Novel MRI Sequence- MR Fingerprinting

NCT number NCT03722459

Document Date October 18, 2018

Novel MRI Sequence- MR Fingerprinting

Protocol Number: 17-2731

National Clinical Trial (NCT) Identified Number: NCT03722459

Principal Investigator: William Hyslop, MD/PhD

Co-Investigator: Yong Chen, PhD

Co-Investigator: Benjamin Mervak, MD

Sponsor: University of North Carolina at Chapel Hill

Funded by: University of North Carolina at Chapel Hill

Version Number: 1

October 18, 2018

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

Table of Contents

1 BACKGROUND AND RATIONALE

1.1 BACKGROUND

Magnetic Resonance Imaging (MRI) has become one of most important medical imaging tools over the past 30 years because it is non-invasive, requires no ionizing radiation, and provides exquisite images of soft tissues and anatomic structures with many tissue/disease specific contrasts. While MRI has served the community well for many years, it is increasingly clear that it also has significant limitations.

One of the principle limitations is the lack of quantitative information for tissue/structure characterization. The current paradigm of MRI is to use a set of scanner settings to generate an image "weighted" by a specific MR contrast mechanism (physical parameter), where it is hoped that variations in the parameter will be accentuated. However, without quantitative knowledge of the parameters, the final image contrast may depend on many factors, which complicates image interpretation and diagnostic performance. Quantitative measurement can provide a great deal of information about tissue properties and pathological conditions, since these parameters ultimately determine the contrast that is observed in conventional images.

1.2 RATIONALE

The purpose of this study is to evaluate novel quantitative MRI techniques in clinical studies to determine whether they can provide better, faster and more useful information for clinical diagnosis. Quantitative MRI has been a continuous interest in the MRI community, but extremely challenging due to long acquisition times and sensitivity to motion. Recently, we have introduced a novel MRI data acquisition approach, namely MR Fingerprinting (MRF), for simultaneous measurement of several important parameters in a single MRI scan.

This work, recently published in Nature, has shown that accurate quantification of proton density, T1 and T2 relaxation times can be achieved which opens the door to rapid multi-parametric MR analysis and potentially leads to new diagnostic methodologies (4). Pilot studies with scans from hundreds of patients have demonstrated that the novel method can provide valuable information for various diseases in brain, liver, and prostate (5–8). While it has shown great promise in these previous studies, clinical evaluation of this technique has been limited to a few medical centers worldwide due to the complexity in installation, implementation and post-processing of the technique.

Dr. Yong Chen, a newly recruited faculty at Department of Radiology, is a key developer of the MR Fingerprinting technique (8–14). In this study, the investigators propose to apply this novel technique at UNC and evaluate its performance for different diseases. These include but not limited to diseases in liver, kidney, cardiac, pancreas etc. The investigators hypothesis that the quantitative MR imaging technique will lead to improved tissue characterization and diagnosis.

2 OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE

To determine the percent of patients with a visible region of interest. MR fingerprinting sequences will be examined to determine their utility for visualizing pathology.

2.2 PRIMARY ENDPOINT

The evaluation of novel quantitative MRI techniques in clinical studies to determine whether they can provide better, faster and more useful information for clinical diagnosis.

3 ELIGIBILITY

3.1 INCLUSION CRITERIA

The study will include English-speaking patients, 18 and over, that are already scheduled to undergo a clinical MRI for diagnostic purposes.

3.2 EXCLUSION CRITERIA

The study will exclude anyone under the age of 18 and pregnant women.

Women will be excluded from the healthy volunteers, due to a lack of funding for pregnancy testing. Funding for this will be considered for the future.

4 STUDY PLAN

4.1 SCHEMA

This is a one arm single center study of 105 participants scheduled to have a clinical MRI that consent to undergo an investigational MR Fingerprinting sequence. The MR fingerprinting technique requires less than 15 minutes and will be added following the standard MRI sequence. There will be 5 healthy male volunteers to practice using the sequence prior to imaging clinical patients.

4.2 ENROLLMENT/RECRUITMENT

A total of 105 participants will be enrolled to this study. The 100 study subjects will be consecutively recruited from patients who are scheduled to undergo a clinical standard of care MRI for diagnostic purposes. There will be 5 healthy male volunteers to practice using the sequence prior to imaging clinical patients. Participant eligibility will be identified by research staff review. Once a patient has been referred, the patient will be approached by a coordinator from Radiology to assess interest in participation.

