input data from MR imaging systems. SyMRI utilizes data from supported MR sequences to generate parametric maps of R1, R2 relaxation rates, and proton density (PD). SyMRI can generate multiple image contrasts from the parametric maps. SyMRI enables post-acquisition image contrast adjustment. SyMRI is indicated for head imaging.

SyMRI is also intended for automatic labeling, visualization and volumetric quantification of segmentable brain tissues from a set of MR images. Brain tissue volumes are determined based on modeling of parametric maps from SyMRI.

When interpreted by a trained physician, SyMRI images can provide information useful in determining diagnosis. SyMRI is intended to be used in combination with at least one other, conventional MR acquisition (e.g. T2-FLAIR).

6.5 Indication and Population

SyMRI is a post-processing software medical device intended for use in visualization of soft tissue and is indicated for head imaging. The intended population is patients of all ages with clinical indications for MR imaging of the head.

6.6 Technical and Functional Features

In essence, SyMRI has the following technical and functional features

1. Generate parametric maps (T1, T2, PD) based on the absolute tissue properties.
2. Generate several contrast weighted images.
3. Visualize the image in three planes (Ax, Cor, Sag).
4. Allow the user to adjust time parameters (TE/TR/TI) post scan.
5. Provide volumetric information for brain, e.g. WM, GM, CSF, MyC.
6. Show the volumetric information compared to a healthy population (reference curves).
7. Export images and information to DICOM or Structured Report.

This investigation covers the use of the contrast weighted images generated from the 3D-QALAS sequence for the brain imaging.

6.7 Manufacturing and Materials

Not applicable since the investigational device is a pure Software Medical Device.

6.8 Training and Experience

There is no specific training required from a regulatory point of view in order to use SyMRI. The output from SyMRI is contrast weighted images, which, when interpreted by a trained radiologist can be used to assist in diagnosing patients according to the intended purpose of the product. SyntheticMR do offer training and guidance to all end-users but these are not mandatory from a safety perspective and focus more on improving the user experience and provide best practice.

For this clinical investigation no specific training of the SyMRI software is planned. The radiologists participating in the study will not use SyMRI directly but only interpret and analyze the contrast weighted images generated from SyMRI. All radiologist participating in the investigation are experienced in neuro imaging and have all the necessary training to interpret the images.

6.9 Installation and Use

No specific medical or surgical procedures are involved in the use of the investigational device.

7 JUSTIFICATION OF CLINICAL INVESTIGATION DESIGN

A 3D version of SyMRI has been developed under research agreement since 2013 when the first feedback relating a 3D version of SyMRI was received from the market. Since then, extensive software system tests of SyMRI have been performed to confirm that specified software requirements are fulfilled. In addition, 5 articles have been published on SyMRI with the use of 3D-QALAS sequence on brain in human subjects[7, 10, 14, 18, 19]. These publications have mainly focused on quantitative measurements (brain volume and cortical thickness) and/or qualitative comparisons between synthetic and conventional MR images in adult healthy volunteers and MS patients. Since SyMRI 15 (3D) is intended to be used in patients of all ages with clinical indications for MR imaging of the head, SyntheticMR has identified that a clinical investigation validating the use of SyMRI 15 (3D) in clinical neuroimaging in individuals of different ages and a broad range of pathologies is needed to support the intended purpose of SyMRI 15 (3D). Thus, the clinical investigation is aiming at confirming the clinical usability and safety of SyMRI 15 (3D), when used according to its proposed labelling, to create support for the current claims and intended purpose. The clinical data retrieved from this clinical investigation will be evaluated and incorporated in the product Clinical Evaluation Report (CER).

7.1 Identification of pathologies to cover in the clinical investigation

As described above, the aim is to include subjects covering a broad range of pathologies seen in brain MRI. The distribution of the pathologies included in the investigation should also reflect the real-life prevalence of the different pathologies in the target population. This means that the aim will be to include a higher number of subjects with the most frequent pathologies and a lower number of subjects with the less frequent pathologies.

Table 1: Pathology groups and prevalence in adult population.

Prevalence	Pathology group	Example of pathology or disease
1	Infectious/Inflammatory/ Demyelinating	MS and other demyelinating disorders Infectious (bacterial, viral, fungi) Vasculitis Autoimmune-mediated encephalitis
1	Vascular Disorders of the Brain	Ischemia/infarcts Hemorrhagic Small vessel disease Venous thrombosis Aneurysm
1	Neuro Degenerative Disorders and Hydrocephalus	Alzheimer's and other primary neurodegenerative disorders Movement disorders, e.g. Parkinson Communicating hydrocephalus Non-communicating incl. normal pressure hydrocephalus
2	Intracranial Neoplasms	Primary Brain tumors Metastasis Extra-axial tumors Cystic lesions Sellar tumors
2	Traumatic Lesions	Intra-axial Hematomas Extra-axial Hematomas Diffuse axonal injury
2	Congenital Malformations	Brain developmental malformations
3	Toxic and Metabolic conditions	Exogenous toxins Drug-induced neurotoxic disorders Radiation and chemotherapy induced injuries Acquired metabolic diseases Leukodystrophies and inherited metabolic conditions

Prevalence rated as 1=most common, 2=common, 3=least common

Table 2: Pathology groups and prevalence in pediatric population.

Prevalence	Pathology group	Example of pathology or disease
2	Infectious/Inflammatory/ Demyelinating	MS and other demyelinating disorders Infectious (bacterial, viral, fungi) Vasculitis Autoimmune-mediated encephalitis
2	Vascular Disorders of the Brain	Ischemia/infarcts Hemorrhagic Venous thrombosis Aneurysm
2	Neuro Degenerative Disorders and Hydrocephalus	Communicating hydrocephalus Non-communicating incl. normal pressure hydrocephalus
1	Intracranial Neoplasms	Low Grade Astrocytomas High Grade Astrocytomas Brain Stem Gliomas Medulloblastomas Ependymomas Sellar tumors
1	Traumatic Lesions	Intra-axial Hematomas Extra-axial Hematomas Diffuse axonal injury
2	Congenital Malformations	Brain developmental malformations
3	Toxic and Metabolic conditions	Exogenous toxins Drug-induced neurotoxic disorders Radiation and chemotherapy induced injuries Acquired metabolic diseases Leukodystrophies and inherited metabolic conditions

Prevalence rated as 1=most common, 2=common, 3=least common

7.2 Justification of clinical investigation design

This premarket investigation is designed as a prospective, multicenter, multireader clinical investigation in which blinded, multiple readers will assess the image quality of synthetic and conventional 3D MR images to determine the clinical usability and performance of synthetic images when used for visualization of the brain.

Since SyMRI 15 (3D) is intended to be used in patients of all ages with clinical indications for MR imaging of the head, subjects from the age of 0 to 99 years, with a broad range of pathologies will be included in the investigation. Among the pathologies listed in Table 1 and Table 2, there are conditions that may involve cognitive impairment, such as Alzheimer's disease. Both children and mentally disabled persons are considered vulnerable according to FDA regulations (21 CFR 56.111) and additional safeguards have been included in the study to protect the rights and welfare of these subjects (see Section 18). The research part for the subject is limited to 5-20 additional minutes in the MRI scan. This is considered to involve no greater than minimal risk to the subjects.

Healthy controls (adults) will also be recruited in order to evaluate potential false positive.

The imaging appearance of a child's brain can appear different than that of an adult. Additionally, images of a child's brain appear different between children of different age groups and different development stages. There are also a number of neurological diseases that are more common in children than adults. MRI protocols and imaging techniques designed and validated in adults are not always applicable to the imaging of a child's brain. This justifies a pediatric population of a broad age span. The sites recruiting children were selected based on well-experienced, leading principal investigators within the field of pediatric neuroradiology. There are no anticipated direct benefits for the subject. However, the results from this research study might help to reduce the scan time for future children.

Sedation and general anesthesia are sometimes utilized, most frequently in children less than 6 years, in order to minimize the motion artifacts that can accompany children and lead to reduced diagnostic efficacy of MRI examinations. The risks of sedation and general anesthesia themselves are very low when managed by providers with appropriate training and experience. Children having anesthesia will be carefully monitored by trained and experienced health care providers throughout the whole MR procedure. These subjects will be included in the sub-group Anesthesia.

A prerequisite for the generation of synthetic MR images with SyMRI 15 (3D) is MRI data acquired using the 3D-QALAS sequence. To date, there are no MRI scanners which are FDA-cleared for the 3D-QALAS sequence available and therefore the access to retrospective data is limited. Thus, a prospective design has been chosen for this investigation. In addition, this enables the use of a standardized MRI protocol ensuring comparable MR images from the different sites. Although the MR images are collected prospectively, the MR images acquired for the investigation will not be used for diagnostic reasons or treatment decisions which means that the subjects will not be affected by the use of SyMRI 15 (3D).

A multicenter approach has been chosen to assure timely inclusion of the pathology groups listed in section 7.1. Furthermore, the sites will consist of a mix of university hospitals and private imaging centers since it is expected that the university hospitals will handle the more unusual pathologies while the private imaging centers will handle larger volumes of the more common pathologies.

The image quality of the synthetic MR images will be evaluated by multiple readers and compared with conventional MR images. A number of 5 readers evaluating all cases in the investigation was deemed sufficient and feasible. The readers will be blinded to image type (i.e. synthetic versus conventional) and the cases will be read in a randomized order to eliminate potential sources of bias.

The three contrast weightings T1w, T2w and T2w FLAIR were chosen for this investigation since these are commonly used in conventional neuroimaging. Since the purpose is to test SyMRI according to its intended used, only the T1w and T2w images will be evaluated, and a conventional FLAIR will be included in all readings of the synthetic images. Conventional 3D images were chosen as the comparator for all three contrast weighted images to allow a robust comparison of the image quality with all three planes with similar resolution available to the readers for all images.

