NYU Langone Health

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IMAGING BIOMARKERS OF KNEE OSTEOARTHRITIS

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List of Abbreviations

CS: Compression Sensing
ECM: Extracellular matrix
KL: Kellgren-Lawrence
KOOS: The Knee Injury and OA Outcomes Score
OA: Osteoarthritis
PASE: Physical Activity Scale for the Elderly
PI: Parallel Imaging
PBS: Phosphate buffered saline
PG: Proteoglycan
WOMAC: Western Ontario and McMaster University OA Index

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Study Summary

Title	IMAGING BIOMARKERS OF KNEE OSTEOARTHRITIS
Short Title	Imaging biomarkers of knee OA
Protocol Number	S16-00918
Methodology	Pilot study
Study Duration	5 years
Study Center(s)	*Single-center*
Objectives	Develop, evaluate and translate highly accelerated imaging sequences for in-vivo knee osteoarthritis
Number of Subjects	90 (60 patients, 30 controls)
Diagnosis and Main Inclusion Criteria	Knee osteoarthritis Inclusion: (i) High risk osteoarthritis patients; (ii) early diagnosis of osteoarthritis (iii) healthy controls
Study Product and Planned Use	3T MRI scanner (Siemens Medical Solutions)
Reference therapy	N/A
Statistical Methodology	Analysis of covariance, Pearson and Spearman rank correlation coefficients

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1 Introduction

This document is a protocol for a human research study. This study is to be conducted in accordance with US government research regulations, and applicable international standards of Good Clinical Practice, and institutional research policies and procedures.

1.1 Background

Osteoarthritis (OA) is a degenerative joint disease, affecting more than 27 million people in the United States alone (2.3). By 2030 approximately 67 million people will be affected by OA (4). This large affected population and the severe consequent debility of OA lead to significant expenses to the health care system (5-7). OA is characterized by biochemical, structural and morphologic degradation of components of the extracellular matrix (ECM) of articular cartilage (8). The ECM is composed of primarily two groups of macromolecules including proteoglycan (PG) and collagen fibers. About 50% of the high risk OA patients are expected to show OA progression within 24 months (1). Current noninvasive imaging methods to evaluate knee joints include plain radiographs, computed tomography (CT), and clinical morphological magnetic resonance imaging (MRI) of joint structures. These techniques can only detect later-stage, macroscopic joint structural abnormalities that are irreversible and not amenable to early therapy.

Early diagnosis of cartilage degeneration would require the ability to non-invasively detect changes in PG concentration and collagen integrity before morphological changes occur. T1ρ and T2 relaxation times are affected by these pathological processes (8-12) and are the most widely used biochemical cartilage MRI sequences worldwide. Several researchers (11-21) have demonstrated that the T1ρ relaxation time is more sensitive to PG content of the cartilage, while T2 relaxation time is more sensitive to collagen orientation and integrity of network and hydration. These imaging biomarkers have potential to detect early stages of the disease (pre-clinical), quantitatively assess disease severity, monitor disease progression and possibly monitor OA therapy. The major limitation with bringing T1ρ measurements to widespread clinical use are long scan times due to use of multiple spin-lock times and high specific absorption rate (8,10,22-24). Although, the multi-echo spin echo 2D-T2 mapping sequence is routinely used in research and a few clinical sites, it has several issues with stimulated echoes, limited volume coverage, magnetization transfer saturation effects and imperfections in refocusing pulse leads to inaccuracies in T2 measurements (20,25). Despite the significant progress made in non-invasive imaging methods for quantitative assessment of early biochemical, structural and morphological changes in cartilage there are still some shortcomings in the existing approaches and scientific gaps in the field for widespread clinical use of these methods. The proposed study addresses this scientific gap by developing a highly accelerated 3D-T1p and T2 methods (each protocol under 5 minutes) with novel acquisition and reconstruction strategies taking advantage of joint compression sensing (CS) and parallel imaging (PI) and validating the methods in model systems, healthy asymptomatic subjects, high risk of OA with knee pain but normal radiographs and mild knee OA patients. Though there is as of yet no cure for OA, the management of risks and predisposing factors are vital in halting, slowing, or reversing disease progression.

