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## CLINICAL TRIAL PROTOCOL

**Study Title:** Comparison of outputs from the STrategically Acquired Gradient Echo (STAGE) Protocol to conventional 1.5 T and 3.0 T MR images

**Short Title:** Comparing STAGE outputs with conventional MR Images

**Study Investigational Device:** STAGE

**Sponsor:** SpinTech, Inc.

**Protocol #:** CP-STAGE-001

**IRB #:** 20193130

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## 1. INTRODUCTION .....

### 1.1. Overview of Device/Procedure

The study objective is to validate STAGE images and, when applicable, their equivalence to conventional MRI through an assessment by a trained certified neuroradiologist in a clinical setting.

The data collected in this study will be utilized to support an FDA 510(k) submission to gain FDA clearance to market the FDA Class II STAGE system in the United States.

*This study does not involve comparing test subjects vs. control subjects, nor does it involve any treatment and follow-up.*

### 1.2. Study Rationale

Several hurdles which radiologists encounter specifically in MRI, are: acquiring the most amount of information; minimizing acquisition time; acquiring images with adequate quality; and standardization of the acquired images. Current neuroimaging protocols are in the realm of 20 minutes which include conventional T1-weighted, T2-weighted, T2 FLAIR imaging and/or Diffusion Weighted Imaging. The image quality depends on several factors including magnetic field strength, coils, image resolution and often differ depending on these factors from scanner to scanner.

The proposed STAGE imaging protocol (Strategically Acquired Gradient Echo) is a multipronged image acquisition and processing approach to address the aforementioned issues. Using specific collection parameters from a 3D gradient echo sequence, MRI scans can be performed for 3/1.5 Tesla magnets across most existing machines, independent of manufacturer. Upon data collection, the images are exported from the PACS archiving system and processed in our STAGE module to generate several weighted contrasts and quantitative maps, then returned to the PACS for radiologic review. All of the contrasts and quantitative maps are co-registered, 3D, and the same image resolution which makes for easy comparison between scans and manufacturers. Having quantitative maps provides source signal which mitigates bias between scanners. This protocol has great potential to decrease scan times, increase hospital and image center throughput, and also provide quality 3D images.

## 2. SUMMARY OF DEVICE DESCRIPTION .....

### 2.1. STAGE

#### 2.1.1.[Device / System Sterile Components]

STAGE is composed of a medical grade computer manufactured by Onyx Healthcare. The system has been tested and certified to ISO standards as well as other compliance standards (see 3.2).

#### 2.1.2.[Device / System Non-Sterile Components]

No non-sterile components exist in the device.

## 3. RISK BENEFIT ANALYSIS .....

### 3.1. Risk Analysis

*The following categories were used to assess the likelihood:*

*"Common" (i.e., approximate incidence > 25%)*

*"Likely" (i.e., approximate incidence of 10-25%)*

*"Infrequent" (i.e., approximate incidence of 1-10%)*

*"Rare" (i.e., approximate incidence < 1%)*

Participation in this study poses a risk for breach of confidentiality. Records will be stored in a safe, lockable storage unit. RARE

MRI may be uncomfortable for some subjects. MRI does not involve the use of radiation; it does however involve the use of a strong magnetic field. Prior to starting the scan each subject will be asked if they have

any metal implanted in their body. The presence of implanted metal will influence the scans. Some subjects who have claustrophobia (fear of small closed places) are concerned about being in the scanner, and if at any point during the scan this concerns the subject, the scanning will be stopped. Some studies, like the MRI, have the potential to cause "peripheral nerve stimulation" (PNS). PNS is a light touching sensation on the skin surface, lasting only for a few seconds and is not harmful to the subject. The MRI machine is operated within federal guidelines so the potential for inducing PNS is low. There is the potential that a magnetic resonance image may reveal an abnormality, such as a cyst or tumor. Many such abnormalities are not clinically significant, but subjects may want to investigate them further. Such a finding may require notifying the subject's primary Physician. RARE

STAGE will use a Medical Grade by Onyx Healthcare, Inc. and may have electrical or power issues. RARE