8 BENEFITS AND RISKS OF THE INVESTIGATIONAL DEVICE, CLINICAL PROCEDURE, AND CLINICAL INVESTIGATION

When discussing risks and benefits of a new medical device, there are different aspects that have to be considered, including the potential risks and benefits for the subjects participating in the clinical investigation and for future patients with clinical use of the new device.

The risk management related to the device has been conducted in accordance with ISO 14971 and included risk analysis and risk evaluation, risk control and pre-production and post-production review.

8.1 Anticipated Clinical Benefits

The anticipated clinical benefits of SyMRI 15 (3D) are:

- Thinner slices and no slice gap compared to SyMRI 2D using the M2D-MDME sequence.
- Ability to visualize the anatomy in three planes (Ax, Cor, Sag).
- Provides valuable volumetric information in the head, including white matter, grey matter, cerebrospinal fluid, Myelin correlated partial volume, brain parenchyma and intracranial cavity.
- Allow the user to adjust time parameters (TE/TR/TI) post acquisition.

8.2 Residual Risks and Anticipated Adverse Device Effects

Entering the MR scanner will follow the sites standard procedure and safety protocols. MR scanners are considered safe since they do not emit ionizing radiation.

After review of risk documentation for SyMRI 15 (3D), the remaining clinical risks after risk control that have been employed are summarized in Table 3 (RMR-8 Risk Management Report[23]). Some of the problems identified in the risk analysis are also well-known issues in conventional images which is a well-tried MRI method with established routines and clinical practices. New users of the product will be informed of the identified risks. When the device is used in accordance with the intended use and recommended system requirements, SyMRI 15 (3D) is considered safe and effective based on the risk-benefit analysis.

Table 3 Residual risks identified for SyMRI14

POTENTIAL CLINICAL EFFECT	HAZARDOUS SITUATION	EXPLANATION
MISINTERPRETATION AND POTENTIAL MISDIAGNOSIS	Image artifacts due to patient movements	Image artifacts due to patient movements (fuzzy images with blurry edges). This kind of image artifacts are common for conventional MR as well, and are well known within currently accepted clinical practices.
	Image artifacts specific to SyMRI	• Images with black blood features due to suppressed signal in image acquisition (due to blood flow or accumulated contrast agents in the tissue), • Ghosting artifacts caused by flow (flow sensitivity), • Small features may disappear and will not be visible in the image if the resolution is too low for the particular feature of interest.
	Quantitative analysis not accurate or reproducible	Inaccurate or irreducible quantitative analysis may lead to incorrect information to support diagnosis, and to incorrect diagnosis. Precision of quantitative measurements depends on all parameters, and scanner setting and magnetic field tolerances for different MR scanner manufacturers may thus reduce the precision. Follow up exams on different MR scanner make and model may lead to small differences in

		the quantitative analysis, and thus to reduced precision of the analysis.
	Incorrect patient data or patient data mix-up	Incorrect patient data may lead to potential incorrect diagnosis. This may be due to: • data transfer to and from PACS system • data security issues (such as corrupt data, tampering with data, network security breach)
LOSS OF FUNCTIONALITY	Tool unavailability	In case SyMRI s not available for use (such as software crash, data transfer errors or network issues, the analysis cannot be performed as intended. The diagnosis will in such cases have to be based on conventional MR.

In this clinical investigation, SyMRI 15 (3D) will be used by Sponsor to generate synthetic MR images after subject has completed the investigation. Site will not have access to the synthetic MR images and diagnoses and treatment decisions will be based on the conventional MR images according to site's clinical routines. Therefore, the use of SyMRI 15 (3D) will not involve any risks to, or affect the care of, the subjects participating in the investigation.

The MRI devices used in the investigation, including the investigational 3D-QALAS sequence, will be within FDA specified parameters and considered to involve no greater than minimal risk to the subjects.

There are no anticipated adverse device effects for the investigational devices, neither for SyMRI 15 (3D) nor for the 3D-QALAS sequence.

8.3 Risks Associated with Participating in the Clinical Investigation

For patients, only subjects scheduled for an MRI of the brain, either according to clinical routine care or as part of other clinical investigation/research study, will be asked to participate in this clinical investigation. Participation will involve 5-20 minutes extra time in the MRI scanner to acquire the investigational MR images. There will be no greater than minimal risk from the additional imaging, but subjects may experience discomfort due to the additional time in the scanner.

For the healthy control group, participation will involve 20 to 30 minutes of scan time in the MRI with no greater than minimal risk for the MRI procedure. Standard site MRI safety procedures will be followed and all images will be reviewed to rule out incidental findings. Site will follow up with subjects where incidental findings occur and guidance for seeking clinical care will be provided. If an abnormality is found, the subject will be informed of the finding and instructed to schedule a follow-up as soon as possible with the appropriate care provider as recommended by the site medical director or his/her primary care provider (PCP). If the incidental finding is considered severe or urgent, immediate intervention/admission to a hospital may be required. If a severe incidental finding is noted by the MRI technician and/or study physician, they will seek immediate internal opinion by a physician. If deemed life threatening the subject will be sent to the appropriate hospital otherwise the appropriate information will be provided to the subject to schedule a follow-up as soon as possible with the appropriate care provider as recommended by the site medical director or his/her PCP.

Anesthesia will be utilized in some of the pediatric subjects. Extended anesthesia is considered to constitute a greater than minimal risk for the subjects. Therefore, these subjects will be included in a separate sub-group (Anesthesia) and additional safety measures will be taken. Children scheduled for MRI under anesthesia will only be included in the study if the physician investigator and the anesthesiologist deem it safe to extend the scan time under anesthesia with 5-20 minutes. The children

will be carefully monitored by licensed anesthesiologists throughout the whole MR procedure. For the informed consent process, see section 18.

Risks associated with MRI scan in general (not specific for the clinical investigation):

- MRI uses a powerful magnet to make images; therefore, persons with metal implants, such as certain types of surgical clips or pacemakers, should not have an MRI.
- Other metal objects such as keys, pocketknives, credit cards, cell phones, and some types of cosmetics or jewelry must be removed prior to entrance to the magnet room. The MRI scanner also uses radio frequency waves that can, on rare occasions, cause a mild warming sensation.
- The MRI scanner makes loud banging noises during the scanning session. Subject will be provided with earplugs/ ear protection to reduce the noise heard from the scanner.
- It is also possible, but rare, that the magnetic fields in the scanner can cause mild twitching in the arms and legs.
- Some people feel uncomfortable and/or claustrophobic when lying inside the MRI scanner. If subject feels nervous or upset during the MRI, the procedure may be stopped.

The risks presented above are associated with the MRI scan and are not predicted to increase due to the additional time in the MRI scanner.

8.4 Possible interactions with concomitant medical treatments

Gadolinium-based contrast agents may affect the appearance of the MR images and therefore, the investigational sequences should be taken before gadolinium is administrated in this clinical investigation.

8.5 Risk Control

The MRI devices used in the investigation, including the 3D-QALAS sequence, will be within FDA specified parameters. Careful attention will be paid to safety procedures to prevent the potential risks associated with MRI scan.

For the pediatric population, anesthesia will be allowed if needed for the scheduled MRI. Inclusion in the investigation will mean an extension of the scan time under anesthesia of 5-20 minutes. FDA classifies prolonged anesthesia as greater than 3 hours[25]. Prolonged anesthesia is not anticipated as part of this study since a single MRI exam never exceeds 2 hours and >99% of all MRI exams at Phoenix Children's Hospital (Site 1) are 1 hour or less. Only subjects without medical condition(s) that, in the opinion of a physician investigator, would prevent safe participation in the study will be included (see exclusion criterion no. 3). This means that only children where the physician investigator and the anesthesiologist deem it safe to extend the scan time under anesthesia with 5-20 minutes will be included in the study. All sites recruiting children are specialized in pediatric neuroradiology and are experienced in performing and monitoring MRI under anesthesia. The sites will follow their clinical routines in terms of pediatric anesthesia.

Risks related to the processing of subjects' personal data, and in particular data concerning health, will be mitigated by use of pseudonymization, whereby the personal data will no longer be attributable to a specific subject without the use of a key which will be kept separately and securely by the PI.

8.6 Benefit-to-Risk Rationale

This investigation is considered a non-significant risk study since the output from the investigational device will not be used for any patient treatment or diagnosis. The subject discomfort for the extra scan time is considered small. The potential benefit for future patients outweighs the risks.

9 OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

9.1 Primary Objective

The primary objective is to demonstrate non-inferiority of synthetic 3D MR images compared to conventional MR images with respect to sensitivity and specificity of pathological findings.

9.2 Secondary Objectives

The secondary objectives are to demonstrate non-inferiority of synthetic 3D MR images compared to conventional MR images with respect to:

- classification of pathological findings,
- diagnostic accuracy in an adult population, and
- diagnostic accuracy in a pediatric population.

9.3 Exploratory objectives

Other exploratory objectives are to evaluate:

- legibility of anatomical structures,
- frequency and type of artifacts,
- inter-rater and inter-method agreement, and
- image quality for T1w and T2w images, with synthetic 3D MR images compared to conventional MR images.

9.4 Hypothesis

The null hypothesis (H_0) is that the difference in sensitivity and specificity of pathological findings (pathology vs normal/no finding) with synthetic 3D MR images compared to conventional MR images is less than or equal to -0.05.

The alternative hypothesis (H_1) is that the difference in sensitivity and specificity of pathological findings (pathology vs normal/no finding) with synthetic 3D MR images compared to conventional MR images is greater than -0.05.

Each of the two one-sided hypotheses will be tested at significance level α=0.025.

9.5 Claims and Intended Performance of the Investigational Device

When interpreted by a trained physician, the information from SyMRI can provide information useful in determining diagnosis.

T1w and T2w images from SyMRI can replace conventional T1w and T2w images of similar resolution and provide the same determination of radiological findings.

