Protocol Title: Assessment of Investigational Magnetic Resonance Imaging and Post-Processing Procedures

Protocol Date: December 13, 2017

Research Project Number: RP0688

Principal Investigator:

Michael V. Knopp, MD, PhD
Professor of Radiology and Novartis Chair of Imaging Research
Vice Chair of Research, Department of Radiology
395 West 12th Avenue, 4th Floor
Columbus, OH 43210

Knopp.16@osu.edu

Office: 614-293-9998
Fax: 614-293-9275

I. Objectives

The purpose of this study is to utilize investigational Magnetic Resonance Imaging (MRI) sequences either in addition to standard of care imaging or as a volunteer based investigational MRI:

1. To develop and optimize MRI acquisition and post-processing techniques.
2. To generate preliminary and comparative data on sequences for potential clinical trials.

II. Background and Rationale

MRI has become a standard of care imaging methodology that continues to benefit from technological developments in applied imaging sequences and ability to post-process magnetic resonance signals. These technological developments require in-vivo evaluation in real clinical applications before specific trials to validate their capabilities can be designed. There is also a tremendous amount of flexibility/parameter optimization that can only be refined utilizing MRI data equivalent to potential future applications. As MRI does not use any ionizing radiation, the performance of additional sequences does not lead to any additional risk exposure.

The FDA considers MRI at field strengths up to 8 Tesla (T) as non-significant risk. MRI at magnetic field strength up to 3T is a standard diagnostic tool for assessment of many types of medical conditions. MRI is well established in defining pathology, including structural anatomic abnormality and/or physiologic changes such as blood flow or tissue chemical composition as well as providing detailed images of structures within the body, in a true three-dimensional volume.

III. Procedures

A. Research Design

This prospective study will utilize investigational MRI sequences both in a volunteer population as well as in patients in addition to standard of care MR imaging to develop and optimize MRI sequence acquisition and post-processing techniques as well as to generate preliminary and comparative data for potential clinical trials. These post-processing techniques include but are not limited to visual inspection of image quality and known anatomy, semi-quantitative analysis including the use of rating schemes, signal-to-noise-ratios and contrast-to-noise-ratios measurements for quantitative assessment, standard fitting procedures for measuring MRI parameters, and using various published methods for image post-processing. The MRI methodologies we plan to use as part of this study will allow us to obtain morphological, functional and molecular information.

For the patient population: Patients receiving a standard of care 1.5 or 3T MRI will be asked by study personnel if they are interested in undergoing additional investigational imaging sequences after their standard of care imaging. If the patient agrees, he/she will remain in the same position on the MRI scanner for up to an additional 30 minutes while more images are obtained. Each patient will be imaged for no longer than 2 hours (standard of care imaging and additional investigational imaging). A routine clinical report will be generated for the clinically indicated MRI by a radiologist. Once this routine clinical MRI scan is dictated and finalized, a study team member will obtain the report via IHIS and manually remove all identifiers. This

report is being obtained for comparative purposes. All the data being compared will be coded using a unique study number.

Patients will be asked to provide study personnel with authorization to their medical records for follow-up on future related procedures as well as the current outcome of their imaging procedure. **There will be no data repository associated with this study.**

For the volunteer population: Healthy volunteers will be recruited through The OSU Wexner Medical Center or accompanying patients to their standard of care imaging appointments at The Wright Center of Innovation. They will be asked by study personnel if they are interested in undergoing investigational MR imaging sequences. If the volunteer agrees, he/she will be imaged on the MRI scanner for up to 60 minutes while images are obtained. Other than the participant signing the informed consent form, no identifying participant information or protected health information (PHI) will be recorded. Following the informed consent authorization, the participant's name will be coded using a unique study number.

B. Sample

The study population will include 200 evaluable volunteer and 200 evaluable patients receiving a standard of care 1.5 or 3T MRI at The Ohio State University (OSU), for a total of 400 participants. Potential participants will be identified by study team members at the time of the patient's standard of care imaging procedure. Volunteers will be recruited by brochures distributed throughout The OSU Wexner Medical Center as well as by recruiting volunteers that are accompanying patients to their standard of care imaging examinations.

Inclusion Criteria:

- Male and female volunteers greater than or equal to 18 years of age.
- Patients receiving a standard of care 1.5 or 3T MRI at The OSU (for the patient population only)
- Healthy volunteers that feel comfortable receiving an investigational MRI

Exclusion Criteria:

- Participants with a contraindication to MRI. Such contraindications include, but are not limited to: pacemaker, metallic cardiac valve(s), magnetic material such as surgical clips, tattoos, implanted electronic infusion pumps or any other condition that would interfere with the MRI, a stent somewhere in the body, a history of allergic reaction to any metals.
- Participants that experience claustrophobia, anxiety and/or vertigo when moved inside the scanner.
- Participants with vital signs outside of normal range.
- Prisoners.
- Subjects incapable of giving informed written consent.
- Participants who are pregnant, healthy volunteers

C. Measurement / Instrumentation

Studies will be carried out using FDA approved 1.5 or 3T MRI units. MRI is routinely used for clinical diagnostic studies, and is considered a noninvasive procedure. The FDA considers MRI at field strengths up to 8 Tesla (T) as non-significant risk.