*What will be done to reduce or monitor these risks?*

- Prospective data will include imaging as well as questionnaire/survey with the neuroradiologist to evaluate the performance of STAGE and its outputs. The study will not consist of retrospective data.
- To minimize the breach of confidentiality risk, the subject's name or hospital number to identify them will not be used on any study records. Instead a unique study number will be assigned to each subject. Only this number will be used on study documents that relate to the subject. The list of subject names and corresponding unique study number will be kept in a secure, locked location. At the end of the project, this list will be destroyed.
- To minimize discomfort during the MRI, pads and blankets will be used to position each subject so they are as comfortable as possible during the scan. Subjects may wear foam earplugs or hearing-protective headphones to reduce hearing the loud noises made by the scanner. Subjects will be able to talk to us throughout the study, and can let us know right away if they want to stop the study and get out of the scanner.

The Onyx High Performance Medical Grade Fanless Box PC (model: MEDPC-9200) which the STAGE software resides has multiple certifications from third parties which conform to safety and quality standards for usage in a clinical environment. The box has certification from:

Presafe: Complies with ISO 13485:2003 requirements

DNV: GL: Complies with ISO 14001:2015, ISO 9001:2015/CNS 12681:2016

Dekra: Complies with FCC CFR Title 47 Part 18: 2016 (subpart C), EN 55011: 2009/A1: 2010 Class B (Group 1), EN 61000-3-2: 2014, En 61000-3-3: 2013, EN 60601-1-2: 2015, IEC 60601-1-2:2014, IEC 61000-4-2 Ed. 2.0: 2008, IEC 61000-4-3 Ed. 3.2: 2010, IEC 61000-4-4, Ed. 3.0: 2012, IEC 61000-4-5 Ed. 3.1: 2014+A1: 2017, IEC 61000-4-6 Ed. 4.0: 2013, IEC 61000-4-8 Ed. 2.0: 2009, IEC 61000-4-11 Ed. 2.1: 2004+A1: 2017.

### 3.2. Justification and Potential Benefit

*To the individual:* There are no benefits for the research subject.

*To society:* Showing that the STAGE protocol has equal to/or better quality than conventional images would have great impact in the clinical realm. Scan times would therefore be reduced, mitigating patient discomfort within the scanner (especially in frail, aged, neurodegenerative subjects, as well as children). The STAGE protocol also an efficient way to collect this many contrasts, and therefore hospitals and imaging centers can increase their throughput. Standardization would also be achieved between manufacturers and field strengths, which allow for ease in longitudinal assessment, repeat scans. Further, standardized data is optimal as input for Artificial Intelligence algorithms for lesion detection, or to discern any abnormalities based on MR signal.

## 4. STUDY OBJECTIVES AND ENDPOINTS .....

### 4.1. Primary Objectives

To evaluate the safety of using the STAGE system in a clinical setting. Potential risks have been mitigated in the User Requirements which will be subject to testing via Verification and Validation.

#### 4.1.1. Secondary Objectives

To evaluate the effectiveness of STAGE output data based on the quality of their image contrasts and maps in comparison with conventional MR images.

### 4.2. Primary Endpoints

4.2.1. Primary Endpoint 1: each STAGE and MRI input or output is graded qualitatively by an experienced individual at the MRI center. Quality grading is performed on a 5-point scale [5=excellent; 4=good; 3=acceptable; 2=poor; 1=unacceptable] on several criteria [blurring/ghosting/ringing; flow artifact; intensity and homogeneity; signal to noise ratio; susceptibility artifacts]. For the questions with a 5-point score, the points will be averaged with scores  $\geq 3$  can be used for clinical diagnosis.

4.2.2. Primary Endpoint 2: contrast appearance will also be graded on a binary basis: passed, failed. All binary questions should have a 'Pass' answer will qualify as "Passed."

### 4.3. Study Success

The study will be considered successful if STAGE data quality is found to be clinically acceptable and generated contrasts are as expected based on statistical testing.

## 5. CLINICAL STUDY DESIGN .....

This is prospective observational, non-interventional cohort study to evaluate the efficacy of the collection protocol and STAGE system processing algorithm. STAGE system output will be compared to the MRI output from the same patient.

### 5.1. Test Arm

n/a.