1.2 Investigational Imaging

Development of rapid relaxation times and compression sensing on 3T-MRI scanner (Siemens Medical Solutions).

1.3 Preclinical Data

See Wang, L. & Regatte, R. (2015). T1p MRI of human musculoskeletal system. *Journal of Magnetic Resonance Imaging* 41:586-600.

1.4 Research Risks & Benefits

1.4.1 Magnetic Resonance Imaging (MRI)

Magnetic Field Risk

MRI uses a strong magnetic field to create images of the body. Because of the strong magnetic field, there are risks. These risks are detailed in this section.

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One possible risk is burns to the skin. There is an increased risk of burns from devices that conduct electrical energy. These devices can include metallic objects, pulse oximeters, EKG leads, or skin tattoos. These devices can be either in or on the patient in order for a skin burn to occur. The FDA has found that 70% of all reported injuries from MRIs were burns to the skin, however, such burns are extremely rare. To reduce this risk, you must complete thorough screening to ensure that no risky conductive materials are present in or on your body.

Another possible risk is that a metal object could be pulled into the scanner and hit you. You could be physically injured as a result. To reduce this risk, everyone near the magnet will remove all metal from their clothing or pockets when in the scanning environment. The door to the scan room will remain closed during the exam for your safety.

There are no known risks or adverse effects resulting directly from exposure to MRI. However, subjects who have a pacemaker or certain metal fragments in their body such as shrapnel or metal in the eye should not have the scan performed. If you have any question about metal implants or metal fragments in the body, you should inform the technologist or investigators before entering the magnet room.

Fear of Confined Spaces: Some people may feel confined and experience anxiety in the MR scanner. If you are unable to tolerate being in the scanner, we can stop the scan immediately at any time.

Noise Levels: The MR scanner produces tapping sounds during operation, which may reach very loud levels. To minimize any discomfort from this noise, you will be given disposable earplugs to reduce the noise levels but will still allow voice communication with the scanner operator.

MRI system failure (quench): In extremely rare cases, a magnet can lose its magnetism, in which case cooling fluids may be released noisily through escape valves and may collect in gas form in the scan room. The gas is not harmful in itself as long as fresh air is available. In this very remote event, you will immediately be brought out of the magnet room.

Neurostimulation and heating: Some subjects may experience muscle twitches or tingling sensations and/or a slight increase in body temperature during some types of scan activity. These are very unlikely under current MRI guidelines.

MRI Sequences: Imaging sequence techniques do not pose any added risk to the patients beyond that of a standard clinical MRI sequences. Sequence development and testing is routine research practice in numerous NYU Radiology research studies.

1.4.2 Other Risks of Study Participation

While all patient information will be handled in a confidential manner, a breach of confidentiality is another potential risk present in this study. To minimize this risk, all documents are managed strictly according to HIPAA guidelines, state and federal laws, and institutional guidelines. All documents will be kept under lock and key in a cabinet located at 650 1st Avenue that is only accessible to the research coordinator.

1.4.3 Potential benefits

There is no direct benefit as this study is not providing treatment or rehabilitation but it is hoped that the knowledge gained will be of benefit to OA patients in the future.

1.4.4 Incidental Findings

Incidental findings are apparent medical abnormalities that may have clinical implications and are observed in the course of research studies but are unrelated to the topic under study. Only those incidental findings that may have clinical significance as determined by the reviewer of the MRI images wil/ be communicated to the subject or to the subject's primary care physician as by the principal investigator.

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2 Study Objectives

The overarching objective of the study is to establish a non-invasive imaging biomarker based on the development of rapid relaxation mapping with compressed sensing (CS) that will be clinically useful for assessment of early OA.

