Ultrasound Evaluation of Crohn's Disease

NCT03235180

September 28, 2017

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IRB Minimal Risk Protocol Template

General Study Information

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Study Title: Ultrasound Evaluation of Crohn's Disease

Protocol version number and date: 9/28/17

Purpose

Hypothesis: Small bowel stiffness and vascularity measured by ultrasound imaging are useful biomarkers for Crohn's disease.

Aims, purpose, or objectives:
The overall goal is to investigate the value of ultrasound measurements of small bowel stiffness and vascularity as new biomarkers for Crohn's disease.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc*.):
Crohn's Disease (CD) is a chronic inflammatory condition in the bowel that affects over 1 million Americans, costing billions of dollars every year. Due to the relapsing nature of the disease, frequent imaging follow-ups are often necessary over many years to monitor treatment response to guide therapy adjustments. An ideal CD imaging method should be able to evaluate both inflammation and fibrosis, as patients with predominantly inflammatory lesions are more likely to respond to medical therapy, while patients with fibrostenotic lesions usually require surgery. Ultrasound is safe, cost-effective, and widely accessible, thus provides an attractive alternative to the clinical standard Computed Tomography (CT, risks of radiation) and Magnetic Resonance Imaging (MRI, more expensive and limited accessibility). Because ultrasound may not be able to image bowel loops deep in the body, its main role is to follow-up after initial screening by CT or MRI (especially for terminal ileum, which is easily accessible by ultrasound and the most frequently affected bowel segment for CD).

In this project, we will study the efficacy of ultrasound shear wave elastography and vascularity imaging for CD evaluation. Literature evidences demonstrate that bowel stiffness is correlated with fibrosis, while bowel vascularity and perfusion is correlated with inflammation. Therefore, we expect the combination of shear wave elastography and vascularity imaging can increase the sensitivity and specificity of CD evaluation.

Aim 1: To evaluate the correlation of ultrasound measurements with clinically indicated Magnetic Resonance Enterography (MRE).
Aim 2: To investigate if ultrasound measurements can be used to predict treatment response for Crohn's disease.

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Subject Information – charts, records, images, or specimens are considered 'subjects'

Target accrual is the proposed number of subjects to be included in your study at your site. "Subjects" may include Mayo Clinic charts, records, or specimens, ***and/or*** *charts, records, or specimens received at Mayo Clinic from external sources for collaborating analysis by the investigator under this IRB application*:

Target accrual: 100

Subject population: patients with confirmed or suspected Crohn's disease.

Inclusion criteria: Crohn's disease patients with involvement of terminal ileum (thickness > 3mm) or other segments of small or large bowel, age above 18,.
Exclusion criteria: patients with change of medicine or going to surgery over the 6-months follow-up period, patients with unreliable ultrasound images due to conditions such as large body habitus or poor ultrasound imaging window; adults lacking capacity to consent; vulnerable subjects such as prisoners. Pregnant women, nursing mothers, patients with known or suspected right-to-left, bi-directional, or transient right-to-left cardiac shunts, patients with history of hypersensitivity allergic reactions to ultrasound contrast agents.

☐ Yes ☒ No Will a Certificate of Confidentiality (COC) be obtained from NIH? If yes,
Who is obtaining the COC: Mayo Clinic investigator, study sponsor, other:
Explain why a COC is needed:

Study Design

Methods: *Describe, in detail, the research activities that will be conducted under this protocol*:

Study Design: We will study the terminal ileum of 100 Crohn's disease patients to investigate the efficacy of ultrasound measurements for disease evaluation and treatment outcome prediction. Patients with ongoing medical therapy or starting a new medical therapy will be recruited. Inflammation and fibrosis evaluated by contrast enhanced MR enterography at baseline and 6-months post therapy will be used as the reference standard. Ultrasound will be performed at baseline, 4-weeks, and 6-months. For Aim 1, correlation of ultrasound measurements with MR enterography results will be evaluated at baseline and 6-months. For Aim 2, we will access the association of the percentage change in ultrasound parameters from baseline to 4-weeks with the percentage change in MR enterography scores from baseline to 6-months. More information about data analysis can be found in the statistical section below.