### 5.2. Control Arm

n/a

## 6. SUBJECT SELECTION

### 6.1. Subject Inclusion Criteria

- Subjects 6-80 years of age, inclusive.
- Literate in English
- No contraindications to MR\*
- Not claustrophobic

\* ACR Guidance Document on MR Safe Practices 2013 J Magn Reson Imaging 2013 Mar;37(3):501-530

### 6.2. Subject Exclusion Criteria

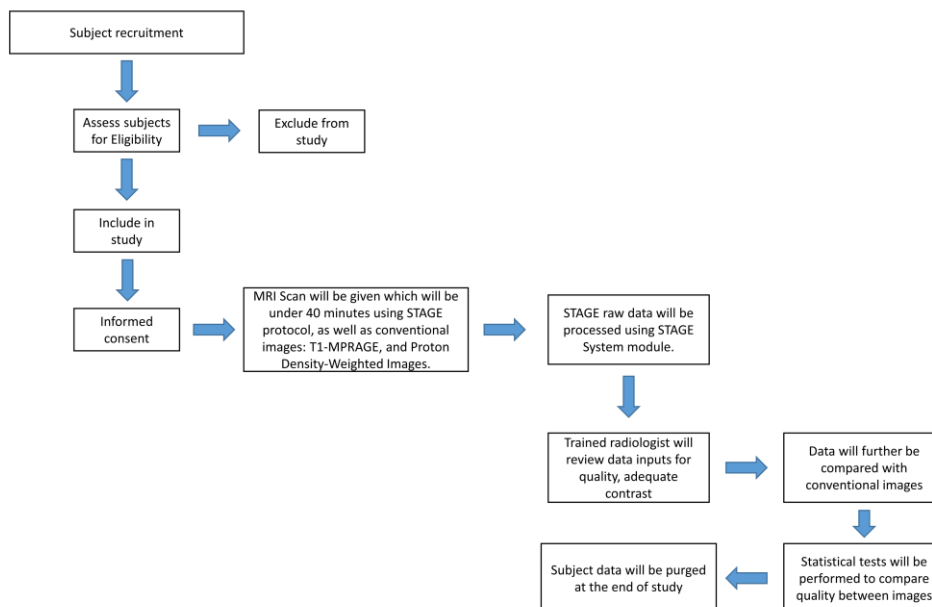
- Subject has diffuse white matter disease or leukoaraiosis.
- Participants, or Subject's parent or guardian unable to read and sign an informed consent.
- Women who are pregnant or breast-feeding.
- Those with major surgery within the past eight weeks or scheduled surgery within 30 days.
- Chronic back pain or inability to lie still for 5 minutes or more.
- History of drug or alcohol abuse.
- Individuals who exceed 38 BMI or 320 lbs.
- Individual whose girth exceeds the magnetic bore.
- Direct employee or student of the PI.
- Participants belong to a vulnerable group.

### 6.3. [Procedure] Eligibility Criteria

All subjects who meet all inclusion and do not meet any exclusion criteria are eligible to participate in the study. Subjects who are eligible will not be compensated for this study.

## 7. STUDY PROCEDURE

### 7.1. Study Diagram



### 7.2. Clinical Procedure for STAGE



### **System setup\***

\*This study assumes the principal investigators and MRI staff have adequate understanding of the MRI sequences involved as well as quantitative mapping involved.

Per user requirements and manual, the STAGE module will be installed by a trained technician from SpinTech, Inc. Tests will be performed to ensure networking setup is successful in which the module is connected to PACS system, with the ability to receive and send data.

The subject will undergo a survey administered by a Physician to determine he/she is cognitively-intact, and meets all of the inclusion criteria and none of the exclusion criteria.

#### **MRI Scan**

Total study time which includes the patient intake and the scans may take up to two hours.

The subject will undergo a brain MRI scan using the STAGE Protocol\* either at 3 Tesla or 1.5 Tesla field strength. The STAGE protocol consists of two flow-compensated spoiled 3D gradient-echo multi-echo scans, run at different specific flip angles.