D. Detailed study procedures

For each participant, written informed consent will be obtained prior to any protocol related activities in a private area with a study team member. As part of this procedure, study personnel will approach eligible participants and explain orally and in writing the nature, duration, and purpose of the study as well as all associated risks and benefits. During the consent process, each participant will also be asked if they are willing to provide a release of their medical records pertaining to future procedures/injuries in the next 10 years. They will inform the participant that he/she may withdraw from the study at any time. The patient will be given time to ask questions and review the consent form on their own.

Following the consent process, participants will be imaged. Each participant will be imaged for no longer than 2 hours (standard of care imaging and additional investigational imaging). Volunteer participants will be imaged for no longer than 60 minutes.

Image Collection:

All participants in the patient population will receive a standard of care MRI, and all those in the volunteer population will receive the investigational MRI only. Patients will be asked to simply lie on the table of the MRI system for the duration of clinically indicated MRI. Subjects participating in the additional investigational imaging sequence will be asked to lie on the table for an additional 30 minutes while images are collected. Participants will not participate in more than a total of 2 hours of imaging time per day because they will become uncomfortable lying still in one position and motion compromises the image quality.

Release of Medical Records:

Those in the patient population will be asked if they are interested in releasing their medical records for up to 10 years after their participation in this study in order to allow study personnel to track the current outcome and/or related procedures in the future. The patient can revoke their consent to this question at any time by contacting the Principal Investigator.

E. Risks, Benefits, Safety and Confidentiality:

MRI at 1.5 and 3 Tesla is considered a minimal risk procedure.

Risks:

There are no additonal safety risks associated with the investigational MRI imaging. For patients receiving investigational 3 Tesla MRI imaging only, the associated risks are the same as those that would normally be encountered in a standard of care MRI examination, and they are as follows:

Magnetic Resonance Imaging devices use three different types of electromagnetic fields that may pose potential risks to subjects undergoing MRI examinations. These are static magnetic fields, time varying magnetic field gradients, and radiofrequency (RF) electromagnetic fields.

1) Static magnetic fields exert forces on magnetic objects and induct electric currents in any conductive material, imposing two main risk categories:

a) Dislodgement or malfunction of medical implants or metallic foreign objects.
b) Current induction in tissue and subsequent alteration of physiologic function.

The FDA has classified MRI up to 8 Tesla as Non-Significant Risk.

In addition, subjects may be harmed by

- Loud noise from the MRI device.
- Some subjects may experience mild transient vertigo and/or metallic taste when they are being moved into the MRI system.
- Subjects may experience discomfort from the blood pressure cuff and finger clamp from the pulse-oximeter. Some subjects may experience feelings of being closed in if they are claustrophobic.
- Long-term effects of high field MRI are not known at this time.

Risk from static, time varying magnetic field gradients and radiofrequency fields are at or below the FDA limits and thus risks are identical to standard field strength MRI units.

All above listed known effects of exposure to static magnetic fields, switched magnetic field gradients and Radiofrequency are transient, i.e. vertigo, spontaneous visual light perceptions, metallic taste, peripheral nerve stimulation as well as RF heating will end once exposure to the fields is ended. Based on this cumulative effects are not expected, however long-term effects are not known at this time.

To minimize risks from the static magnetic field as with standard MRI, the following subjects will be excluded from this study (see MRI Safety Screeing Forms for further details):

- Subjects who have any type of bioimplant activated by mechanical, electronic, or magnetic means (e.g., cochlear implants, pacemakers, neurostimulators, biostimulators, electronic infusion pumps, etc.).
- Subjects who have any type of ferromagnetic bioimplant that could potentially be displaced or damaged.
- Subjects who have cerebral aneurysm clips.
- Subjects who may have shrapnel imbedded in their bodies (such as from war wounds), metal workers and machinists (potential for metallic fragments in or near the eyes), severe car accident victims.

Because effects of high field MRI are not known at this time also excluded are:

- Pregnant healthy subjects who are pregnant or suspect they may be or have become pregnant. If reasonable doubt exists, self-testing with a provided over-the-counter

urine pregnancy kit is required. However, inclusion of participants who are pregnant or suspect that they may be or have become pregnant but are required to get an MRI as part of standard of care is permitted.
- Subjects who have permanent tattoo (e.g., eye liner) (may contain metallic coloring).
- Subjects whose vital signs are not within the range of normal criteria (see Project Protocol).