Ultrasound Procedure: Patients will be fasting for 4 hours before ultrasound scans to reduce bowel air and peristalsis. The ultrasound transducer will be sanitized as per clinical routine before each use. The terminal ileum (TI) will be located by B-mode ultrasound. The TI lesion with the most significant thickening will be

identified in B-mode images for subsequent measurements. Repeated measurements of shear wave speed (which represents bowel stiffness) at the TI lesion will be obtained using the GE Logiq E9 ultrasound scanner. Vascularity images of the TI lesion will be obtained using the Verasonics ultrasound scanner. We will obtain ultrasound images before and after the administration of contrast microbubbles to evaluate the benefit of contrast agents. Lumason, a FDA approved ultrasound contrast agent for liver imaging, will be used (IV injection) for this study. The subject will be instructed to briefly hold his/her breath during each ultrasound acquisition. Sometimes it can be difficult to find the same bowel lesion for imaging for longitudinal studies. We will measure the distance of the lesion from the ileocecal valve and use this information to help locating the same lesion for longitudinal studies.

Safety of Lumason Administration: Lumason is approved by FDA as an ultrasound contrast agent for routine clinical use. In this study, the dosage and route of administration of Lumason will comply with the guideline of the package insert of Lumason. Our study team member will screen participants to exclude pregnant women, nursing mothers, patients with known or suspected right-to-left, bi-directional, or transient right-to-left cardiac shunts, patients with history of hypersensitivity allergic reactions to ultrasound contrast agents. If a female patient with childbearing potential is not sure of her pregnancy status, a urine pregnancy test will be done. Potential side effects will be monitored by sonographer and/or radiologists: Radiology has protocols on how to respond to adverse reaction of Lumason and Definity ultrasound contrast agents

[redacted]

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.)*:
We have commitments from all participating personnel. Patients will be referred and recruited by participating physicians. We have a GE Logiq E9 and a Verasonics ultrasound scanner that can be used for this study.

Check all that apply. If none apply, leave blank:

☐ This is a multisite study involving Mayo Clinic and non-Mayo Clinic sites.
When checked, describe the research procedures/activities being conducted **only** at Mayo Clinic:

☐ Mayo Clinic staff will be engaged in research activity at a non-Mayo Clinic site. *When checked, provide the location and a detailed description of the Mayo Clinic research staff involvement*.

☐ This study is to establish and/or maintain an ongoing database or registry for research purposes only.

☐ The research involves contact or interaction with subjects, for example, surveys, questionnaires, observation, blood draw.

☐ The study involves photographing, audiotaping or videotaping subjects (and guests).

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Blood Collection

If this study involves prospective blood collection by finger, heel, ear stick or venipuncture, complete the following:

☐ **From healthy, non pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _____ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

☐ **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _____ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.)_____

Review of Chart, Images, Specimens

Provide the date range for collection of data and/or specimens that will be included in your research dataset. *Example: 01/01/2000 to 12/31/2013* or all records through mm/dd/yyyy.

4/1/2017 to 4/1/2025

For a retrospective chart review, enter the date range:

Check all that apply:

☐ This study involves only data and/or specimens that exist at the time this application is submitted to the IRB (IRB submission date). No data or specimens will be collected beyond this date.

☒ This study involves only data and/or specimens that will be collected after submission to the IRB.

☐ The study involves data and/or specimens that exist at the time of submission to the IRB **and** data and/or specimens that will be collected after submission to the IRB, for example a study that includes collection of existing data and prospective collection of specimens.

☐ Data and/or specimens used in this study are collected under another IRB protocol. *When checked, provide the IRB number(s) from which the research material will be obtained. When appropriate, check the box below to attest that subjects have provided consent for future use of their data and/or specimens, as described in this protocol*.

IRB Number/s - Data Only: _____

IRB Number/s - Specimens Only: _____

IRB Number/s - Data and Specimens: _____

Note: When subjects provided consent for use of their data and/or specimens, as described in this protocol.

☐ Other data sources will be utilized in this study, e.g. receiving data/specimens from an external party. When checked, provide all data sources:

Data Confidentiality, HIPAA Subject Identifiers

Review the list of subject identifiers below and, if applicable, check the box next to each subject identifier being recorded at the time you are collecting/abstracting data/specimens for use in this study.

Subject Identifiers: Individually identifiable information, including demographic data, that identifies the individual or for which there is reasonable basis to believe it can be used to identify the individual. NOTE: Identifiers apply to subjects enrolled in your study and to the subject's relatives, household members, employers, etc.