For 3T\*\* scan parameters are as follows: FOV: 256x192 mm, matrix size: 384x288 or 384x384, slices:  $\geq 64$ , slice thickness: 1.34mm and 2mm, TE= 7.5/12.5/17.5ms, bandwidth per pixel <240Hz, and TR=25ms. Two multi echo scans will be run: with FA = 6° and one with FA = 24°. Data will be collected with In-plane resolutions of 0.67x1.33mm and 0.67x1mm (freq dir x phase dir). Scanner options for partial fourier and elliptical sampling should be turned on if available. The total protocol time will be roughly 5 minutes.

For 1.5T\*\*, the scan parameters are: FOV: 256x192 mm, matrix size: 384x288 or 384x384, slices:  $\geq 48$ , slice thickness 2.7mm and 2mm, TE= 10/20/35ms, bandwidth per pixel <200Hz, and TR = 40ms. Data will be collected with in-plane resolutions of 0.67x1.33mm and 0.67x1mm (freq dir x phase dir). Two multi echo scans will be run: One with with FA of 7° and one with 35°.

Upon collection, the subject's raw DICOM files transferred to the PACS system and then manually sent by the user to the STAGE module for post-processing. (*note: the subject need not be present for this step*) The processed STAGE images will be sent back to the PACS system where they remain within the participant's scan folder and are clearly labeled. They can then be viewed at an integrated workstation. Original and temporary data linked to the patient will be deleted from the module after it is processed.

The generated contrasts are the following:

- Enhanced T1-weighted images (T1We)
- Susceptibility Weighted Images (SWI)
- T1 Maps
- Proton Density Maps
- R2\* Maps
- Susceptibility maps (SWIM)
- Pseudo and modified pseudo SWIM
- True SWI (tSWI)
- Dual inversion recovery images of the CSF, White matter, and Gray matter
- MRA
- Maximum or minimum intensity projections of SWI, tSWI, R2\*

Options for outputting sagittal and coronal reformatted images will be provided for the T1We and T1 maps. Additionally, all images will have an option for skull stripping as well as a 1x1x2 sliding window filter.

\*No contrast administration is required in this protocol.

\*\* These parameters may vary slightly depending on the limitations of the scanner software version.

For the purposes of validation, additional data will be collected as a gold standard to compare with the STAGE inputs outputs. This includes 3D T1 MP-RAGE and proton density weighted imaging, which are to be collected at recommended parameters, but with similar FOV and matrix size to the images in the STAGE imaging protocol. Scan collection times will range from about 5 – 10 minutes, depending on the field strength.

The MD will be given a survey with questions concerning image quality, whether contrasts based on the tissue properties match the input and outputs, or if anatomical structures appear or not.

No biological specimens will be collected in this study. The study involves MR imaging. STAGE involves an Investigational medical device which is labeled for Investigational Use Only, per FDA IDE labeling requirements/research purposes only.

For children (subjects aged 6-17 years) involved in this study, headphones will be provided to ensure comfort. The subject may need to stay still for a time period up to 40 minutes. A sedative may be prescribed by the subject's primary physician to be taken prior to the scan to mitigate motion during the scan. This study will not involve any intravenous sedation. The subject will be informed that he or she can rest shortly between sequences (each sequence may last 5-10 minutes) if needed, and that the study can be stopped at any time if he or she needs.

### 7.3. Follow-up Procedures

No follow-up procedures are required for this study. As of 8/26/2020, the protocol parameters were optimized to improve the scan quality. Some subjects may be scanned a second time as a replacement data set for the initial scan. A new informed consent form should be signed. In the situation when a participant cannot be recalled/retained within the study then their original data will not be used towards proving the study endpoints, and a new participant will be recruited.

### 7.4. Patient Management

#### 7.4.1. Treatment Failure

n/a

#### 7.4.2. Loss to Follow-up

n/a

## 8. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN .....

### 8.1. Analysis Samples

The data from up to one hundred twenty (120) subjects will be analyzed. A radiologist will review the quality of the STAGE inputs and outputs as acceptable or not acceptable for clinical review as adjunctive imaging. For each image (STAGE and MRI) input or output, the radiologist will answer survey questions which pertain to the contrast quality and the tissue(s) involved. They will be further compared with output from conventional MR images for quality.

