TITLE: Helmsley 3.0: Abbreviated MRE

1. ABSTRACT:

MRI of the bowel, or MR enterography (MRE), is commonly performed to evaluate children and adults with known or suspected inflammatory bowel disease, including Crohn's disease (CD). This noninvasive test, which traditionally requires oral contrast material, intravenous contrast material, and anti-peristaltic medication (i.e., glucagon), can be used to detect and characterize intestinal inflammation, identify disease related complications, and assess change over time, including treatment response. In its current form, clinical MRE examinations are lengthy and poorly tolerated by patients. In the current study, we propose to compare a novel abbreviated MRE protocol to conventional, standard of care MRE protocols in children and adults with CD at three large medical centers.

2. PURPOSE OF STUDY:

The purpose of our study is to compare a novel abbreviated MRE protocol to conventional, standard of care MRE in children and adults with CD at three large medical centers, with CCHMC serving as the lead site The novel MRE protocol will not require an intravenous catheter, intravenous contrast material, or anti-peristaltic medication (i.e., glucagon) and the MRE scan time will be reduced, taking approximately 15 minutes. In addition, we will compare patient experiences and preferences between the two different MRE protocols, including willingness to trade diagnostic performance for patient experience. We hypothesize that a patient-centric, noncontrast, abbreviated MRE protocol is non-inferior (and will be preferred) compared to standard-of-care MRE in children and adults with CD with regards to detection of clinically meaningful small bowel active inflammation and detection/characterization of stricturing complications.

3. BACKGROUND:

MRI of the bowel, or MR enterography (MRE), is the reference standard for radiologically diagnosing and following children and adults with small bowel Crohn's disease (CD). This imaging test has been shown to have excellent diagnostic performance for detecting intestinal inflammation, assessing disease severity, and identifying stricturing and penetrating complications. Standard-of-care MRE consists of a combination of noncontrast and contrast-enhanced sequences requiring about 45-minutes to acquire and has remained mostly unchanged over the past 15-years. In addition, this technique requires intravenous catheter placement, exogenous contrast material (i.e., an intravenously administered gadolinium chelate and orally administered hyperosmotic agent), and the intravenous or intramuscular administration of a gastrointestinal paralytic agent (typically glucagon). Intravenous and oral contrast materials are associated with a variety of physiologic side effects and less often allergic / allergic-like reactions, while glucagon has been shown to cause nausea and/or emesis in up to 48% of patients. We propose a patient-centric, noncontrast, abbreviated MRE protocol that can be performed in less than 15 minutes, on average, without the use of an intravenous catheter, intravenous contrast material, or glucagon. We believe such an abbreviated protocol will be shown to be non-inferior to the standard-of-care protocol and will demonstrate considerably better patient acceptance. Furthermore, such an abbreviated MRE protocol could have downstream

implications related to improved access and healthcare costs, potentially impacting the overall cost-effectiveness of MRE.

4. STUDY DESIGN:

The proposed prospective investigation will be designed as a non-inferiority study. Study sites will identify and recruit children and/or adults with known CD that are undergoing routine clinical MRE examinations for staging / restaging of intestinal inflammation, follow-up of luminal narrowing / stricturing disease, or follow-up of patients with known internal penetrating disease. Enrolled participants will 1) undergo a dedicated research abbreviated MRE examination within ±10 days of their clinical MRE, at the convenience of the participant, and 2) participants will be surveyed about their preference / patient experience for the standard-of-care vs. abbreviated MRE protocol. Furthermore, we will ask a series of "trade-off" questions to understand patients' willingness to tolerate a loss of examination performance to improve patient experience. These tradeoff questions will use a survey method called a discrete choice experiment (DCE), which is a technique based on behavioral economic theory that asks respondents to make a series of discrete choices between medical care strategies.

The parents/guardians of pediatric participants (10-17 years of age) also will receive a similar survey to understand their perspective, and how it may differ from their children.

Board-certified, fellowship-trained radiologists will review both the standard-of-care and abbreviated MRE examinations in separate sessions to document the presence and severity of small bowel inflammation; the presence and features of stricturing disease (and penetrating disease, if present) also will be recorded. The diagnostic performance of the abbreviated MRE protocol will be determined for individual readers and all readers combined, using the standard-of-care protocol as reference standard.