Internal refers to subject identifiers that will be included in the dataset maintained by the study team.
External refers to subject identifiers that will be shared with persons outside of the immediate study team, for example, sent to an external collaborator or shared with a national registry.

SUBJECT IDENTIFIERS **Check all that apply**	INTERNAL IDENTIFIER	EXTERNAL IDENTIFIER
Name	x	
Social Security number		
Medical record/patient registration number, lab accession, specimen or radiologic image number	x	
Study number, subject ID, or any other unique identifying number, characteristic or code that can be used to link the identity of the subject to the data	x	
Dates: All elements of dates [month, day, and year] directly related to an individual. Their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	x	
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes		
Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
If None of the above identifiers will be recorded or maintained in the dataset and/or sent outside of the study team, please check "None".	☐ None	☒ None

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Statistical Information

Note: Power analyses and study endpoints are not needed for a pilot or feasibility studies.

☐ No statistical information. *If checked, please explain*:

Statistical Considerations

Power Statement:
The sample-size for the present investigation was determined for the primary aim of assessing the correlation between ultrasound parameters and the MaRIA score (a score calculated from MR enterography, which reflects bowel inflammation [1]). For ultrasound to have meaningful clinical utility we would require a correlation with MaRIA score of at least 0.70. For the primary analysis, the correlation between ultrasound measurements and MaRIA score will be compared to 0.70 using a two-tailed, alpha=0.05 level test. Under the assumption that the "true" correlation is 0.82, a sample-size of N=100 will provide statistical power of 82% for the primary analysis.

Data Analysis Plan:
Disease activity measurements will be obtained via MR enterography at baseline and 6-months following treatment, and via ultrasound at baseline, 4-weeks and 6-months after treatment. Two quantitative ultrasound parameters will be obtained: A) shear wave speed obtained from the GE Logiq E9; B) vessel density (the percentage of pixels in the bowel lesion with blood flow compared to the total area of the lesion) obtained from the Verasonics. For each ultrasound parameter, the mean of all repeated measurements will be used as the representative value for a given patient at a given time. Measurements obtained following baseline will be expressed as percentage change from baseline. For inflammation evaluation, the correlation of each ultrasound parameter with MaRIA score will be assessed using a point estimate and 95% confidence interval. In addition, using a MaRIA cut-point of 11, patents will be categorized as having mild versus severe disease [1]. As a secondary analysis, logistic regression with corresponding ROC (Receiver Operating Characteristic) analysis will be used to assess whether ultrasound measurements can distinguish between mild versus severe inflammation. Findings from these analyses will be summarized using the point-estimate and 95% confidence interval for the area under the ROC curve (AUROC). In addition to univariate analyses, exploratory multivariable analyses will be performed to assess whether combination of ultrasound parameters can increase the performance relative to the univariate findings. Similar analyses will be performed to assess whether ultrasound parameters are useful for fibrosis evaluation: for these analyses, the MR enterography percentage gain change (PGC) will be used for correlation analysis, and a PGC cut point of 23.5% will be used to categorize fibrosis as mild or severe for ROC analysis [2].

For Aim 2, a series of analyses will be performed to assess whether ultrasound parameters obtained at baseline and 4-weeks can predict 6-month treatment outcome. A correlation analysis will be performed to assess the association of the percentage change in ultrasound parameters from baseline to 4-weeks with the percentage change in MaRIA score from baseline to 6-months. In addition, treatment outcome will be dichotomized (responder, non-responder) based on the 6-month MR enterography. Univariable and multivariable logistic

regression with corresponding ROC analyses will be used to assess whether percentage change in ultrasound measurements at 4-weeks can predict treatment outcome. Findings from these analyses will be summarized using the point-estimate and 95% confidence interval for the AUROC. In all cases, distributional assumptions will be evaluated with transformations or non-parametric methods used as appropriate. Two-tailed p-values < 0.05 will be considered statistically significant.

Endpoints
Primary: please see detailed description above.

Secondary: please see detailed description above.

References:

1. Rimola, J., et al., *Magnetic Resonance Imaging for Evaluation of Crohn's Disease: Validation of Parameters of Severity and Quantitative Index of Activity.* Inflammatory Bowel Diseases, 2011. **17**(8): p. 1759-1768.
2. Rimola, J., et al., *Characterization of Inflammation and Fibrosis in Crohn's Disease Lesions by Magnetic Resonance Imaging.* American Journal of Gastroenterology, 2015. **110**(3): p. 432-440.