## 8.2. Sample Size Justification

Up to one hundred twenty (120) subjects (aged 6-80 years) will be enrolled in this study, with an expected data attrition rate of 20% which may be due to poor data quality from motion artifact or withdrawal from the study. Eighty subjects, minimum, will provide at least 90% power (with two-tailed alpha of 0.05) to reject the null hypothesis that STAGE images have lower or equal score to conventional MRI images. This was calculated from a paired t-test which has a slightly higher sensitivity than a Wilcoxon-test. Differences of STAGE-scores and MRI-scores will be paired. For the power calculation I assume a mean difference of STAGE-score – MRI-score of 0.5 points with STD =1.

### 8.2.1.Total Sample Size

Total sample size is expected to be a a minimum total of 80 cases divided amongst the magnets from either one site or multiple sites.

## 8.3. DATA ANALYSIS AND REPORTING OF RESULTS

### 8.3.1.Analysis of Effectiveness Endpoints

- 8.3.1.1. Primary Endpoint 1: The score of each STAGE and MRI input or output across individuals will be analyzed using a Mann-Whitney tests.
- 8.3.1.2. Primary Endpoint 2: General image quality on a binary basis (passed, failed) will be required to pass in all cases where the input data was found to be clinically useable.

Alpha of  $p < 0.05$  will be considered significant.

## 9. ADVERSE EVENT REPORTING.....

### 9.1. Definitions of Adverse Events

An **Adverse Event** is an event that occurs during the course of a research protocol that either causes physical or psychological harm, or increases the risk of physical or psychological harm, or results in a loss of privacy and/or confidentiality to a research participant or others (such as family members).

Adverse events for MRI scans are very rare. Millions of MRI scans are performed in the US every year, and the FDA receives around 300 adverse event reports for MRI scanners and coils each year from manufacturers, distributors, user facilities, and patients. The majority of these reports describe heating and/or burns (thermal injuries). Second degree burns are the most commonly reported patient problem. Other reported problems include injuries from projectile events (objects being drawn toward the MRI scanner), crushed and pinched fingers from the patient table, patient falls, and hearing loss or a ringing in the ear (tinnitus). The FDA has also received reports concerning the inadequate display or quality of the MR images.

An **Anticipated Adverse Event** is one that is reasonably expected and/or listed in the protocol and consent form as a risk of participating in the research. Examples of an anticipated adverse event include, but are not limited to, the following:

- Discomfort during MRI scan which may stem from patient claustrophobia
- Injury from the strong magnetic field attracting projective magnetic objects

- Hearing harm from the loud knocking noises for the magnetic field and gradients
- Heating of the body from the radiofrequency energy during the MRI scan.
- The strong magnetic field may affect tattoos, metal implants or accessory medical devices, and/or can lead to burns or efficacy of device

An **Unanticipated Adverse Event** is one that was not reasonably expected and/or is not listed in the protocol and consent form as a risk of participating in the research.

A **Serious Adverse Event** is one whose magnitude or frequency is above expectation.

A **Related adverse event** is one that, in the opinion of the investigator, is likely caused by or affects the research.

## 9.2. Reporting of Events by Clinical Sites

### 9.2.1. Relationship to the Study System

All adverse events will be reported to the IRB as soon as they occur, but no later than 5 working days of becoming aware of the event's occurrence.

### 9.2.2. Degree of Severity

The degree of severity will be graded for the purposes of reporting as follows:

0-No AE (or within normal limits).

1-Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

2-Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

3-Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

4-Life-threatening consequences; urgent intervention indicated.

5-Death related to AE.

## 9.3. Device Failure and Malfunctions

Any device failure or malfunctions will be reported to the committee no later than 5 working days since the occurrence. FDA team will review the cause of the malfunction and if any sources are linked to 3<sup>rd</sup> party systems or software, they will be notified of the failure or malfunction.

## 10. TEAMS

### 10.1 Study Administrator

The Study Administrator is responsible for review of data from ongoing studies. Administrative personnel, under appropriate supervision, may be delegated tasks such as setting up files and labeling and filing of documents.

### 10.2 Study Monitor

The Study Monitor is a qualified individual responsible to oversee the progress of a clinical study and to act as liaison between the Sponsor and the Investigator/Site. A Study Monitor assigned to a study site is responsible for maintaining the Investigator study file for that site.