2.1 Primary Objective

To develop highly accelerated imaging sequences for ex-vivo knee OA applications on a standard clinical 3T scanner using novel CS and parallel imaging (PI) strategies.

2.2 Secondary Objective

Use our imaging techniques in-vivo to determine whether the accelerated baseline imaging biomarkers will predict incident OA, OA progression and worsening of clinical outcomes (pain, function scores) over 24 months

3 Study Design

3.1 General Design

I. Sequence development and optimization will begin by conducting 3T MRI scans on 30 whole knee joint specimens with Outerbridge classification grade 1 and 2 (n=15, age range 40-75 years) and grade 3 and 4 (n=15, age range 40-75 years) that will be purchased from the National Human Tissue Resource Center (NDRI, www.ndriesource.org) in accordance with IRB and HIPAA guidelines. The grade classifications correspond to the degree of cartilage degeneration. Each specimen will be thawed and soaked in phosphate buffered saline (PBS) for one hour prior to MRI, blotted dry, and wrapped in parafilm to reduce dehydration during the imaging experiment. Specimens will be stored in the wet lab freezer located on the 2nd floor of CBI. Specimens will be imaged with a 3T whole-body MRI scanner employing a Tx/Rx knee coil with 15 coil-elements (QED, Cleveland OH) and will be discarded in red biohazard bags and according to biohazard regulations. The coil is FDA-approved, not an investigational device and is used routinely for clinical scans at The Center for Biomedical Imaging,

II. A total of 90 subjects including 30 patients with high risk of developing knee OA, 30 patients with mild OA and 30 healthy controls will be accrued. We estimate that about 105 patients will sign consent but as some will be lost to follow up or withdrawn. Controls will be age/gender matched to patients within 2 years of age. “High risk of developing knee OA” has been defined by having knee pain but normal radiographs (Kellgren-Lawrence score 0 i.e. KL0) on both knees but at least one abnormal finding on clinical MR protocol such as overweight, prior knee injury (ligaments or menisci) or traumatic bone marrow edema lesions. Based on recent systematic review and meta-analysis (26) suggest that knee pain with these abnormalities will be potential risk-factors for development of knee OA.

Patients (early OA and high risk OA Patient participation will consist of 3 visits: an initial screening, a baseline knee MRI without contrast and a 24 month follow up in order to compare the data. All scans will take place on a 3T Prisma MRI Scanner (Siemens Medical Solutions) located at the NYU Center for Biomedical Imaging using our standard knee coil that is used routinely for clinical knee scans.

During the patient’s first visit they will complete three standard questionnaires in a private room adjacent to the MRI scanners. The questionnaires are standard assessments used routinely by OA clinicians The three questionnaires are:
(i) The Knee Injury and OA Outcomes Score (KOOS),
(ii) Western Ontario and McMaster University OA Index (WOMAC). The KOOS similar to the WOMAC uses a 5 point scale (0-4) but with the scales reversed; sub scores are calculated and transformed to a 0-100 scale, with 0 representing poor outcomes and 100 representing improved function and better quality of life; and

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(iii) Physical Activity Scale for the Elderly (PASE) which is an instrument for assessing multiple domains of activity in older adults but that has been validated for use in persons with knee OA (25). The questions will evaluate both occupational and non-occupational knee bending, squatting and stair climbing, will be adapted from a widely used instrument that has shown associations of these activities with knee OA in multiple studies (28). These are routine questionnaires used by OA clinicians.

During this visit, Dr. Abramson or Dr. Krasnokutsky will administer a brief non-invasive knee examination on OA patients to ensure the absence of any signs of knee disorders such as tenderness, instability or inflammation.

If the patient is taking medication it will be recorded using the medical inventory method, in which the participant brings in all medications they are currently taking and the brand name, generic name or active ingredients are recorded and matched to an entry (seven digit code) in an online medical dictionary (27). Finally nutritional and health supplements that influence the intake of nutrients of potential importance for the course of OA or that may affect biochemical markers during the study will be assessed with the 25 minute Block Brief 2000 food frequency questionnaire.