9.6 Risks and Anticipated Adverse Device Effects

One risk from the risk analysis will be assessed during the clinical investigation: the risk for misinterpretation and potential misdiagnosis due to possible novel image artifacts specific to SyMRI or synthetic MR images. Image artifacts in conventional MR are well-known and can be easily identified by a trained radiologist or MR technician. This clinical investigation will assess the risk for possible novel image artifacts that could arise when using SyMRI.

10 DESIGN OF THE CLINICAL INVESTIGATION

10.1 General

This is a pre-market, prospective, multicenter, reader clinical investigation in which blinded, multiple readers will assess the image quality of synthetic and conventional 3D MR images to evaluate the performance of the SyMRI 15 (3D) software when used for visualization of the brain. The investigation consists of two parts, the image acquisition and the image review.

For the image acquisition part, subjects will be recruited at 5-10 sites in the US. Subjects will consist of individuals aged 0-99 years, who either are patients scheduled for MRI of the brain or healthy controls. The aim is to include subjects covering a broad range of pathologies reflecting the intended use population. All subjects will undergo an MRI scan of the brain, using a fixed set of scanning parameters on a 3T MRI scanner from Philips. From each subject, the following sequences will be acquired for the investigation:

- 3D T1w (conventional image)
- 3D T2w (conventional image)
- 3D T2w FLAIR (conventional image)
- 3D-QALAS (data for generation of synthetic images)

For the image review part of the investigation, SyMRI 15 (3D) will be used to post-process data from the 3D-QALAS acquisition to generate synthetic T1w and T2w images. For each subject, the reader will either have synthetic T1w and T2w plus a conventional FLAIR, or will have only conventional images. The images will be assessed by 5 blinded, experienced neuroradiologists who will assess the images with regards to image quality, legibility of anatomical structures, artifacts, and radiological findings. The readings will be separated into two reading sessions with a 4-week memory-washout period.

Results will be analyzed for the whole cohort, a pediatric sub-population (subjects aged 0–17 years) and an adult sub-population (subjects aged 18–99 years).

10.2 Investigation Endpoints

10.2.1 Primary performance endpoint

- Difference in sensitivity of pathological findings (pathological vs normal/no finding) between synthetic and conventional MR images on the full analysis set.
- Difference in specificity of pathological findings (pathological vs normal/no finding) between synthetic and conventional MR images on the full analysis set.

The ground truth is the site-determined diagnosis (pathological vs. normal/no finding).

10.2.2 Secondary performance endpoints

- Difference in diagnostic accuracy of radiological findings (radiological finding class) between synthetic and conventional MR images on the subgroup of pathological patients. The ground truth is the site-determined diagnosis (radiological finding class).
- Primary and secondary endpoints (sensitivity, specificity, accuracy) in adults (18–99 years).
- Primary and secondary endpoints (sensitivity, specificity, accuracy) in pediatrics (0–17 years).

10.2.3 Exploratory endpoints

- Legibility of anatomical structures, per structure.
- Presence and type of artifacts, per contrast weighting (T1w, T2w).
- Inter-rater agreement (agreement, kappa coefficient and Gwet's AC1 coefficient) with regards to radiological finding classes.

- Inter-method agreement (agreement, kappa coefficient and Gwet's AC1 coefficient) with regards to radiological finding classes.
- Image quality score per contrast weighting (T1w, T2w).

10.2.4 Safety endpoints

- Incidence of Adverse Events (AE), Adverse Device Effects (ADE), Serious Adverse Events (SAE), Serious Adverse Device Effects (SADE), Unanticipated Adverse Device Effect (UADE), Unanticipated Serious Adverse Device Effect (USADE) and Device Deficiencies (DD).

10.3 Investigational Device(s) and Comparator(s)

10.3.1 Investigational device - SyMRI 15 (3D)

SyMRI 15 (3D) will be used to post-process data from the 3D-QALAS acquisition to generate synthetic contrast weighted images with virtual scanner settings corresponding to the conventional images and thus generate synthetic T1w and T2w images. The post-processing will be carried out by the Sponsor and thus, neither the subjects nor the readers will be exposed to or handle the investigational device.

The comparator is conventional 3D MR images, which will be considered as ground truth in the investigation.

10.3.2 Other medical device to be used during the clinical investigation

All scanning will be done on 3.0T MRI machines from Philips. An investigational pulse sequence called 3D-QALAS from Philips will be used to generate the data necessary for SyMRI. This sequence is not yet cleared by FDA and will be provided to each site prior to investigation start via a research agreement between site and Philips.

10.4 Subjects

10.4.1 Inclusion Criteria

The subjects must meet all of the following criteria to be eligible to participate the investigation:

	INCLUSION CRITERIA
1	Any gender, aged 0-99 years
2	Subject scheduled for MRI of the brain **OR** Healthy control with passed screening form
3	Subject suitable for MRI as judged by investigator
4	Subject agrees to 5-20 min extra MRI scan time
5	Subject able to understand written and verbal information in English or Spanish
6	Provision of informed consent (and assent if applicable)

10.4.2 Exclusion Criteria

Subjects meeting any of the following criteria will not be permitted to participate in the investigation:

	EXCLUSION CRITERIA
1	Have contraindication(s) to MRI scanning per the routine MR Safety Screening policy of the investigational site
2	Have severe trauma, disability or pre-existing pathology that is expected to interfere with normal conduct of MRI scanning or complete scanning of the brain
3	Have medical condition(s) such as those requiring urgent medical care that, in the opinion of a physician investigator, would prevent safe participation in the study
4	Adult subjects (aged 18-99 years) in need of anesthesia during MRI scanning

5	Pregnancy at time of enrollment determined according to the clinic's MR Safety Screening policy
6	Previous enrollment in this investigation

10.4.3 Relationship of Investigation Population to Target Population

SyMRI 15 (3D) is indicated for head imaging. The investigation population has been selected to represent the most common pathologies and abnormalities in the brain examined by MRI in the target population (see Section 7). Since SyMRI 15 (3D) is intended to be used in patients of all ages, subjects ranging from 0 to 99 years of age will be included in the investigation (see Section 20).

10.4.4 Number of Subjects

In total 180 evaluable subjects will be recruited.

Approximately 120 will be patients, whereof 65 adult subjects (age 18-99 years) and 55 pediatric subjects (age 0-17 years). The pediatric population will consist of two groups, one with subjects receiving anesthesia (Sub-group Anesthesia) and one with subjects not receiving anesthesia (Sub-group No-anesthesia).

In addition, a group of approximately 60 evaluable, healthy adult controls will be included in the clinical investigation to be able to evaluate the specificity of the investigational device.

The aim is to include 5-14 subjects in each pathology group as specified in Table 4. The number of subjects per pathology groups is based on the prevalence of these pathologies (see Section 7.1). For the adult population, the aim is to include ≥10 subjects in the most common groups, ≥5 subjects in the intermediate group and ≥3 subjects in the least common groups. Corresponding figures for the pediatric group are ≥7 subjects in the most common groups, ≥4 subjects in the intermediate group and ≥2 subjects in the least common groups.

Prevalence was rated from 1 to 3 (1=most common, 2=common, 3=least common) as seen in Table 1 and Table 2.

Table 4: Target number of subjects per pathology group and sub-population

	Pediatric population		Adult population		
Pathology group	Prevalence	Target number of subjects	Prevalence	Target number of subjects	Total
Infectious/Inflammatory/Demyelinating	2	≥ 4	1	≥ 10	≥ 14
Vascular Disorders of the Brain	2	≥ 4	1	≥ 10	≥ 14
Neuro Degenerative Disorders and Hydrocephalus	2	≥ 4	1	≥ 10	≥ 14
Intracranial Neoplasms	1	≥ 7	2	≥ 5	≥ 12
Traumatic Lesions	1	≥ 7	2	≥ 5	≥ 12
Congenital Malformations	2	≥ 4	2	≥ 5	≥ 9
Toxic and Metabolic conditions	3	≥ 2	3	≥ 3	≥ 5
Normal/no findings		N/A		N/A	

A Normal/no findings-category exists because some subjects are expected to present without any clinical findings.

Recruitment to the different pathology groups will be monitored during recruitment period. When the number of subjects in a pathology group is deemed sufficient by the Sponsor, recruitment to this specific group will be stopped to avoid overrepresentation of that pathology in the investigation population compared to the target population.

Each investigational site is estimated to recruit 20-30 patients. The healthy controls will be recruited by one of the investigational sites.

A subject is defined as evaluable in the study if they have completed the necessary scans as described in this protocol. If a sequence is missing, or if settings did not follow the acquisition parameters (e.g resolution), or if the subject did not complete all scans, the subject images will be excluded from the image review.

10.4.5 Methods of Assigning Subjects to Different Treatment Arms

Not applicable since all subjects will undergo the same investigational procedures and no treatment is given to the subjects.

10.4.6 Subject Withdrawal, Discontinuation, or Lost to Follow-up

Subjects are free to discontinue participation in the clinical investigation at any time and are not required to give a reason for their decision. However, subjects who discontinue the investigation should always be asked about the reason(s) for their discontinuation and about the presence of any adverse event (AE) /adverse device effect (ADE) and, if possible, be assessed by an investigator. Discontinuation from the clinical investigation will not affect the future treatment/care of the subject.

If the subject will withdraw his/her consent no further data will thereafter be recorded. Data collected up to the date of withdraw of informed consent will be used in the data analysis and for the Clinical Investigation Report (CIR). In case of withdrawal, all AEs/ADEs should be followed up.

Subjects may be withdrawn from the clinical investigation and assessments at any time, if deemed necessary by the Principal Investigator.

Specific reasons for withdrawal of subjects from this clinical investigation are:

a) The decision of a subject to withdraw from the investigation (including if the subject withdraws informed consent);
b) The Principal Investigator deems the subject unfit for the investigation or suspects poor CIP compliance;
c) The subject is not able to lay still in the MRI, causing poor quality of the MRI scans;
d) The Principal Investigator deems it is in the subject's best interest to be taken out of this investigation, e.g. due to claustrophobia.