### 10.3 Study Sponsor (SpinTech, Inc.)

The Study Sponsor is required to demonstrate that the studies are conducted according to the generally accepted principles of Good Clinical Practice.

The Sponsor, or other owners of the data, should retain all of the Sponsor-specific essential documents pertaining to the trial. The Sponsor should retain all Sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the Sponsor intends to apply for approval(s).

If the Sponsor discontinues the clinical development of an investigational product (i.e. for any or all indications, routes of administration, or dosage forms), the Sponsor should maintain all Sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

The Sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in and ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the Sponsor.

### 10.4 Qualification team

Per the SOP, the Qualification Team consists of members from the Clinical Affairs Department and other **SpinTech, Inc.'s** departments, as appropriate. The team is responsible for identifying, qualifying, and selecting Investigators.

The team will review the CV of the Investigators and assess the Investigator's qualifications, credentials, and experience in the intended therapeutic area. The team is also responsible to verify that medical licenses for all Investigators are current.

The team should also check the names of prospective Investigators against the FDA list of "Investigators Ineligible to Receive Investigational Products" (the "Blacklist") and the FDA/ORA Bioresearch Monitoring Information Page in order to research past issues with both the Investigator and site.

### 10.5 Principal Investigator and Co-Investigators

The Investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period. The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period, and should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

The investigator should ensure that all persons assisting with the trial are adequately informed about and trained on the approved protocol, the investigational product(s), and their trial-related duties and functions. A qualified physician, who is an Investigator for the trial, shall be responsible for all trial-related medical decisions. During and following a subject's participation in a trial, the Investigator should ensure that adequate

medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The Investigator should inform a subject when medical care is needed for intercurrent illness(es) of which the Investigator becomes aware.

It is recommended that the Investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed. Although a subject is not obliged to give his/her reasons(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

## 11. ADMINISTRATIVE RESPONSIBILITIES

### 11.1. Ethics Committee / Institutional Review Board Approval

An IRB/Ethics Committee reviews the appropriateness of the clinical trial protocol as well as the risks and benefits to study participants. It ensures that clinical trial participants are exposed to minimal risks in relation to any benefits that might result from the research.

IRB/Ethics Committee will review all study related materials before and during the trial.

The Ethics Committee should be collectively qualified to review the scientific, medical, and ethical aspects of the trial. An IRB/Ethics Committee should be composed of the following:

- at least 5 members
- members with varying backgrounds
- at least one member must represent a non-scientific area
- at least one member not affiliated with the institute or the trial site (independent member)
- competent members who are able to review and evaluate the science, medical aspect, and ethics of the proposed trial

### 11.2. Informed Consent

Informed consent is an ongoing process that must occur before any clinical trial-related procedures are conducted. The process consists of a document and a series of conversations between the clinical trial participant and the PI or study coordinator and delegated health care professionals, as appropriate.

The PI or study coordinator discusses the trial's risks, benefits and other aspects with the potential participant and, if required, the participant's legal representative, before the trial begins.

The PI or study coordinator gives the potential participant ample time and opportunity to ask questions about the trial and discuss it with relatives and family members.

If the potential participant decides to get involved in the trial, he or she provides voluntary consent by signing and dating the written informed consent document of which he or she also receives a copy. The participant has the right to withdraw consent at any time without penalty, repercussions or reason.

While the PI or study coordinator may delegate the task of administering and obtaining informed consent to a qualified individual, he or she is ultimately responsible for ensuring the process is conducted properly.

Informed Consent Guidelines

Investigators must follow the International Council on Harmonization (ICH) good clinical practice (GCP) guidelines. Section 1.28 describes the informed consent process, while the requirements and process for obtaining informed consent from a clinical trial participant are explained in section 4.8.

In addition to following ICH guidelines, investigators need to adhere to national and local regulatory requirements, sponsor requirements and privacy and personal data security regulations applicable in the country in which the study is being conducted.

The informed consent document must be fully approved by an institutional review board (IRB) or an independent ethics committee (IEC) prior to its use with trial participants.

#### Elements of Informed Consent Document

The informed consent form, which is a legal document, must include 20 ICH-required elements (section 4.8.10 of the GCP guidance). They include the purpose, duration, risks, benefits, costs and additional expenses of the trial; a description of the trial procedures; alternative care options; and volunteers' rights.