Patients will return at their earliest convenience for a second visit to have a one hour MRI of the knee, without contrast. The only difference between a clinical knee MRI and our research MRI is that the images will be acquired using our novel imaging sequences, otherwise the procedures are the same. A follow up will take place 24 months later for a second MRI (exactly as it occurred during Visit 2), and the patients will retake the questionnaires. The purpose of the follow up exams is to determine whether the accelerated baseline 3D-T1p and T2 mapping can predict OA progression and worsening of morphological and clinical scores over 24 months.

Controls: Controls will be asked to come for one visit for a one-hour MRI exactly the same way as the patients. Controls will be age/gender matched to the patients. They will not be required to take the questionnaires nor will they have a physical exam. Their images will be used for comparison with the OA patients.

Timeline

Procedures	Year 1	Year 2	Year 3	Year 4	Year 5
Develop and optimize accelerated imaging techniques in ex-vivo whole knee joints	X	X			
Evaluate these imaging techniques in patients and controls		X	X	X	
Determine whether imaging techniques can predict worsening of clinical outcomes over 24 months			X	X	X

3.2 Primary Study Endpoints

Quantitative MRI sequences 3D-T1ρ and T2 mapping protocols without and with undersampling factors of R2-R6 will be acquired using the specimens. Following the MRI experiments the 3DT1ρ and T2 mapping will be reconstructed as a function of undersampling factors of R2-R6 in ex-vivo whole knee joint specimens. This will address the performance of accelerated 3D-T1ρ and T2 mapping protocols quantification accuracy and reproducibility when compared to standard reference maps.

3.3 Secondary Study Endpoints

We will compare baseline 3D-T1ρ and T2 relaxation measurements of cartilage to determine if they can predict worsening of symptoms based on the KOOS, WOMAC and PASE scores at 24 months.

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4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

4.1.1 Patients in the HJD OA database, ages 40-75 with high risk of developing OA as defined by:
(i) KL score of 0
(ii) Knee pain present in at least 1 knee
(iii) Normal radiographs,
(iv) At least one abnormal clinical MR finding such as prior knee injury, overweight or traumatic bone marrow edema lesions

4.1.2 Patients ages 40-75 with early OA as determined by KL scores 1-2

4.1.3 Healthy controls in the HJD OA database (KL score 0, no knee pain, no meniscal or ligament tears)

4.1.4 Healthy controls from the NYU Radiology volunteer database with no prior medical history of OA, knee pain, meniscal or ligament tears,

4.2 Exclusion Criteria

4.2.1 Contraindications for MRIs (e.g. pacemakers, ferromagnetic vascular clips, metal implants, claustrophobia, etc).

4.2.2 Subjects with any joint disease (example: Rheumatoid or inflammatory arthritis) other than knee OA, corticosteroid injections within the previous 3 months, and history of avascular necrosis, Paget's disease of bone, Wilson's disease, gout, total knee replacement (or plan for replacement within next 24 months).

4.2.3 Major co-morbidities such as diabetes, mellitus, cancer, congestive heart failure and chronic infectious diseases.

4.2.4 Alignment interventions such as insoles and knee braces

4.2.5 Vulnerable patients will not be recruited for this study

4.3 Subject Recruitment and Screening

Participants will be recruited from the NYU-HJD Osteoarthritis Database and from the NYU Radiology Research database, which has over 400 knee OA patients and 300 healthy controls. Drs. Abramson and Krasnokutsky maintain the database and will identify potential subjects for this study. All subjects will be given a telephone screening by Dr. Chang (see attachment). In order to access the patient's PHI for the purposes of conducting a pre-screening over the telephone we will obtain a waiver of documentation of consent in order to screen potential participants via telephone. The phone screening is minimal risk and PHI will only be recorded if the patient is eligible and agrees to participate. If the patient is ineligible or declines to participate their PHI will be deleted immediately.