Incorrectly enrolled subjects will be withdrawn from further assessments.

10.4.7 Subject Follow-up and Care

After completed MRI scan, there is no follow-up of the subjects within the investigation. Instead, subjects will be treated according to site's clinical routine.

10.5 Readers

All readers participating in the image review part of the study will have more than 10 years of post-graduate experience within neuroradiology. All readers will be US ABR and CAQ certified neuro-radiologists.

The readers will be blinded to site-determined diagnosis to reduce information bias.

The following information will be collected from all readers: Name, Country, Job Title, Fellowship status, Practice focus, Years of experience (post-graduate), CV and Certificates.

10.6 Clinical Investigation Duration

Recruitment of patients:

Point of enrolment:	June 2022
Enrolment period:	June 2022-December 2023

Expected duration of each subject's participation:	1 day
Total expected duration of the clinical investigation:	18 months

Recruitment of healthy controls:

Enrolment period:	August 2023-December 2023
Expected duration of each subject's participation:	1 day

10.7 Clinical Investigation Procedures

The assessments and procedures that will be performed during the clinical investigation are shown in the table below.

10.7.1 Schedule of Clinical Investigation Procedures /Assessments

Table 5: Schedule of the Clinical Investigation procedures

Assessment	Image Acquisition	Image Review			
	Visit 1 MR exam	**Generation of Synthetic Images**	**Image Review Part I[2]**	**Image Review Part II**	**Transfer of Image Review data**
Responsible	Site	Sponsor	Reader	Reader	Sponsor
eCRF[1]	Viedoc	Viedoc	CARPL	CARPL	Viedoc
Subject visit	X				
Informed consent	X				
Subject Eligibility Verification	X				
Demography	X				
MR Scanning	X				
Use of 3D-QALAS	X				
Anonymization of MRI	X				
Upload of MR images in eCRF	X				
Adverse events	X				
Device Deficiencies	X	X			
Site-determined diagnosis	X				
Subject termination	X				
Use of Investigational Device SyMRI		X			
Image review by readers			X	X	
Transfer of image review data from CARPL eCRF to Viedoc eCRF					X

[1] Two eCRFs will be used in this clinical investigation; Viedoc eCRF for subject-related data and CARPL eCRF for image review data. When image review is complete, image review data will be extracted from CARPL and uploaded in Viedoc for archiving purposes.
[2] The image review will be conducted over 2 sessions (Part I and Part II) with a 4-week memory washout period in-between to minimize recall bias. The blinded reader will evaluate the synthetic MR images of a case in one session and the conventional MR images of the same case in the other session.

10.7.2 Image Acquisition

10.7.2.1 Visit 1 – MR exam

Before any investigation-related procedures are initiated, the informed consent (and if applicable assent) must be signed and dated by the subject (or their legally acceptable representative and/or witness, as applicable) and by the Investigator who gave the subject the verbal and written information. The original document will be retained in the Investigator Site File (ISF) and a copy provided to the subject. For further details on the informed consent process please see section 18.

After written informed consent has been obtained and it has been confirmed that the subject fulfills all the inclusion criteria and none of the exclusion criteria, the subject will be considered enrolled in the clinical investigation. The subject will be allocated to a unique subject identification number and demographic data will be collected.

The subject will then undergo an MRI scan which will consist of:

1. the MRI scan that the subject was originally scheduled for, and
2. the additional investigational MRI scan (=1-4 additional pulse sequences depending on subject's routine protocol, corresponding to an addition of 5-20 minutes to the length of the subject's scheduled scan)

For the healthy controls, a screening form will be used to identify eligible subjects. Subjects interested in participating in the study will be interviewed over phone according to the screening form by PI or delegate. The screening form is designed to rule out subjects with important medical history that could interfere with the study's objective to include healthy controls.

Healthy controls that pass the screening will be scheduled for an MRI. On the day of the MRI the informed consent form will be signed and dated by the subject and investigator or delegate.

For the healthy controls, only the investigational scans specified in Table 6 below will be performed.

NB: MRI scans for the investigation should be performed before any gadolinium-based contrast agent is given to the subject.

For the pediatric population, anesthesia is allowed if needed for the scheduled MRI and should follow site's clinical routines. These subjects will be included in the sub-group with pediatric subjects receiving anesthesia (Sub-group Anesthesia). Children having anesthesia will be carefully monitored by licensed anesthesiologists throughout the whole MR procedure. Sedation and general anesthesia are sometimes utilized, most frequently in children less than 6 years, in order to minimize the motion artifacts that can accompany children.
Use of contrast agents and anesthesia will be collected in the Viedoc eCRF.

10.7.2.1.1 MRI Protocol

All MRI scans will be performed on a 3.0T MRI from Philips. For the investigation, images will be acquired using a fixed set of scanning parameters according to Table 6. The resolution will be similar for all sequences or as close as possible depending on MRI scanner.

Table 6: Acquisition parameters for 3D-QALAS and conventional sequences

Imaging Parameters	*3D T1w*	*3D T2w*	*3D T2w FLAIR*	*3D-QALAS*
FOV (mm)	220-250	220-250	220-250	220-250
Resolution	0.9-1.2 mm iso	0.9-1.2 mm iso	0.9-1.2 mm iso	1.2 mm iso
TR	Site dependent	Site dependent	Site dependent	Shortest
TE				2.3
TI				-
ETL				150
Bandwidth (Hz/px)				393
Acceleration technique	SENSE or CS-SENSE	SENSE or CS-SENSE	SENSE or CS-SENSE	CS-SENSE
Scan time (estimate)	2-4 min	2-4 min	3-6 min	5-6 min

Since this is a multi-site study with six sites, some difference in the image acquisition between the conventional images will need to be accepted. For example, resolution is allowed to range between 0.9-1.2 mm isotropic for the conventional images. FOV can vary depending on patient head size. Acceleration technique and amount of acceleration may also be different for conventional images from the different sites.

If any of these sequences are available in the standard protocol, with the requested resolution, this will be used as input for this clinical investigation. It is likely that some of these sequences with the specified resolution will need to be added after the routine clinical scan. This means that depending on the standard protocol used by the site for the specific clinical question, this may add an extra 1-4 sequences

for the subject. The conventional 3D images can be generated with either Turbo Spin Echo sequences or Gradient Echo sequences, therefore all imaging parameters are not specified beforehand.

After completed MRI scan, subject ends his/her participation in the clinical investigation.

10.7.2.1.2 Anonymization of MRI files

Before DICOM images are uploaded to the Viedoc eCRF the images need to be anonymized. For the sites that have processes and tools in place for how to correctly anonymize DICOM images this process can be used.

SyMRI requires certain DICOM tags to work properly. A DICOM Conformance Statement is available from SyntheticMR specifying the requirements. To make sure these are not removed during anonymization, a test scan matching the study protocol should be acquired, anonymized and evaluated. If required tags are removed the anonymization process will need to be adjusted.

If necessary, the Sponsor can recommend site with tools and guide for how to safely and efficiently anonymize DICOM images.

10.7.2.1.3 Labelling and uploading of MRI files

After anonymization, a zip file should be created, containing all DICOM images from all four investigational sequences (3D-T1w, 3D-T2w, 3D-T2w FLAIR and 3D-QALAS). The zip file should be named with site number and subject ID as in the example below. The zip file can then be uploaded in the Viedoc eCRF.

Example file name 01-101
02-003

10.7.2.1.4 Site-determined diagnosis

MR images acquired during the MRI scan will be sent to a radiologist for evaluation as per site's clinical routines. The site will decide the site-determined diagnosis for each subject on the basis of the results from MR imaging studies and work-up performed according to the standard of care by clinical neuroradiologists. This means that the radiologist will have access to the subject's medical records, and that the site-determined diagnosis will be based on more information than what is available for the readers in this clinical investigation, e.g. for the site determined diagnosis the neuroradiologist may also have access to DWI or SWI which will not be available in this clinical investigation.

For the healthy control group, the site determined diagnosis will be considered normal/no finding if the PI determine that no pathology is identified in the brain on the conventional MRI. Minor non-exclusionary incidental findings will be allowed for the healthy control group in order to take into consideration normal variance that is typically seen in MR imaging and normal ageing. The following list is used to categorize incidental findings:

Non-exclusionary incidental findings

1. Non-neoplastic cysts: small (<2cm) arachnoid cyst, pineal gland cyst, enlarged perivascular spaces
2. Vascular encephalopathy, defined as Fazekas grade 0 or 1, in patients older than 18 years old

Exclusionary incidental findings

3. Cysts that are larger than 2cm
4. Intracranial tumors: intra-axial (tumors in brain parenchyma); extra-axial (tumors in bone and meninges)
5. Vascular malformations
6. Major developmental disorders
7. Chronic brain injury and acquired focal or diffuse loss of normal parenchyma regardless of the etiology with the exception of age-related cerebral volume loss (e.g., prior stroke, brain

surgery, trauma, atrophy due to neurodegenerative disease such as frontotemporal degeneration; or other causes)

8. Vascular encephalopathy, defined as Fazekas grade 2 or 3, in patients older than 18 years old

The site-determined diagnosis is considered the ground truth.

The sites report the site-determined diagnosis by using the same scale as the study readers will, see Table 7. The site should also add a summary of the radiological findings in free text with more information about type of pathology or diagnosis seen in the subject.

The site-determined diagnosis and radiological findings will be entered into the Viedoc eCRF by site personnel.

Table 7: Site-determined diagnosis is reported on the following groups

RADIOLOGICAL FINDING CLASSES
Infectious/Inflammatory/Demyelinating
Vascular Disorders of the Brain
Neuro Degenerative Disorders and Hydrocephalus
Intracranial Neoplasms
Traumatic Lesions
Congenital Malformations
Toxic and Metabolic conditions
Normal / No findings

A subject can only belong to one pathology group. If there are more than one pathology (or pathology options) in one case, the site-determined diagnosis will be based on the most appropriate or significant pathology group.