The document also must have at least two signature and date lines: one for the participant and another for the health care professional conducting the informed consent discussions with the participant.

Both the written document and the verbal consenting process must be presented in language the participant understands. It also needs to be documented appropriately.

#### Revisions to Informed Consent

Informed consent documents must be revised every time new safety information becomes available or there is a change in trial procedures, participant compensation or personnel noted on the consent form. Revisions to the informed consent document must be approved by an IRB/IEC prior to its use, and the informed consent process with the new information and documentation needs to be repeated with every clinical trial participant. The participant is then required to sign the revised form.

Consent: Written informed content will be obtained from the participant to ensure the subject understands the nature of the study, has adequate time to evaluate whether to participate in the study, also does not feel coerced in any way to undertake participation in the study. Subjects from vulnerable groups will not be included: non-English speakers, persons with diminished capacity, cognitive impairment, or mental illness, non-consenting participants (in emergency situations), pregnant women, fetus or neonates, terminally ill subjects, prisoners, or economically or educationally disadvantaged persons.

The participant will be informed that participation is voluntary and that he or she can withdraw from the study at any time.

### 11.3. Patient Recruitment

Patient recruitment will take place using the University's, Hospital's, or Imaging Center's protocols. Contact: Participants will be recruited by a notice/flyer at the clinical site as well as by person to person interaction/word of mouth. They will not have any cost or monetary incentive to be involved in the study. All participants must sign an informed consent to be involved in the study. The study requires one visit by the participant which will require 2 hours of their time. The participant will be explained the study and then given time to review and sign the informed consent as well as ask any questions they may have before signing. Review and signing of informed consent, participant intake including MRI survey including assessment that participant meets all inclusion/exclusion criteria, and imaging will take place in that time. No level of deception is made towards the participants and their scan data will not be made available to them under normal conditions. It will be conveyed to the participants that the study is to validate a new MRI method which decreases the scan time and that their images will be evaluated by a trained neuroradiologist

for the contrast and quality of the images. The informed consent will be presented by a research assistant, PI, or research nurse. Controls will be recruited from the local hospital/imaging center by word of mouth or the placement of flyers across campus. Additional recruitment will take place from lists in which subjects who have voluntarily showed interest through the university/hospital's research portal.

#### 11.4. Confidentiality

The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

#### 11.5. Amending the Protocol

A sponsor of an IND application is expected to submit a protocol amendment in cases when there are changes in the existing protocol that significantly affect safety of subjects, scope of the investigation, or scientific quality of the study. Such amendment should contain a brief description of the change and reference (date and number) to the submission that contained the original protocol.

For example, changes requiring an amendment to an IND application may include:

Any significant change in the design of a protocol (such as the addition or elimination of a control group).

Addition of a new test or procedure intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or elimination of a test intended to monitor safety.

Note: a protocol change intended to eliminate an apparent immediate hazard to human subjects may be implemented immediately, provided that FDA is subsequently notified by protocol amendment and the reviewing IRB is also notified.

#### 11.6. Protocol Deviations

The IRB Committee will ensure the Investigators follow Good Clinical Practice (GCP) Guidelines according to the FDA. "The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB...of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s))." (4.5.2 at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073122.pdf>)

Protocol deviations can be classified into three different categories, each type having a different IRB reporting requirement.

- A. Emergency Deviations require prompt reporting to the IRB promptly after they occur
- B. Major, non-emergent deviations require approval by the IRB before they occur
- C. Minor or administrative protocol deviations require reporting to the IRB at continuing review

The PI is responsible for ensuring compliance with any IRB/EC procedures or requirements. He or she may deviate from the study protocol without prior IRB/EC approval only to eliminate immediate safety hazard to a study participant. In addition, the PI must notify the IRB/EC of any departures from the protocol as soon as possible.



### 11.7. Site Noncompliance

Non-compliance is defined as any:

- violation of any regulation that governs human subject research or of any institutional policy for human subjects research,
- violation of any conditions imposed by the IRB on the approval of the study or conduct of the research, or
- deviation or departure from an IRB-approved protocol.