Subjects who agree to participate will be given the consent form to read and sign in a private room adjacent to the MR scanners at CBI. All participants will be given ample time to read the consent form, ask any questions and will be given a signed copy of their consent form. Subjects will complete an MRI screening form to ensure the absence of MRI contraindication and a physical screening by Drs. Abramson or Krasnokutsky to ensure the absence of any signs of knee disorders such as tenderness, instability or inflammation (see Section 6. for order of visit procedures).

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects who wish to withdraw from the study: The PI and research team will be alerted immediately by the interviewer, will meet with the participant to address concerns, in person if possible and, if the participant wishes to withdraw, will complete a change of status form; the participant will be dropped from the study.

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The PIs will also give the participant the telephone number for the NYULMC Radiology IRB, should the subject wish to discuss any issues with a representative of the Board.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

If after several attempts to reach patients over the phone to schedule follow-up visits they will be considered lost to follow up.

5 Study Procedure/Imaging

5.1 Description

The implementation of the study scan will be the same as any clinical knee scan e.g. participants will be asked to lie down on the scanning table, they will be given a bulb that allows them to communicate with the MRI technicians and participants can stop the scan at any time by squeezing the bulb. They will be given ear plugs to block out noise emanating from the MRI. Their knee will be placed into the knee coil which is routinely used at CBI for clinical patients.

The only difference between a routine clinical scan and our research scan is the use of our imaging sequences to acquire the images. The imaging sequence techniques do not pose any added risk to the patients beyond that of a standard clinical MRI.

5.2 Specific Scan Information

All scans will be performed on a PRISMA 3T MRI scanner (Siemens Medical Solutions) located at 660 1st Avenue. A baseline MRI exam consisting of accelerated 3D-T1p, and T2, MRI will be performed. Longitudinal follow-up MRI exams (24 months) will be repeated on the same knee on all OA patients.

5.3 Implementation of Study Imaging Scan

See Description in 5.1

5.4 Subject Compliance Monitoring

The research team will track subject visits to ensure the subject is compliant with research procedures (baseline through visit 3).

5.5 Prior and Concomitant Therapy

All currently used (past 30 days) prescription medications will be captured using the medical inventory method, in which the participant brings in all medications they are currently taking and the brand name, generic name or active ingredients are recorded and matched to an entry (seven digit code) in an online medical dictionary (69). Finally nutritional and health supplements that influence the intake of nutrients of potential importance for the course of OA or that may affect biochemical markers during the study will be assessed with the Block Brief 2000 food frequency questionnaire as well as by targeted questions.

6 Study Procedures

6.1 Visit 1- Initial Screening (Patients only)

Patients will be consented according to the procedures outlined in Section 4.3. No procedures will take place until all questions are answered and the subject signs the consent form. In a private room located adjacent to the MRI scanners at CBI, three standard questionnaires (KOOS, WOMAC and PASE) and a physical examination to ensure there are no signs of knee inflammation or tenderness will be administered by Dr. Abramson or Dr. Krasnokutsky. Medications and other nutritional information will be collected from patients as described in section 5.5.

The total amount of time to complete the consent process, administer the assessments, conduct the physical examination and collect medication information will be approximately 60 minutes.

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6.2 Visit 2- Baseline MRI (Patients and Controls)

This will occur as soon as possible after Visit 1 depending on patient availability. Subjects will undergo the same procedures during this visit. Subjects will be given a standard MRI screening form to complete to ensure there are no contraindications for MRI. This is a standard form that every person having an MRI must be complete. Participants will be asked to lie down on the scanning table, they will be given a bulb that allows them to communicate with the MRI technicians and participants can stop the scan at any time by squeezing the bulb. They will be given ear plugs to block out noise emanating from the MRI. Their knee will be placed into the CBI approved knee RF coil that is routinely used on our clinical patients. Coils are used to translate information from the scan into a picture on a computer. The only difference between the routine clinical scan and our research scan is the use of the accelerated imaging sequences to acquire the images. The imaging sequence techniques do not pose any added risk to the patients beyond that of a standard clinical MRI.