10.7.3 Image Review

When all subjects have been included and the image acquisition part of the investigation has been completed the image review can begin.

10.7.3.1 Generation and upload of synthetic images

Sponsor will download the MRI files from the Viedoc eCRF. By using SyMRI 15 (3D), Sponsor will post-process data from the 3D-QALAS acquisition to generate synthetic contrast weighted images with virtual scanner settings corresponding to the conventional images and thus generate synthetic 3D T1w and T2w images.

Table 8: Settings for Repetition time, Echo time and Inversion time used in SyMRI to generate synthetic images.

	T1w	*T2w*
TR	650	6000
TE	10	100
TI1	-	150

Sponsor will then upload the conventional and the synthetic MR images into the online imaging platform CARPL (Mahajan Imaging, India) on which the images will be evaluated by the readers. CARPL contains full DICOM viewing functionalities including windowing/level, pan, zoom, ability to show multiple series and synchronized scroll. In this investigation the readers will also use the MPR functionality (Multi Plane Reformat) to view the images in three planes. The platform also contains ability to create survey questions. A survey with questions for the investigation endpoints will be prepared by Sponsor and answered by the readers during the image review.

10.7.3.2 Image Review part 1 + memory washout-period + Image Review part 2.

During the image review the readers will either read the synthetic T1w and T2w images plus a conventional FLAIR, or only read the three conventional images.

Synthetic	***Conventional***
Synthetic T1w	Conventional T1w
Synthetic T2w	Conventional T2w
Conventional T2w FLAIR	Conventional T2w FLAIR

The image quality will be evaluated by 5 blinded neuroradiologist by using the online imaging platform CARPL. The image review will be conducted over 2 sessions with a 4-week memory washout period in-between to minimize recall bias. Images from the same subject will be separated and read across the 2 sessions, meaning that the reader will evaluate the synthetic MR images of a case in one session and the conventional MR images of the same case in another session. To minimize bias, the reader will be blinded to the type of image being reviewed (i.e., conventional vs synthetic), and the conventional and synthetic images will be mixed in a randomized order within a reading session. All readers will evaluate all images in the investigation.

10.7.4 Data collected during Visit 1 – MR exam

- Eligibility
- Signed Informed Consent / Assent
- Demographics
  - Age
  - Sex
- MRI Examination
  - Use of anesthesia
  - Use of contrast agents during investigational sequences
  - MRI performed according to CIP
  - Upload of MRI files
- Site-determined diagnosis
  - Primary Pathology Group
  - Summary of radiological findings
- Adverse Events
- Device Deficiencies

10.7.5 Performance Variables and Measurements

10.7.5.1 Radiological findings

The radiologist will be asked to interpret the case based on T1w, T2w, and T2w FLAIR images and choose the primary radiological finding class that they think is the reason behind the radiological findings in the images. There may be more than one pathology (or pathology options) in each case so the reader is asked to choose the most appropriate or significant pathology group. Not all patients are expected to have clinical findings, so a normal/no finding category is also included.

RADIOLOGICAL FINDING CLASSES
Infectious/Inflammatory/Demyelinating
Vascular Disorders of the Brain
Neuro Degenerative Disorders and Hydrocephalus
Intracranial Neoplasms
Traumatic Lesions
Congenital Malformations

Toxic and Metabolic conditions
Normal / No findings

The ground truth will be the site-determined diagnosis on the basis of the results of conventional MR images and standard of care by neuroradiologist. This means that the ground truth may be based on more information than what will be available for the readers in this clinical investigation, e.g. for the site determined diagnosis the neuroradiologist may also have access to DWI or SWI which will not be available in this clinical investigation.

10.7.5.2 Image Quality

The radiologist will be asked to rate the image quality for the T1w and T2w images. A 5-point Likert scale will be used. Ratings of ≥3 will be considered clinically useable.

RATE IMAGE QUALITY
5 - Excellent
4 - Good
3 - Acceptable
2 - Poor
1 - Unacceptable

10.7.5.3 Legibility of anatomical structures

The radiologist will be asked to evaluate the legibility of anatomical structures in the T1w and T2w images. The anatomical structures are defined in the list below. Each anatomical structure will be rated on a binary scale (legible/illegible). Legibility is defined as the ability to see structures and margins associated with the key anatomic/morphologic feature to the extent necessary to be clinically usable.

ANATOMICAL STRUCTURES
Central sulcus
Cerebral peduncle
Corticomedullary junction
Head of caudate nucleus
Middle cerebellar peduncle
Posterior limb of internal capsule

10.7.5.4 Artifacts

The radiologist will be asked to record presence and type of artifacts per contrast weighting. Type of artifact can be chosen from the pre-defined list below. If the artifact is not defined in the list the reader is asked to describe the artifact.

ARTIFACTS
Motion
In-folding and wrap-around
Flow or phase-encoding
Magic angle effect
Water-fat shift / chemical shift
Magnetic susceptibility artifact
Low resolution
Low Signal to Noise

Low tissue contrast
Other, please specify

10.7.6 Safety Variables and Measurements

The safety measurement will be the onset, severity, duration and frequency of AEs (anticipated and unanticipated), including determination of causality. Only events, which are new after the consent has been signed or have increased in severity after the consent has been signed, will be recorded. All AEs will be recorded and reported, and all data required both to assess the safety and to comply with the IRB and FDA requirements will be collected. All events will be followed up until resolved or judged as clinically stable according to the investigator or designee, if possible.

10.7.7 Activities Performed by Sponsor

The Sponsor will provide instructions to site personnel on how to perform the investigational pulse sequences. This will take place during site initiation and thereafter as required, e.g. if new site personnel or any re-training is required.

10.7.8 Potential Confounding Factors

No potential confounding factors have been identified.

10.7.9 Future use of data obtained from subject

The anonymized MR images collected from the subjects may be used for future research, product development, and inventions by the Sponsor, hospitals, universities and other businesses.

11 MONITORING PLAN

A detailed description of monitoring activities will be provided in a separate, investigation-specific risk-based monitoring plan.

11.1 Subject Records and Source Data

Subject data recorded directly in electronic case report form (eCRF) (and not into the medical record) will be considered source data. It is the responsibility of the PI to record essential information in the medical records, in accordance with regional and national regulations and requirements. The origin of source data in this clinical investigation will be further specified in a separate document ("Source Data Location Agreement").

In general the following information should be recorded in the medical records:

- Investigation code, and or investigational title
- Subject ID
- That informed consent for participating in the clinical investigation was obtained, and the date of collection
- Diagnosis
- Visit number and visit date
- All AEs
- Treatments and medications
- Subject health service identification number, if applicable

The PI is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the eCRFs. Signed sections of eCRFs will be monitored on a regular basis.

11.2 Access to Source Data and Documentation

The PI should guarantee access to source documents for the monitor and auditors as well as for inspection by appropriate Regulatory Agencies, and Institutional Review Boards (IRBs), if required.

12 STATISTICAL CONSIDERATIONS

12.1 Statistical Design, Method and Analytical Procedures

12.1.1 Analysis populations

- The full analysis set consists of all subjects with at least one pair of synthetic-conventional MR image readings from at least one reader.
- The pathological subgroup consists of all subjects with a pathological finding according to site-determined diagnosis.
- The control group consists of all non-pathological subjects, including both healthy volunteers and subjects classified as normal/no-finding according to site-determined diagnosis.
- The adult sub-population consists of all subjects aged 18–99 years.
- The pediatric sub-population consists of all subjects aged 0–17 years.

12.1.2 General Statistical Methodology

Descriptive statistics of subject demographics, characteristics of readers, and performance endpoints will be summarized descriptively at the patient, reader and image level. Continuous variables will be described with mean, standard deviation, median, minimum, and maximum value, and categorical variables with numbers and percentages.

Statistical analyses will be performed on the patient level. Comparisons between conventional and synthetic MR images will be conducted using non-inferiority testing procedures.

The mean difference will be presented with corresponding two-sided 95% confidence interval. Non-inferiority will be established if the lower limit of the two-sided 95% confidence interval for the mean difference (i.e., intercept) is strictly greater than a pre-specified non-inferiority margin. The primary analyses will be performed on the full analysis set. Separate analyses on adult and pediatric sub-populations, and separate analyses by reader, will also be performed.

For the primary and secondary endpoints, a non-inferiority margin of -0.05 will be used. All tests will be one-sided and conducted at significance level α=0.025. In case of a successful non-inferiority test for the two primary performance endpoints, the entire probability mass α=0.025 will be transferred to the secondary performance endpoints in the order specified in Section 10.2.2 *Secondary performance endpoints*. Non-inferiority will then be declared for all secondary performance endpoints with a successful non-inferiority test until the first encounter of a non-successful non-inferiority test. Estimates and confidence intervals of remaining performance endpoints will be presented descriptively but not considered as confirmatory findings.

12.1.3 Primary Performance Analysis

Sensitivity of pathological findings

The sensitivity of pathological findings will be calculated as the sample proportion of true positive (pathological) findings across all patients and readers. The difference in sensitivity between synthetic

and conventional MR will be evaluated using non-inferiority testing procedures with GEE for binary variables as described in Section *12.1.1 General Statistical Methodology*. A non-inferiority margin of -0.05 will be used.

Specificity of pathological findings
The specificity will be calculated as the sample proportion of true negative (non-pathological) findings across all patients and readers. The difference in specificity between synthetic and conventional MR will be evaluated using non-inferiority testing procedures with GEE for binary variables as described in Section *12.1.1 General Statistical Methodology*. A non-inferiority margin of -0.05 will be used.

Both primary endpoints will be tested at significance level α=0.025, one-sided test. Non-inferiority of diagnostic accuracy with synthetic MR images compared to conventional MR images will be declared if non-inferiority is demonstrated in both primary endpoints.