All eligible patients who agree to participate in the study will be asked to come to their scheduled MRI appointment thirty minutes early to complete the informed consent process.

Review of the consent will take place in the privacy of an exam room, or when possible, a sample consent form will be sent to the patient via email prior to the patient's visit to allow for ample review. As the investigational sequences are in addition to the standard of care (SOC) MRI sequences, patients will follow the SOC guidelines. Non-ionizing imaging, such as MRI (3T or less) or ultrasound, requires that the subject be questioned about pregnancy status using the pregnancy screening form and direct questioning. As an additional step, we as the study team will also question patients about their pregnancy status prior to enrolling in this study. If there is any question for women of childbearing potential, they will not be enrolled.

Once the patient has consented, they will be escorted by the research coordinator to a dressing room, where the subject will change into appropriate clothing for scanning.

4.3 STUDY DESIGN

Investigational sequences will be developed at UNC. The study will be performed on either 1.5T or 3T MR scanners. Scanners at both field strengths are FDA approved and all new sequences possess the same safeguards as standard (FDA approved) clinical sequences to prevent harm to subjects. The study does not need any contrast administration unless it is required for standard clinical examination. For each consented subject, the additional scans will add no more than 15 minutes to the total scanning time.

The investigational MR protocol will be implemented on the existing MR scanners without any modifications to the existing, FDA approved machine, equipment, or safety standards. Patients will receive their standard of care imaging. In addition, they will receive the research sequence. The additional sequences will be performed at no cost to the patient other than a small increase in the amount of time spent inside the MR scanner. The additional sequences are less than 15 minutes and do not place individuals at any increased risk.

4.4 STUDY DURATION

It is anticipated that the total clinical study duration encompassing recruitment, enrollment, and data analysis will take approximately 3 years. Active patient participation will last approximately 1 visit (consent and imaging).

5 UNANTICIPATED CONCERNS

5.1 UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as "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" (21 CFR 812.3(s)).

5.2 UNANTICIPATED PROBLEMS (UP)

As defined by UNC's IRB, unanticipated problems involving risks to study subjects refers to any incident, experience, or outcome that:

- Is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

- Is related or possibly related to a subject's participation in the research; and

- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

5.3 REPORTING

5.3.1 Unanticipated Adverse Device Effects

UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB, as described below:

- For this device study, investigators are required to submit a report of a UADE to the FDA, the manufacturer of the device and the UNC IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.150(a)(1)), using the MedWatch Form 3500A. Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, the UNC IRB, and participating investigators within 10 working days after the sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1)).

For this study, the additional sequences are less than 15 minutes and do not place individuals at any increased risk outside of their standard of care imaging.

5.3.2 Unanticipated Problems

Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the Study Coordinator using the IRB's web-based reporting system.

6 ADVERSE EVENT (AE)/SERIOUS ADVERSE EVENT (SAE)

6.1 DEFINITION OF ADVERSE EVENT (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a patient or clinical investigation subject administered a pharmaceutical product and which does not

necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

6.2 DEFINITION OF SERIOUS ADVERSE EVENT

A serious adverse event (SAE) is defined as an adverse event that:

i) results in death

ii) led to a serious deterioration in health that either:
   (1) results in a life-threatening illness or injury, or
   (2) results in a permanent impairment of a body structure or a body function, or
   (3) requires in-patient hospitalization or prolongation of existing hospitalization, or
   (4) Results in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
   (5) Results in a persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.

iii) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

6.3 REPORTING ADVERSE/SERIOUS ADVERSE EVENTS

IRB Reporting Requirements:

- UNC will submit an aggregated list of all SAEs to the UNC IRB annually at the time of study renewal according to the UNC IRB policies and procedures.

- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system (see section 8.2) within 7 days of the Investigator becoming aware of the problem.

7 DATA SAFETY AND MONITORING

The new sequences will be examined to determine their utility for visualizing pathology; however, no formal comparisons with statistical analysis will be performed. This is a minimal risk study. All settings for the research sequence are within the FDA guidance for not more than minimal risk (provided in the attachments). The additional sequences are less than 15 minutes and do not place individuals at any increased risk.

8 STATISTICAL CONSIDERATIONS

This is a nonrandomized, single-center study. The new sequences will be examined to determine their utility for visualizing pathology; however, no formal comparisons with statistical analysis will be performed.