For controls, this will be their only visit. They will undergo the same consenting and MRI procedures described above. Controls will not undergo a physical exam nor will they be required to take the three questionnaires.

This visit will take approximately 90 minutes for both patients and controls.

6.3 Visit 3- Two year follow up (Patients only).

Patients will fill out the same three questionnaires they had in visit 1 and will have another MRI scan as described in Visit 2.

7 Statistical Plan

7.1 Sample Size Determination

The sample size of 30 ex-vivo specimens was selected so that study will have at least 80% power to detect a concordance correlation of magnitude ≥0.5 and a mean difference ≥5% between the accelerated and reference protocols in terms of their T1ρ and T2 values. The sample size of 60 was chosen to provide 80% power to detect mean T1ρ and T2 differences between the healthy controls and each of the high risk of OA and mild OA groups ≥20% of the mean for controls.

7.2 Statistical Methods

A point estimate and 95% confidence interval (CI) will be provided for the mean and standard deviation of the T1p and T2 measures within each group and for the mean difference between each pair of groups. The group comparisons will be based on analysis of covariance (ANCOVA). A separate ANCOVA will be conducted for each global and regional measure T1p and T2 measure. The accuracy of the regional and global T1p and T2 measures from the accelerated protocol relative to the reference (fully sampled) protocol will be assessed using: (1) RMSE, the concordance correlation coefficient and the Bland Altman 95% limits of agreement to assess the association between accelerated and reference values of 3D-T1p and T2; (2) paired-sample Wilcoxon signed rank tests to compare the accelerated and reference protocols in terms of regional and global T1p and T2; (3) receiver operating characteristic curve (ROC) an analyses to compare the accelerated and reference protocols in terms of area under the ROC curve as a measures of diagnostic accuracy for discriminating high risk and mild OA.

Pearson and Spearman rank correlation coefficients will be used to characterize the association of each imaging measure with each clinical assessment.

7.3 Subject Population(s) for Analysis

Healthy and OA patient groups will have equal representation of both genders. The Hospital for joint diseases is one of the major Orthopedic Institutes in New York and sees a diverse population especially African American and Asian American community. For these reasons, we believe that a representative ethnic mix will be obtained from our patient population. Since healthy subjects are required from the same

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general area, we believe that this population will also have the similar representative ethnic mix as the patient population.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Unanticipated Adverse Device Effect
An Unanticipated Device Effect is 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.

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse device effect
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.2 Reporting of Adverse Device Effects and Unanticipated Problems

8.2.1 Investigator reporting: *Notifying the study sponsor*

The following describes events that must be reported to the study sponsor in an expedited fashion.
Initial Report: within 24 hours:
The following events must be reported to the study sponsor by telephone within 24 hours of awareness of the event:

- Unanticipated adverse device effect, regardless of seriousness or severity
- Unanticipated problems related to study participation

Additionally, an FDA Form 3500A must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator shall maintain a copy of the MEDWATCH Form on file at the study site.

Sponsor: National Institute of Health, (301) 496-4000

Follow-up report: within 48 hours:

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Within the following 48 hours, the investigator shall provide further information, as applicable, on the unanticipated device event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse device effects shall be provided promptly to the study sponsor.

Other Reportable events:

- **Deviations from the study protocol**
  Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but ***no later than 5 working days*** of the protocol deviation.
- ***Withdrawal of IRB approval***
  An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but ***no later than 5 working days*** of the IRB notification of withdrawal of approval.

8.2.2 Investigator reporting: *Notifying the IRB*

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

Report Promptly, but no later than 5 working days:
Researchers are required to submit reports of the following problems promptly but no later than10 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events*** **that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:
The following events also require prompt reporting to the IRB, though no later than10 working days:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more

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severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process
The reportable events noted above will be reported to the IRB using the form: "Reportable New Information" in Research Navigator or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

8.3 Medical Monitoring

Safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will be conducted by Drs. Abramson, Krasnokutsky or Chang.