12.1.4 Secondary Performance Analyses

Diagnostic accuracy of radiological findings
The accuracy of radiological findings will be calculated as the sample proportion of correctly identified radiological findings (radiological finding class) across all patients and readers. The difference in accuracy between synthetic and conventional MR will be evaluated using non-inferiority testing procedures
A non-inferiority margin of -0.05 will be used, significance level α=0.025, one-sided test. The radiological finding classes will be cross-tabulated for synthetic and conventional images vs site-determined diagnosis (ground truth).

Other secondary endpoints
The remaining secondary performance endpoints will be evaluated according to the methodology above in the following order:

- Sensitivity of pathological findings in adult sub-population
- Specificity of pathological findings in adult sub-population
- Diagnostic accuracy of radiological findings in adult sub-population
- Sensitivity of pathological findings in pediatric sub-population
- Specificity of pathological findings in pediatric sub-population
- Diagnostic accuracy of radiological findings in pediatric sub-population

In case of a successful non-inferiority test for the two primary performance endpoints, the entire probability mass α=0.025 will be transferred to the secondary performance endpoints in the order listed above. Non-inferiority will be declared for all primary and secondary performance endpoints with a successful non-inferiority test until the first encounter of a non-successful non-inferiority test. Estimates and confidence intervals of remaining performance endpoints will be presented descriptively but not considered as confirmatory findings.

12.1.5 Exploratory Analyses

Legibility
The percentage of legibility for each of the anatomic structures will be cross-tabulated for synthetic vs conventional for the contrast weighted images (T1w, T2w).

Artifacts
Each of the artifacts will be cross-tabulated synthetic vs conventional per contrast weighting (T1w, T2w). Any novel or previously unforeseen artifacts will be listed and described.

Inter-rater and inter-method agreement of radiological findings
Each of the radiological finding classes will be cross-tabulated for synthetic vs conventional images, followed by calculation of percent agreement, Cohen's kappa coefficient, and Gwet's AC1 coefficient between methods and readers. Inter-method agreement will be analyzed to evaluate agreement between synthetic and conventional images, i.e., if the readers draw the same general conclusions regardless of image type. Inter-rater agreement will be calculated to evaluate how well the different readers agree with each other on the radiological findings when either synthetic or conventional images are used.

Image quality of T1w and T2w images
The difference in image quality score will be analyzed using linear mixed effects models as described in Section *12.1.1 General Statistical Methodology*.

12.1.6 Safety Analysis
Safety variables will be summarized descriptively.

12.1.7 Justification of choice of non-inferiority margin
A non-inferiority margin of -0.05 for the mean difference in sensitivity, specificity and diagnostic accuracy will be used.

12.2 Sample size

A total of 180 evaluable subjects (90 pathological, 90 controls) and 5 readers will be included in the study to obtain 80% simultaneous power in both primary endpoints using one-sided test, significance level α=0.025, non-inferiority margin -0.05. The calculations are based on the following assumptions:

12.3 Drop-out Rates

No drop-out is expected from the evaluable subjects.

For the healthy controls, a 10% drop-out is estimated considering incidental findings which will exclude subjects after scan, and some subjects not showing up the scheduled appointment.

12.4 Level of Significance and Power

All tests will be one-sided and conducted at significance level α=0.025. The power for each of the primary endpoints is 90% and power for both primary endpoints simultaneously is 80%. No multiplicity adjustment is needed for the primary endpoints since non-inferiority in both primary endpoints is required to declare non-inferior diagnostic accuracy (sensitivity/specificity) with synthetic MR images compared to conventional MR images. Secondary performance endpoints will be evaluated using a hierarchical testing procedure only if the pass criteria for the primary endpoints is fulfilled.

12.5 Pass / Fail Criteria

The study will be passed if non-inferiority of synthetic compared to conventional MR images can be established with respect to both primary performance endpoints *Sensitivity of pathological findings* and *Specificity of pathological findings* on the full analysis set using one-sided test, non-inferiority margin –0.05 and significance level α=0.025.

12.6 Interim Analysis

No interim analysis will be performed.

12.7 Reporting of Deviations from the Original Statistical Analysis Plan (SAP)

Any deviations discovered throughout the study from the original Statistical Analysis Plan (SAP) described in this CIP, will be described with justification in a CIP amendment to the final report, as deemed appropriate.

12.8 Subgroups for Analysis

Separate analyses for adult and pediatric sup-populations will be performed. Separate analyses across readers will also be performed.

12.9 Procedures that Take into Account all the Data

Outliers will be included in summary tables and listings, and will not be handled separately.

12.10 Missing, Unused or Spurious Data

Available data from prematurely withdrawn subjects will be included in the analysis as far as possible. Only pairs of synthetic and conventional images evaluated by the same reader will be included in the analysis.

12.11 Exclusion of Particular Information from the Testing of the Hypothesis

If only one type of image (either synthetic or conventional) of an image pair is evaluated by a reader, this image read will be excluded from the analysis.

13 DATA MANAGEMENT

Two eCRFs will be used in this clinical investigation; Viedoc eCRF for image acquisition data and CARPL eCRF for image review data. When image review is complete, image review data will be extracted from CARPL and uploaded in Viedoc for longtime storage.

13.1 Data Management – Image acquisition part

Data management and handling will be conducted according to the investigation specific Data Management Plan (DMP) in accordance with applicable guidelines and CRO's Standard Operating Procedures (SOPs). Any deviations, i.e. discrepancies and additions from the process defined in the DMP will be described in an investigation specific Data Management Report (DMR).

Data will be collected in an eCRF specifically designed in Viedoc for this clinical investigation. The PI or an authorized person will record subject data in the Viedoc eCRF in a precise and accurate manner. Abbreviations should not be used. The PI is responsible for the data entered in the Viedoc eCRF and for signing-off at the end of the clinical investigation. The data should be recorded as soon as they are generated.

The person entering data into the database is not allowed to attempt any personal interpretation or to make any decisions on the data other than self-evident corrections as listed in the investigation data entry instructions or data handling report. Data for screening failures (not included subjects) will not be collected in the eCRF.

Data validation/data cleaning procedures are designed to assure validity and accuracy of clinical data. These procedures consist of manual review during data entry and computerized edit checks and queries for identifying data values that are outside the allowed range, incomplete or inconsistent, and CIP deviations. The Data Validation Plan (DVP) specifies the checks that are to be performed on subject data for the clinical investigation. All investigation-specific and standard data validation programming will be tested in a separate testing environment prior to use in the clinical investigation.

When all data from all endpoints have been entered, discrepancies solved and all reconciliation with the safety database is complete, the Viedoc eCRF will be locked and the data will be analyzed.

13.2 Data Management – Image review part

The following work will be done by the sponsor during the image review part of the investigation:

DICOM images and information about site-determined diagnosis will be downloaded from Viedoc eCRF and stored in a suitable structure. Sponsor will then generate synthetic contrast weighted images using investigational device SyMRI 15 (3D) with an automated script. Some DICOM tags (e.g. study and series description) need to be adjusted on both conventional and synthetic images in order to completely blind readers to the type of image they review. The images will be given a new identifier to be used for the Image Review part.

The contrast weighted images will then be upload to CARPL. Sponsor will assign the cases to the readers for Image Review part 1. When all readers have completed the reading, the access to the images from part 1 will be removed. Sponsor will then assign the cases to the readers for Image Review part 2. After the memory washout period the readers can start Image Review part 2.

When part 2 of the Image Review is completed, the Sponsor will download the answers from image review part 1 and part 2 from CARPL and will incorporate the answers with the original Subject ID and site-determined diagnosis. This data will be transferred to Viedoc eCRF for long-term storage and will be analyzed according to the SAP.

13.3 Data Retention

The medical records of clinical investigation subjects must be retained in accordance with local legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

The PI shall retain all clinical investigation records during the investigation and for the period required by the applicable regulatory requirements or for at least 10 years after the premature termination or completion of the clinical investigation, whichever ever is the longest. The PI must take measures to prevent accidental or premature destruction of these documents. The PI should contact the Sponsor prior to destruction of any records or reports pertaining to the clinical investigation in order to ensure they no longer need to be retained. In addition, if the PI leaves the hospital, he/she should provide the Sponsor with the name and address of the person who will look after and be responsible for the clinical investigation-related records. If the records will be transferred to another person/party, the transfer will be documented at the investigation site or at the Sponsor.

The Sponsor will retain the Study Master File (SMF) in line with applicable regulations or for at least 10 years after the clinical investigation has ended, or, in the event that the device is subsequently placed on the market, at least 10 years after the last device has been placed on the market.

13.4 Monitoring, Audits and Inspections

During the clinical investigation, the monitor will have regular contacts with the investigation site. These contacts will include visits to confirm that the facilities remain adequate to specified standards and that the investigation team is carrying out the procedure stated in the CIP. All data must be accurately recorded in the eCRF. Source data verification (SDV), a comparison of data in the eCRF with the subject's medical records and other records at the investigation site, will also be performed. The eCRF and source documents and records must be made accessible during the monitoring visit.

The monitor or other Sponsor personnel will be available between visits if the PI or other investigation staff at the site needs information and/or advise. Authorized representatives of the Sponsor and/or international Regulatory Agencies may visit the site to perform audits/inspections, including SDV.

14 AMENDMENTS TO THE CIP

Any change to the approved clinical investigation documents will be documented and include a written justification. Any effects of the implemented changes on other clinical investigation documents shall be evaluated and documented. If deemed necessary, affected documents shall be properly updated and relevant parties notified. The version number and date of amendments shall be documented.

All amendments to the CIP will be documented in an amendment log and communicated to relevant parties.

Proposed amendments to the CIP shall be agreed upon between the Sponsor and PI, or the Coordinating Investigator. The amendments to the CIP shall be notified to, or approved by, the IRB and Regulatory Agencies, if required.