9 STUDY MANAGEMENT

9.1 INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL AND CONSENT

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol. In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP).

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations.

Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form. Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

9.2 REQUIRED DOCUMENTATION

Before the study can be initiated at any site, the following documentation must be provided to the Study Sponsor.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- A copy of the IRB approved consent form

9.3 ADHERENCE TO THE PROTOCOL

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

9.4 CONFLICT OF INTEREST

Any investigator who has a conflict of interest (COI) with this study as defined by the policies of the University of North Carolina will have the conflict reviewed by a properly constituted Conflict of Interest Review Committee with a committee-sanctioned conflict management plan that has been reviewed and approved by the IRB prior to participation in this study. All University of North Carolina investigators will follow the University conflict of interest policy.

10 PROTOCOL DEVIATIONS/VIOLATIONS

10.1 PROTOCOL DEVIATIONS

UNC personnel will keep a log of any protocol deviations and report them to the study sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

10.2 PROTOCOL VIOLATIONS

Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

11 RECORD RETENTION

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. Study documents should be kept on file until three years after the completion and final study report of this investigational study.

12 OBLIGATIONS OF INVESTIGATORS

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

13 REFERENCES

1. Fuchs VR, Sox HC. Physicians' views of the relative importance of thirty medical innovations. Health Aff.2001;20:30–42.

2. Yokoo T, Bae WC, Hamilton G, et al. A quantitative approach to sequence and image weighting. J. Comput. Assist.Tomogr. 2010;34:317–31. doi: 10.1097/RCT.0b013e3181d3449a.

3. Fenlon HM, Tello R, DeCarvalho VL, Yucel EK. Signal characteristics of focal liver lesions on double echoT2-weighted conventional spin echo MRI: observer performance versus quantitative measurements of T2 relaxation times.J. Comput. Assist. Tomogr. 2000;24:204–11.

4. Ma D, Gulani V, Seiberlich N, Liu K, Sunshine JL, Duerk JL, Griswold MA. Magnetic resonance fingerprinting. Nature2013;495:187–92.

5. Badve C, Yu A, Dastmalchian S, et al. MR fingerprinting of adult brain tumors: Initial experience. Am. J. Neuroradiol.2017;38:492–499.

6. Badve C, Yu A, Rogers M, Ma D, Liu Y, Schluchter M, Sunshine J, Griswold M, Gulani V. Simultaneous T1 and T2 Brain Relaxometry in Asymptomatic Volunteers Using Magnetic Resonance Fingerprinting. Tomography [Internet] 2015;1:136–144.

7. Yu AC, Ponsky LE, Dastmalchian S, Rogers M, Mcgivney D, Griswold MA. Development of a Combined MR Fingerprinting and Diffusion Examination for Prostate. Radiology 2017; 283:729–738.

8. Chen Y, Jiang Y, Pahwa S, Ma D, Lu L, Twieg MD, Wright KL, Seiberlich N, Griswold MA, Gulani V. MR fingerprinting for rapid quantitative abdominal imaging. Radiology 2016;279:278–286.

9. Chen Y, Mehta BB, Hamilton JI, Ma D, Seiberlich N, Griswold MA, Gulani V. Free-breathing 3D abdominal magnetic resonance fingerprinting using navigators. Int. Soc. Magn. Reson. Med. 2016:p716.

10. Chen Y, Pahwa S, Hamilton JI, Dastmalchian S, Plecha D, Seiberlich N. 3D magnetic resonance fingerprinting for quantitative breast imaging. Radiology 2017:Submitted.

11. Gao Y, Chen Y, Ma D, et al. Preclinical MR fingerprinting (MRF) at 7 T: effective quantitative imaging for rodent disease models. NMR Biomed. 2015;28:384–394.

12. Hamilton JI, Jiang Y, Chen Y, Ma D, Lo WC, Griswold M, Seiberlich N. MR fingerprinting for rapid quantification of myocardial T1, T2, and proton spin density. Magn. Reson. Med. 2017;77:1446–1458.

13. Ma D, Coppo S, Chen Y, McGivney DF, Jiang Y, Pahwa S, Gulani V, Griswold MA. Slice profile and B 1 corrections in 2D magnetic resonance fingerprinting. Magn. Reson. Med. In press.

14. Pierre E, Ma D, Chen Y, Badve C, Griwold MA. Multiscale Reconstruction for Magnetic Resonance Fingerprinting. Magn. Reson. Med. 2016;75:2481–2492.