8.4 Stopping Rules

N/A

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

P.I and co-investigators will maintain all the MRI data, and save the data on CDs, which will be stored in a secure cabinet located at 660 1st Avenue and is only accessible to the PI and research team. A copy of this data will be on the PI's workstation, which has a secure password protection. Data will be anonymized by assigning codes to subjects. Every attempt will be made by the investigators to maintain all information collected in this study strictly confidential, except as may be required by court order or by law. Consent forms will be stored in a locked cabinet located at 650 1st avenue and is only accessible to the Research Coordinator.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Records Retention

It is the investigator's responsibility to retain study essential documents for at least two years after the study closure.

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10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. department, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Data Safety Monitoring Plan

The risks associated with this MRI study are deemed to be at minimal risk. This research study does not involve testing and administration of any drugs or intervention. However, any adverse events to the participants will be immediately reported to the IRB as described above, as well as our departmental research committee that oversees clinical research.

Periodic meetings among members of the research team will be held to ensure that the study is being done according to the protocol and if any changes or amendments are necessary, also to ensure that the safety and privacy of subjects who are participating are being respected.

It will be the responsibility of the Principal Investigator to oversee the safety of the study at the study site. This safety monitoring will include careful assessment and appropriate reporting of adverse events in a timely manner as described above. A Data Safety Monitoring Report will be submitted to the IRB annually in conjunction with the study's continuation. The Data Safety Report will include a summary of adverse events, number of withdrawn subjects and reasons for withdrawal.

10.3 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, NIH, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal

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consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

This study is financed through a grant from the US National Institute of Health.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYU investigators will follow the applicable University conflict of interest policy(ies).

12.3 Subject Stipends or Payments

Subjects and controls will be compensated $50 per visit for participating in this study. Participants or their insurance companies will not be responsible for the costs of any research procedures.

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

14 References

1. Prasad AP, Nardo L, Schooler J, Joseph GB, Link TM. T(1)rho and T(2) relaxation times predict progression of knee osteoarthritis. Osteoarthritis Cartilage 2013;21(1):69-76.
2. Felson DT. An update on the pathogenesis and epidemiology of osteoarthritis. Radiol Clin North Am 2004;42(1):1-9
3. Felson DT. Risk factors for osteoarthritis: understanding joint vulnerability. Clin Orthop Relat Res 2004(427 Suppl):S16-21.
4. Hootman JM, Helmick CG. Projections of US prevalence of arthritis and associated activity limitations. Arthritis Rheum 2006;54(1):226-229.
5. Sun BH, Wu CW, Kalunian KC. New developments in osteoarthritis. Rheumatic Diseases Clinics of North America 2007;33(1):135-148.
6. Bitton R. The economic burden of osteoarthritis. Am J Manag Care 2009;15(8 Suppl):S230-235.
7. Yelin E. The earnings, income, and assets of persons aged 51-61 with and without musculoskeletal conditions. J Rheumatol 1997;24(10):2024-2030.
8. Borthakur A, Mellon E, Niyogi S, Witschey W, Kneeland JB, Reddy R. Sodium and T1rho MRI for molecular and diagnostic imaging of articular cartilage. NMR in biomedicine 2006;19(7):781-821.
9. Wang L, Regatte RR. Quantitative mapping of human cartilage at 3.0T: parallel changes in T(2), T(1)rho, and dGEMRIC. Acad Radiol 2014;21(4):463-471.
10. Wang L, Regatte RR. T MRI of human musculoskeletal system. J Magn Reson Imaging 2014.
11. Li X, Majumdar S. Quantitative MRI of articular cartilage and its clinical applications. J Magn Reson Imaging 2013;38(5):991-1008.
12. Oei EH, van Tiel J, Robinson WH, Gold GE. Quantitative radiologic imaging techniques for articular cartilage composition: toward early diagnosis and development of disease-modifying therapeutics for osteoarthritis. Arthritis Care Res (Hoboken) 2014;66(8):1129-1141.