At the end of the proposed study, we will have shown if a patient-centric, noncontrast, abbreviated MRE protocol can be used to evaluate children and adults with CD as well as if such a protocol offers an improved patient experience. If successful, such an abbreviated protocol could enable more frequent patient follow-up imaging, with more individualized patient management and improved patient outcomes, including more frequent transmural healing. Such an abbreviated protocol also could be used in the research setting to assess the effectiveness of candidate anti-inflammatory and anti-stricture (i.e., anti-fibrotic) therapies.

5. DURATION:

Patients will be recruited, enrolled, and imaged over a 36-month period. Data analysis will begin approximately month 30 and will require approximately 12 months to complete.

6. SELECTION & RECRUITMENT OF PARTICIPANTS:

Study sites (CCHMC, Mayo Clinic, and NYU Langone Health) will identify and recruit children and/or adults with known CD that are undergoing clinical MRE examinations for staging / restaging of intestinal inflammation, evaluation of known or suspected luminal narrowing / stricturing disease, and/or evaluation of known or suspected internal penetrating disease. CCHMC will recruit predominantly pediatric CD patients, while Mayo Clinic and NYU Langone Health will recruit

predominantly adult CD patients. Approximately one hundred participants will be enrolled and imaged at each site. Participants need to be English speaking in order to follow breath-hold commands and to complete the preference and "trade-off" surveys.

Inclusion Criteria:

Subjects will be recruited for our study using the following inclusion criteria:

- Established Crohn's disease diagnosis in patients 10 years of age and older
- Undergoing clinical MRE examinations for any reason(s) below:
    - Staging / restaging / follow-up of intestinal inflammation
    - Evaluation of known or suspected luminal narrowing / stricturing disease
    - Evaluation of known or suspected internal penetrating disease

Exclusion Criteria:

- Undergoing initial imaging for suspected CD where the diagnosis of CD has yet to be definitively established
- New CD diagnosis, undergoing baseline imaging
- Isolated colonic disease
- Known or suspected pregnancy
- Contraindication to MRI (e.g., due to certain implanted medical devices)
- Ileostomy or prior ileal resection
- Less than 10 years of age
- Unable or unwilling to follow imaging procedures
- Non-English speaking

7. PROCESS OF OBTAINING CONSENT:

Only outpatient CD patients receiving clinically indicated imaging will be recruited for this study. Participants will be screened in advance of enrollment by study personnel to determine baseline eligibility for participation. Each subject will be informed that participation in the study is completely voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

Verbal phone consent (using the phone script) will be obtained by a designated study team member from parents/guardians of subjects < 18 years of age and from subjects themselves when ≥ 18 years of age prior to the research MR visit to confirm that subjects understand they should not eat or drink 4 hours prior to the study.

Written informed consent and assent will be obtained by assigned study personnel at the first study visit. Parents/guardians (one per participant) of minor participants also will be consented themselves in order to perform a patient experience and patient preference survey from their perspective. Potential participants will be informed that study participation is voluntary and will not impact their medical care.

8. STUDY PROCEDURES:

Study participation may require up to 2 research encounters, depending on if the clinical or research MRE is performed first. If the research MRE is performed first, participants will undergo a dedicated research imaging visit as well as a second research encounter to complete a patient experience and preference survey (e.g. the DCE) following their clinical MRE. If the clinical MRE is performed first, then participants will undergo research imaging as well as patient experience and preference survey during a single encounter.

Research Abbreviated MRE

The abbreviated MRE imaging protocol eliminates the need for the post-contrast imaging sequences that are required for the clinical MRE. A MR cine sequence that is not utilized in the clinical MRE protocol will be employed in the abbreviated MRE imaging protocol. These differences in the MR imaging protocols result in the research MRE scan time to be approximately 35 minutes faster than the clinical MRE.

All sequences utilized for the research MRE are FDA approved and exist on all commercially available clinical MR scanners.

Clinical MRE Standard Sequences	Research Abbreviated MRE
Coronal BTFE	Coronal SSFSE
Coronal SSFSE	Axial SSFSE
Axial SSFSE	Axial SSFSE with Fat Saturation
Axial SSFSE with Fat Saturation	Diffusion Weighted Imaging
Coronal Pre-Contrast	Cine Coronal BTFE
Arterial coronal Post-Contrast	
Venous Coronal Post-Contrast	
Axial Post-Contrast	
Diffusion Weighted Imaging	

Survey

The survey will be administered on a tablet/ipad that will be supplied by a study team member. The survey will present hypothetical scenarios describing an MRE strategy. Participants will be asked to make a choice between two separate MRE imaging strategies with defined characteristics (see figure immediately below as an example). Characteristics will relate to multiple domains, including IV contrast, oral contrast, side effects such as nausea and vomiting, cost, exam time, and exam diagnostic performance. The survey will describe the attributes and walk respondents through a practice question to introduce the concept of discrete choice tasks.