15 DEVIATIONS FROM THE CIP

A CIP deviation is a failure to follow, intentionally or unintentionally, the requirements of the CIP. Every effort should be made to comply with the requirements of the CIP and the investigator is not allowed to deviate from the CIP. Furthermore, waivers from the CIP is prohibited.

As required by national regulations or guidelines, requests for deviations and reports of deviations will be provided to the IRB if the deviation affects subject's rights, safety and well-being, or the scientific integrity of the clinical investigation.

Under emergency circumstances deviations from the CIP may proceed without prior approval by the Sponsor and favorable opinion of the IRB if the rights, safety and well-being of human subjects need to be protected. Such deviations will be documented and reported to the Sponsor and IRB as soon as possible in accordance with national regulations.

When the monitor or Sponsor identifies that the PI is out of compliance, this will be notified to the PI in writing, with a request to correct the source of the deviation immediately. Corrective action will be implemented to avoid repeated non-compliance, which will usually include re-training and may include terminating the clinical investigation at the site.

The Sponsor is responsible for analyzing deviations and assessing their significance. Corrective action(s) will be implemented to avoid repeated deviations, which may include suspending the clinical investigation at the investigation site or disqualify the PI.

16 DEVICE ACCOUNTABILITY

Device accountability at site is not applicable since the Investigational Device, the software SyMRI will not be distributed to site in the clinical investigation. Instead, the Sponsor will use SyMRI to generate the synthetic contrast weighted images which will be sent to the readers for evaluation during the image review part. The Sponsor will store relevant software version information in DICOM tag SyntheticMR private group (3005).

Regarding the 3D-QALAS sequence, a research agreement between site and Philips will regulate site's access to the sequence.

17 STATEMENTS OF COMPLIANCE

This clinical investigation will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (Appendix C). Furthermore, the clinical investigation will be conducted in compliance with ISO 14155:2020 and applicable regional or national regulations.

17.1 Institutional Ethics Review

The final CIP, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB and Regulatory Agency before enrolment of any subject into the clinical investigation. The PI is responsible for informing the IRB of any amendment to the CIP as per local requirements.

Any additional requirements imposed by the IRB or Regulatory Agency shall be followed.

17.2 Insurance

The Sponsor will purchase insurance to cover its liability under applicable tort law for bodily injury sustained by a clinical investigation participant.

18 INFORMED CONSENT PROCESS

All subjects will receive written and verbal information regarding the clinical investigation prior to any investigation-related procedures take place. This information will emphasize that participation in the clinical investigation is voluntary and that the subject may withdraw from the investigation at any time and for any reason. All subjects will be given the opportunity to ask questions about the investigation and will be given sufficient time to decide whether to participate in the investigation or not. If any new important information arise during the clinical investigation the subject will be informed both orally and in writing.

The written subject information explains that data will be collected and compiled maintaining confidentiality in accordance with national data legislation, and that authorized representatives of the Sponsor, international Regulatory Agencies or IRBs may require direct access to those parts of the medical records relevant to the investigation, including medical history, for verification of data. Additionally, the written subject information specifies that data will be recorded, collected, processed and may be transferred (within the US and to non-US countries). In accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the General Data Protection Regulation (GDPR) 2016/679, the data will not identify any subjects taking part in the investigation.

Before any investigation-related procedures, the Informed Consent Form will be signed and dated by the subject (or their legally acceptable representative and/or witness, as applicable) and by the Investigator who gave the subject the verbal and written information.

If a child is to be enrolled in the clinical investigation, the parent(s) or guardian must provide permission, with the assent of the child when appropriate, as described in 21 CFR part 50, subpart D.

The child and the parent(s) or guardian(s) will be given adequate time and an adequate place to read and review the Informed Consent Form and Assent form. The Assent form is a shorter, more understandable consent form that is given to the child for them to agree to the study on. The study will be explained to the child in an age-appropriate language that the child can understand. The child will be given an opportunity to ask questions about the study (without the presence of the parent or guardian, if requested and appropriate) before signing.

Age-appropriate Assent Forms for children will be used in this clinical investigation. The Assent forms should be signed by the child and the Informed Consent Form should be signed by the parent(s) or guardian(s). For children who are deemed too young to give assent (age defined by reviewing IRB), no signature is required by the child. The sub-group Anesthesia will have a higher risk determination than children not receiving anesthesia and consent will therefore be required from both parents/legal guardians. For children not receiving anesthesia (Sub-group No-anesthesia), consent will be required from one parent/legal guardian.

If a child, who understands the procedures of the investigation, do not want to participate in the investigation, this decision must be respected.

For vulnerable adult subjects, e.g. subjects with Alzheimer's disease, an altered informed consent process will take place. The study will be explained using appropriate, simplified language, and the subject will be given ample time to ask question and to involve family member(s), significant other(s) and/or a Legally Authorized Representative (LAR). If needed, the LAR will sign the Informed Consent Form on behalf of the vulnerable subject. The LAR must provide consent prior to subject participation in the study.

19 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

The definitions and procedures for reporting Adverse Events (AE), Adverse Device Effects (ADE), Serious Adverse Events (SAE), Serious Adverse Device Effects (SADE), Unanticipated Serious Adverse Device Effects (USADE) and Unanticipated Adverse Device Effects (UADE) are presented in the subsections below. It is of utmost importance that all staff involved in the investigation is familiar with the definitions and procedures and it is the responsibility of the Principal Investigator to ensure this.

19.1 Definitions

Adverse Device Effect (ADE) [ISO 14155:2020]
Adverse event related to the use of an investigational medical device.

Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Note 3: This includes 'comparator' if the comparator is a medical device.

Adverse Event (AE) [ISO 14155:2020]
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 and whether anticipated or unanticipated.

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 the use of investigational medical devices or comparators.

Device Deficiency [ISO 14155:2020]
Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

Note 1: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

Note 2: This definition includes device deficiencies related to the investigational medical device or the comparator.

Serious Adverse Device Effect (SADE) [ISO 14155:2020]
Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious Adverse Event (SAE) [ISO 14155:2020]
Adverse event that led to any of the following:

a) death,

b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
   i. A life-threatening illness or injury, or
   ii. A permanent impairment of a body structure or a body function including chronic diseases, or
   iii. In-patient or prolonged hospitalization, or
   iv. medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,
c) foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment.

Note: Planned hospitalization for pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious Health Threat [ISO 14155:2020]
Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons.

Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

Unanticipated Serious Adverse Device Effect (USADE) [ISO 14155:2020]
Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

Note: Anticipated Serious Adverse Device Effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

Unanticipated Adverse Device Effect (UADE) [21 CFR 812.3(s)]
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

19.2 Non-reportable adverse events

Not applicable

19.3 Methods for discovering and documenting AE/ADE

All subjects will be carefully monitored for the occurrence of AEs throughout the clinical investigation. Events prior to inclusion will be considered medical history. The Principal Investigator will collect safety information using non-leading questions such as "have you experienced any new health problems or worsening of existing conditions?". Events directly observed or spontaneously volunteered by subjects will also be recorded throughout the clinical investigation.

Clearly related signs, symptoms and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible.

All AEs, including but not limited to events reported by the subject or reported in response to an open question by the Principal Investigator or member of the investigation team, which fall into any of the

previously defined definitions must be recorded as an AE in the Viedoc eCRF and should include the following information:

- Brief description of the event (diagnosis)
- Date of event onset
- Date of event resolution
- Severity
- Seriousness
- Causality assessment (i.e. relationship to medical device and/or procedure)
- Unanticipated ADE (Yes, No)
- Event treatment
- Event outcome / resolution

If the AE is classified as an Unanticipated ADE and meets the seriousness criteria, i.e. an USADE/UADE, it should be subject to expedited reporting as described in 19.5.

A system generated e-mail notification to Sponsor and CRO will be triggered whenever an SAE or a USADE/UADE is entered or updated in the Viedoc eCRF, allowing immediate monitoring of the event.

19.3.1 Severity

Severity describes the intensity of an AE and will be assessed as:

- Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: minimal, local or non-invasive intervention indicated, limiting age-appropriate instrumental activities of daily living.
- Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.
- Life-threatening consequences; urgent intervention indicated.
- Death related to AE.

If an AE changes in severity, it should be reported as an AE of new severity but with the same description and identifier.

19.3.2 Causality

Causality is the relationship between the use of the medical device (including the investigational device, the comparator and the medical – surgical procedure) and the occurrence of each AE.

During the causality assessment, clinical judgment shall be used and the relevant documents, such as the CIP or the risk analysis report shall be consulted, as all the foreseeable AEs and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

For the purpose of harmonizing reports, each AE will be classified according to four different levels of causality. The Sponsor and the Principal Investigator will use the following definitions to assess the relationship of the AE to the investigational medical device, the comparator, or the medical – surgical procedures:

- **Not related:** relationship to the device or procedures can be excluded when:
  - The event has no temporal relationship with the use of the investigational device or the procedures related to the investigational device;

- The serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- The discontinuation of medical device application or the reduction of the levels of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- The event involves a body-site or an organ than cannot be affected by the device or procedure;
- The serious event can be attributed to another cause (e.g. an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors);
- The event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

- **Possible:** the relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
- **Probable:** the relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot bereasonably be explained by another cause.
- **Causal relationship:** the serious event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:
  - The event is known side effect of the product category the device belongs to or of similar devices and procedures;
  - The event has a temporal relationship with investigational device use/application or procedures;
  - The event involved a body-site or organ that:
    - The investigational device or procedures are applied to;
    - The investigational device or procedures have an effect on;
  - The serious event follows a known response pattern to the medical device (if the response pattern is previously known);
  - The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of activation/exposure), impact on the serious event (when clinically feasible);
  - Other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
  - Harm to the subject is due to error in use;
  - The event depends on a false result given by the investigational device used for diagnosis, when applicable;

  In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The Sponsor and the PI will distinguish between AEs related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An AE can be related to both the procedures and the device. Complications of procedures are considered not related if the said procedures would have been applied to the subjects also in the absence of device use/application.