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13. Regatte RR, Akella SVS, Lonner JH, Kneeland JB, Reddy R. T1rho relaxation mapping in human osteoarthritis (OA) cartilage: comparison of T1rho with T2. Journal of magnetic resonance imaging : JMRI 2006;23(4):547-553.
14. Regatte RR, Akella SV, Wheaton AJ, Lech G, Borthakur A, Kneeland JB, Reddy R. 3D-T1rhorelaxation mapping of articular cartilage: in vivo assessment of early degenerative changes in symptomatic osteoarthritic subjects. Acad Radiol 2004;11(7):741-749.
15. Friedrich KM, Shepard T, Chang G, Wang L, Babb JS, Schweitzer M, Regatte R. Does joint alignment affect the T2 values of cartilage in patients with knee osteoarthritis? European radiology 2010;20(6):1532-1538.
16. Friedrich KM, Shepard T, de Oliveira VS, Wang L, Babb JS, Schweitzer M, Regatte R. T2 measurements of cartilage in osteoarthritis patients with meniscal tears. AJR American journal of roentgenology 2009;193(5):W411-415.
17. Li X, Wyatt C, Rivoire J, Han E, Chen W, Schooler J, Liang F, Shet K, Souza R, Majumdar S. Simultaneous acquisition of T1rho and T2 quantification in knee cartilage: repeatability and diurnal variation. J Magn Reson Imaging 2014;39(5):1287-1293.
18. Kijowski R, Blankenbaker DG, Munoz Del Rio A, Baer GS, Graf BK. Evaluation of the articular cartilage of the knee joint: value of adding a T2 mapping sequence to a routine MR imaging protocol. Radiology 2013;267(2):503-513.
19. Dardzinski BJ, Mosher TJ, Li SZ, VanSlyke MA, Smith MB. Spatial variation of T2 in human articular cartilage. Radiology 1997;205(2):546-550.
20. Mosher TJ, Dardzinski BJ. Cartilage MRI T2 relaxation time mapping: overview and applications. Semin Musculoskelet Radiol 2004;8(4):355-368.
21. Xia Y, Farquhar T, Burton-Wurster N, Lust G. Origin of cartilage laminae in MRI. Journal of Magnetic Resonance Imaging 1997;7(5):887-894.
22. Li X, Han ET, Ma CB, Link TM, Newitt DC, Majumdar S. In vivo 3T spiral imaging based multi-slice T(1rho) mapping of knee cartilage in osteoarthritis. Magn Reson Med 2005;54(4):929-936.
23. Holtzman DJ, Theologis AA, Carballido-Gamio J, Majumdar S, Li X, Benjamin C. T1Ï_ and T2 quantitative magnetic resonance imaging analysis of cartilage regeneration following microfracture and mosaicplasty cartilage resurfacing procedures. J Magn Reson Imag;32(4):923.
24. Wheaton AJ, Borthakur A, Shapiro EM, Regatte RR, Akella SV, Kneeland JB, Reddy R. Proteoglycan loss in human knee cartilage: quantitation with sodium MR imaging--feasibility study. Radiology 2004;231(3):900-905
25. Martin KA, Rejeski WJ, Miller ME, James MK, Ettinger WHJ, Messier SP. 1999. p 627-633
26. Silverwood V, Blagojevic-Bucknall M, Jinks C, Jordan JL, Protheroe J, Jordan KP. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage 2014
27. Pahor M, Chrischilles EA, Guralnik JM, Brown SL, Wallace RB, Carbonin P. Drug data coding and analysis in epidemiologic studies. European Journal of Epidemiology 1994;10(4):405-411.
28. Coggon D, Croft P, Kellingray S, Barrett D, McLaren M, Cooper C. Occupational physical activities and osteoarthritis of the knee. Arthritis & Rheumatism 2000;43(7):1443-1449.

15 Attachments

- Consent Form
- Waiver of documentation of consent
- Telephone Screening

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