If you had to choose an exam for follow-up, which exam would you prefer?		
	Option A	**Option B**
Accuracy	90%	80%
Exam time (minutes)	45	10
Out-of-pocket cost	$500	$400
IV contrast required	Yes	No
Please select one	☐	☐

If you had to choose an exam for follow-up, which exam would you prefer?	
☐	Standard MRE
☐	Abbreviated MRE
☐	I don't know

Study Chronology:

Procedure:
Telephone NPO Consent*
Informed Consent
Medical History
Clinical MR
Abbreviated Research MRE**
Patient Experience and Preference Survey (Discrete Choice Experiment)***

*Using the phone script, verbal consent will be obtained prior to the research MRI study to confirm participants will not eat or drink for 4 hours prior to the research MRE.
**Research MRE may occur ±10 days from Clinical MRE.
*** Once the research MRE and the clinical MRE are completed, participants and a parent of a participant age 10-17 will be asked to complete a questionnaire. This may require a second research encounter depending upon whether the research MRE or clinical MRE is performed first.

The participants must be nil per os (NPO) 4 hours prior to both the clinical and research MRE exams. If a participant is not NPO 4 hours prior to their MRE exams and is able to reschedule within window (if applicable) the participants visit(s) will be rescheduled.

For the dedicated research imaging visit, enrolled participants will undergo dedicated research, abbreviated MRE examination within ±10 days of their clinical MRE, at the convenience of the participant. Research MRE examinations will be standardized across sites, while clinical MRE examinations will be performed at each site using standard-of-care protocols. Clinical MRI examinations will be performed on both 1.5-T and 3-T MRI scanners from all major scanner manufacturers (i.e., GE HealthCare, Philips Healthcare, and Siemens Healthineers).

Research MRE examinations will be performed on dedicated research MRI scanners which will facilitate participant scheduling. 3-T scanners will be used at Mayo Clinic (Philips Healthcare) and NYU Langone Health (Siemens Healthineers). 1.5-T and 3-T scanners will be used at CCHMC (Philips Healthcare). We plan for these examinations to be performed in less than 15 minutes of scan time, on average.

For research MRE examinations, patients will ingest a standardized volume (weight-based, approximately 20 ml/kg, maximum of 1500ml) of water during the 45-minute period prior to their scheduled imaging time. At ~10% participant recruitment, research MRE examinations will be reviewed to ensure that water is providing adequate bowel distention and image quality.

During and after each research MRE examination, the research coordinator conducting the study visit will document any patient discomfort / distress such as, nausea, vomiting, etc.

Pertinent participant characteristics, including demographics, relevant clinical and laboratory data, and most recent MRI or CT comparison imaging (both reports and DICOM images) will also be obtained at the time of the research visit.

Fellowship-trained, board-certified radiologists from multiple institutions will independently review both the clinical standard-of-care and research abbreviated MRE examinations in separate sessions using a cloud-based image viewer to document the presence and severity of intestinal inflammation. Prior clinical MRE or CT examinations may be made available for comparison. The diagnostic performance of our abbreviated MRE protocol will be determined for individual readers and all readers combined, using standard-of-care clinical MRE examinations as reference standard.

Patient Preference Survey

Following the completion of both clinical and research only MRI examinations, participants will be formally surveyed about their "patient experience", including their preference for the standard-of-care vs. abbreviated MRE protocol should they need future imaging. Furthermore, we will ask a series of "trade-off" questions to understand patients' willingness to accept a loss in MRE examination performance to improve their patient experience. The survey tool will be constructed under the guidance of Shireen Hayatghaibi, PhD, a health services researcher in the CCHMC Department of Radiology and a member of the Society for Medical Decision Making. This survey will be reviewed and approved by the IRB prior to distributing it to participants and their parents.