Particular attention shall be given to the causality evaluation of USADE/UADE, since the occurrence of USADE/UADE could suggest that the clinical investigation places subjects at increased risk of harm than was expected beforehand.

In case of disagreement between the Sponsor and the PI assessments of the AE, both opinions shall be communicated to concerned parties.

19.4 Methods for Discovering and Documenting Device Deficiencies

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance shall be reported as a device deficiency without unnecessary delay to the Sponsor by using the device deficiency form. It is the PI's responsibility to record every observed device deficiency together with an assessment. The Sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SADE. Device deficiencies that are assessed to or have SADE potential should be subjected to expedited reporting as described in Section 19.5.

A system generated e-mail notification to Sponsor and CRO will be triggered whenever a DD is entered or updated in the Viedoc eCRF, allowing immediate monitoring of DDs.

19.5 Reporting of USADE/UADE

Since the US IDE definition of a UADE is very similar to the ISO 14155 definition of a USADE, any serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment will be classified as a USADE in this clinical investigation.

USADEs must be reported by the PI to the Sponsor and the reviewing IRB, as described below:

- PI is required to submit a report of a USADE to the Sponsor and the reviewing IRB as soon as possible, but in no event later than **10 working days** after the investigator first learns of the event (21 CFR 812.150(a)(1)).
- Sponsor must immediately conduct an evaluation of a USADE and must report the results of the evaluation to FDA, all reviewing IRBs, and all participating PIs within **10 working days** after the Sponsor first receives notice of the effect (21 CFR 812.46(b), 812.150(b)(1)).

The initial report should contain as much information as possible, but as a minimum the following information:

- Subject ID
- Adverse Event ID
- Date of procedure/first use
- Date of event onset
- Age (years)
- Patient gender (female, male, other, unknown)
- Classification of event:
    - death,
    - life-threatening illness or injury,
    - permanent impairment/chronic disease,
    - hospitalization,
    - medical or surgical intervention,
    - fetal distress, fetal death or congenital physical or mental or birth defect,
    - not applicable[1]
- Description of event:

[1] This option is only to be selected in case of reportable device deficiencies that did not lead to an SAE.

  - Nature of the observed symptoms
  - Duration and severity of the symptoms
  - Date of onset of first signs of the event (before it became a SAE)
  - Medical background of the patient
  - Medical care of the patient
  - Comments on the event in relation to already known safety data
- Action/treatment/outcome
- Relationship to procedure (not related, possible, probable, causal)
- Relationship to the device (not related, possible, probable, causal)
- Unanticipated SADE (Yes, No)
- Investigation arm (test group, comparison group, blinded, not applicable)
- Event status (resolved, resolved with sequelae, ongoing, death)
- Date of event resolution (if ongoing enter not applicable)

SAE/SADE EMERGENCY CONTACT DETAILS
Name: Madeleine Enström, QA/RA Manager, SyntheticMR
Phone: +4673-0690490
Email: madeleine.enstrom@syntheticmr.com

19.6 Foreseeable adverse events and anticipated adverse device effects

Foreseeable adverse events associated with MRI:

- the MRI scanner uses radio frequency waves that can, on rare occasions, cause a mild warming sensation similar to what you feel on a warm day
- the MRI scanner makes loud banging noises during the scanning session
- the magnetic fields in the scanner can cause mild twitching in the arms and legs
- some people feel uncomfortable and/or claustrophobic when lying inside the MRI scanner

There are no anticipated adverse device effects in the clinical investigation.

19.7 Data Monitoring Committee

Establishment of a Data Monitoring Committee (DMC) is not considered necessary for this pre-market clinical investigation since 1) the Magnetic Resonance Imaging (MRI) devices used in the investigation, including the 3D-QALAS sequence, will be within FDA specified parameters and 2) the MR images acquired for the investigation will not be used for diagnostic reasons or treatment decisions which means that the subjects will not be affected by the use of the Investigational Device SyMRI 15 (3D). In case data retrieved during the clinical investigation contradicts this decision, it will be reconsidered.

20 Vulnerable Population

The investigation population has been selected to represent the most common pathologies and abnormalities seen in brain MRI of the target population.

For the adult population, this means that vulnerable subjects with e.g. Alzheimer's disease and other disorders which could involve cognitive impairment, may be included in the investigation. For this group of patients, a modified informed consent process will be used including the possible use of a Legally Authorized Representative (LAR), see Section 18.

For the pediatric population, subjects aged 0-17 years will be included. Pediatric subjects are per se described as a vulnerable population according to ISO 14155:2020 and FDA regulations provide additional safeguards for children enrolled in clinical investigations (21 CFR part 50, subpart D). Therefore, also the potential subjects' legal representative(s) will receive information both verbally and written about the study prior any decision about the subjects' participation. The subject will be informed about the clinical investigation within his/her ability to understand, i.e. additional versions of the subject information have been developed to target different ages. If the subject will have difficulties to understand the contents of participating in the clinical investigation, i.e. as a child may have, additional time will be given for questions regarding the investigation as well as consent procedure. For more information on the consent process for pediatric subjects, see Section 18.

21 SUSPENSION OR EARLY TERMINATION OF THE CLINICAL INVESTIGATION

If the clinical investigation is terminated early or suspended due to reasons of safety, the Sponsor will promptly inform the PI(s) and the investigation site(s) of the termination or suspension and the reason(s) thereof. The IRB will also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the PI(s) / investigation site(s).

In addition, CIP violations may result in termination of the Clinical Investigation at a site.
CIP violations are deviations made without permission as a result of error or fraud/misconduct. Where the monitor or Sponsor identifies that the Principal Investigator is out of compliance, this will be noted to the PI in writing, with a request to correct the source of the deviation immediately. Corrective actions will be implemented to avoid repeated non-compliance, including re-training. However, in case of repeated non-compliance despite implemented corrective actions, the clinical investigation will be terminated at the site.

21.1 Subject Follow-up

If the clinical investigation is prematurely terminated, the Sponsor and the PI(s) will assure that adequate consideration is given to the protection of subjects' interest, including subject follow-up.

22 PUBLICATION POLICY

The clinical investigation will be registered in a publicly accessible database before recruitment of the first subject.

A final report of the clinical investigation (CIR) will be completed, even if the investigation is prematurely terminated. The report will be prepared by the Sponsor according to the guideline presented in Annex D of ISO 14155:2020.

All information supplied by the Sponsor in connection with this investigation will remain the sole property of the Sponsor and is to be considered confidential information. No confidential information will be disclosed to others without obtaining prior written consent from the Sponsor and will not be used except in the conduct of this investigation.

The Sponsor may choose to publish or present data from this clinical investigation. If a Principal Investigator is offered first authorship, he/she will be asked to comment and approve the publication. The Sponsor has the right to use the results for registration and internal presentation and for promotion.

Following completion of the entire investigation at all sites, Sponsor shall use reasonable endeavors to encourage appropriate publication or other dissemination based on the data collected in the investigation. The aim is to create two multi-center publications, one for the pediatric sub-population and one for the adult population. Co-authorship will be given to one person per site that contributed with data for the specific population.

Institution shall not publish data/results derived from the individual institution site until such appropriate publication or other dissemination has been published in a multi-center publication.

Sponsor will make the entire (anonymized) data collected in the Study available to all participating Principal Investigators and their Institutions for further research purposes after the investigation is concluded. In case publications are created based on the investigation data the Principal Investigator agrees to give credit to the original Institution and Investigator that participated in the Image Acquisition in accordance with good academic practice.

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24 APPENDICES

24.1 Appendix A – Clinical Investigation Plan Agreement Form

Investigation code: CIP-003

CIP version: K

I agree to the terms of this CIP. I will conduct the investigation according to the procedures specified herein.

Site No.:

Coordinating/Principal Investigator

Name:

Signature: _____

Date (dd-Mmm-yyyy): _____

24.2 Appendix B – Clinical Investigation Contact List

COORDINATING INVESTIGATOR
Name: Dr. Jeffrey Miller
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CLINICAL INVESTIGATION SITES
A separate contact list of all principal investigators, investigation sites, and institutions will be available in the Study Master File (SMF).

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Site 2
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Site 3
Replaced by Site 7

Site 4
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Site 5
Name: Nemours Children's Health, Nemours Children's Hospital, Florida
Address: 6535 Nemours Pkwy, Orlando, FL 32827, USA

Site 6
Name: ProScan Imaging
Address: 1020 Crosspointe Dr Suite 103, Naples, FL 34110, USA

Site 7
Name: DENT Neurologic Institute
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24.3 Appendix C – Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

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, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

PREAMBLE

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 be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

GENERAL PRINCIPLES

3. 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."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. 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 proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must 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.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this 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.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

RISKS, BURDENS AND BENEFITS

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

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

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

VULNERABLE GROUPS AND INDIVIDUALS

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research

SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS

21. 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.

22. The design and performance of each research study involving human subjects must be clearly described and justified 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, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions

RESEARCH ETHICS COMMITTEES

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. 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. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

PRIVACY AND CONFIDENTIALITY

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

INFORMED CONSENT

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, 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, post-study provisions 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.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must 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 must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised 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 group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent 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 authorised representative. The potential subject's dissent should be respected.
30. 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 group. In such circumstances the physician must seek informed consent from the legally authorised 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 must be obtained as soon as possible from the subject or a legally authorised representative.
31. The physician must fully inform the patient which aspects of their 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 adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

USE OF PLACEBO

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

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option

POST-TRIAL PROVISIONS

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

RESEARCH REGISTRATION AND PUBLICATIONS AND DISSEMINATION OF RESULTS

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers 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. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

UNPROVEN INTERVENTIONS IN CLINICAL PRACTICE

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.