Also excluded are subjects incapable of giving informed written consent
- Subjects who cannot adhere to the experimental protocols for any reason, or have an inability to communicate with the researcher.
- Subjects who have limited mental ability to give informed consent, mentally retarded, altered mental status, mental disability, confusion, or psychiatric disorders.
- Prisoners

To minimize discomfort we will also exclude subjects who exhibit noticeable anxiety and/or claustrophobia or who exhibit severe vertigo when they are moved into the MRI system.

All subjects will be given ear protection to prevent risks from loud noise

The risk to subjects is minimal, the experimental techniques have been performed in the past with no adverse consequences. There are no known direct benefits to individual subjects that can be attributed to participation in this research study.

Incidental Findings:
Anytime an imaging study is performed, there is some risk than an incidental finding is observed. There will be minimal risk or likelihood in the patient population, as they are already undergoing standard of care ultrasound or physical exams.

The risk or likelihood will be slightly higher in the volunteer population as they will not be receiving standard of care studies. Informed consent form does ask subjects to identify if they would like to be directly informed of an incidental finding and if this finding should be communicated to the health care provider of their choice.

Incidental findings are not intended to be released to patients or subjects at the time of the scan and are part of the reporting survey that will be filled out at the end of each study. These reports will be gathered and reviewed by the PI or appropriate delegates to determine the appropriate level of next steps. The communication will follow the choice indicated on the ICF form.

Benefits:
It is hoped that the information from this study will enable improved MRI imaging capabilities and MRI sequences as well as leading to improved imaging quality.

Safety Monitoring:

As part of the standard of care imaging procedure, safety monitoring measures will be taken on all participants. This will include the monitoring of the physiologic parameters that are deemed appropriate in the evaluation of potential risk during the acquisition process (electrocardiogram, respiration rate, core body temperature). These parameters are monitored to ensure that they do not approach potentially hazardous levels. The Principal Investigators or Co-Investigators are able to respond immediately to ensure the safety of the patients and volunteers participating in the research study. Our research monitoring methods will control and limit known risks of psychological (feeling of claustrophobia) or physiological adverse events from occurring. The Principal and/or Co-Investigators or Key Personnel will be present at the time of all magnetic resonance acquisition to ensure this.

Patient participation maximum duration and frequency is defined by protocol as follows: Duration of data acquisition in the magnetic resonance system per patient is limited to no more than 2 hours total per day consisting of one or more acquisitions. In the volunteer population, the duration of data acquisition in the magnetic resonance system is limited to no more than 1 hour.

In the event of any medical emergency, accident or trauma while the subject is in the laboratory, our contingency plans for emergency situations are as they would be for any medical facility and clinical magnetic resonance imaging facility. Our emergency protocol fully prepares us to provide access to emergency treatment for our patients, resuscitation, life support and medical care as needed.

Considering that the volunteer subjects and patients studied to date at other high field magnetic resonance research sites have not experienced any deleterious adverse effects, long-term follow-up for this patient population is deemed unnecessary, nor is it within the scope of this investigation, particularly since any physiologic changes noted rapidly return to baseline levels and at all times are within safe physiologic thresholds and limits.

Confidentiality of Records:
All paper and electronic data/information will be coded prior to any review or analysis. All paper documents will be stored in a locked file cabinet with limited access in the Department of Radiology at The Ohio State University. All electronic data obtained through PACS or IHIS will be stored in a coded manner on password protected servers with limited access in the Department of Radiology at The Ohio State University. No individual identities will be used in any publications resulting from this study. Officials from examining bodies such as the U.S. Food and Drug Administration or NIH may inspect records pertaining to this study.

F. Internal Validity

Image data will be evaluated following standard published procedures. This includes but is not limited to visual evaluation of images by a radiologist, using semi-quantitative visual rating schemes for assessing overall image quality and/or quality of depiction of anatomic structures, quantitative measures for assessing image quality such as signal-to-noise-ratio (SNR) or contrast-to-noise-ratio (CNR) between different tissue types and measurement of quantitative MRI parameters such as T1, T2 and T2* relaxation times. This should ensure internal and

external validity of the data and avoid study bias. Functional and molecular read outs will be established according to methodologies.

G. Data Analysis

As the purpose of this data is to demonstrate feasibility in real life applications, we do not intend to perform a statistical assessment beyond classifying the characteristics of pilot data and comparing observational trends either to the standard of care imaging data or other known reference data. For our purposes, imaging that presents lower imaging quality or more artifacts would to not be pursued for further evaluation. Only images that suggest equivalent or improved image quality would be evaluated for the potential use of preliminary data toward a formal Phase I/II clinical trial.