Principal Investigators (PI) are responsible for promptly reporting all suspected incidents of non-compliance that could potentially be considered serious or continuing within 72 hours of being known.

### 11.10. Sponsor Responsibilities

The sponsor for the study will be a representative from SpinTech, Inc. who will select the qualified investigators and provide them with the information needed to conduct the study. They will also ensure proper monitoring, ensure IRB review and approval, submit IDE application to the FDA, and ensure IRB and FDA are informed of any new information about an investigation. He or she will ship investigational device only to qualified investigators, obtain signed investigator agreements and financial disclosure from all investigators, and select qualified monitors.

### 11.11. Closeout Visits

Once all of the data have been collected. The Study Sponsor will return to the site for a last visit to collect the STAGE module (Onyx box), and shut down the site with respect to this study. The documentation will be collected from the study which should provide adequate details to re-create exactly what occurred at all points of the study as needed for regulatory purposes.

## 12. INVESTIGATOR RESPONSIBILITIES .....

### 12.1. Study Coordinator

Ensures that investigation is conducted according to the Investigator Statement (TBD), to provide Informed Consent forms to the subject, and to keep and maintain records of Informed Consent, subject surveys given prior to imaging, and MRI scan data until the conclusion of the study. Study coordinator will also schedule MRI scans for eligible subjects.

### 12.2. Records

Records and scan data will be protected in a locked-storage unit within a locked office.

## 13. APPENICES .....

n/a

## 14. TABLES AND FIGURES .....

FIGURE 1: STAGE Design / Schema

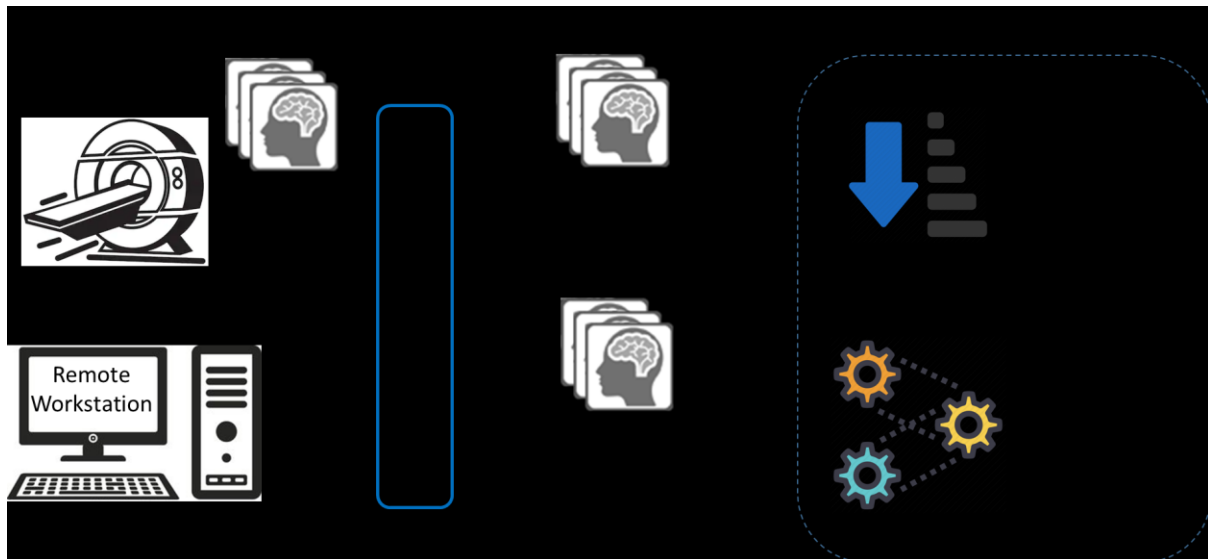


Figure 1: MRI images will be collected from scanners which will already be FDA-approved. The data collected will be de-identified with no information able to be traced back to the subject. Then the data will be sent to Picture Archiving and Communications System. From there, the raw DICOM will be sent to a node on the processing module in which it is sorted and read, then processed using the STAGE algorithms to generate the images listed in Section 7.2. Then the data are sent back to the PACS for the radiologist to review at his/her workstation.