Phase 1 Designing DCE

To inform the design of the DCE survey, our first stage of attribute selection is key. Patient's preferences can only be quantified relative to other attributes included in the study. To ensure the study includes attributes that patients' value, we will engage patient stakeholders from the Crohn's and Colitis Foundation (or local patients with Crohn disease as an alternative) in a focus group. This group will include between 7 and 12 participants and will last < 2 hours. During this focus group, we will expand and refine the characteristics used in the preliminary attitudes survey.

We will then create the final DCE experimental design using Sawtooth software. This software helps users develop 'efficient' DCE designs. Here, an efficient design is needed because testing all combinations of attributes and their levels is typically not feasible (for example, in a DCE with three attributes, each with four levels and two attributes with two levels each would result in a survey with 324 (34 x 22) possible combinations to test). This software will randomize the questions that will be asked.

Phase 2 Fielding the DCE

This is a cross-sectional survey. We will not collect any follow-up data. The survey will take approximately 15 to 30 minutes to complete. Data analysis will take approximately 3 months.

We will not enter any names, email addresses, phone numbers, or other PHI into the Sawtooth-hosted survey.

9. DATA ANALYSIS/METHODS:

The diagnostic performance of our abbreviated MRE protocol will be determined for individual readers and all readers combined, using standard-of-care clinical MRE examinations as reference standard. The presence of clinically meaningful (i.e., moderate-severe) active intestinal inflammation will serve as our primary outcome of interest. These analyses will be performed at the overall examination and individual bowel segment level. Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value will be calculated, with 95% confidence intervals. In addition, the global and individual bowel segment sMaRIA scores will be compared and correlated between clinical and research examinations using Mann-Whitney U tests and Spearman rank-order correlation. The diagnostic performance of the abbreviated MRE protocol for detecting luminal narrowing, stricture disease, internal penetrating disease, and perianal disease will also be calculated, again using clinical MRE examinations as the reference standard. Finally, Fleiss' kappa statistics will be used to evaluate inter-reader agreement for the different imaging features documented. The above results may be compared between readers without and with access to prior MRE or CT imaging when interpreting both the research and clinical MRE examinations.

Survey Analysis:

The analysis will be conducted in STATA, a statistical program. The unit of analysis for all analyses will be the individual participant. We will obtain data on respondent demographics and health characteristics, from baseline questions in the survey. We will summarize continuous outcome measures using means and standard deviations. We will compare continuous outcome measures

across groups (e.g. low versus middle versus high income levels, parent education level, proportion using a CGM) and test for statistical differences between groups using t-tests. We will summarize categorical outcome measures using frequencies and proportions and test for statistical differences between groups using chi-square tests. All statistical analyses will be conducted in Sawtooth Software and Stata (version 17).

We will estimate preferences for imaging using a mixed logit model (i.e., a random coefficient logit model), a statistical model designed to analyze discrete choices. Variation in preferences related to health and demographic characteristics will be captured through specification of covariates in the model. The coefficients of each attribute in the mixed logit model represent estimates of the probability of choosing an imaging strategy as a function of the levels of the attributes. Results from the main effects model will be used to estimate the marginal willingness to accept an imaging strategy for each level of an attribute by looking at the ratios of the coefficients between an attribute level. Statistical significance from 0 for coefficients t will be assessed at p-value <0.05.

The survey will include an attention check to determine whether respondents will choose the correct alternative when one choice is clearly the same or better on all attribute levels. We will run sub-analyses that eliminate responses that failed the attention check twice.

No identifiable information will be provided via the Sawtooth survey. Therefore, risks of respondent's privacy being breached online will be minimal.

10. FACILITIES and PERFORMANCE SITES:

The proposed study will be performed at three sites – CCHMC, Mayo Clinic, and New York University Langone Health. CCHMC will be the lead site and serve as the Institutional Review Board of record for all participating sites. Clinical imaging will be performed using MRI scanners in approved clinical locations, while research imaging will be performed using dedicated research scanners that are FDA-cleared for clinical use and that are operated within appropriate safety limits.

11. POTENTIAL BENEFITS:

There are no direct study-related benefits. However, participants could benefit from our abbreviated research MRE protocol in the future, should it be determined to be non-inferior to conventional, standard of care MRE. The abbreviated MRE could be better tolerated, allow more frequent imaging, have shorter examination times, and have lower healthcare costs.

12. POTENTIAL RISKS, DISCOMFORTS, INCONVENIENCES AND PRECAUTIONS:

There are minimal risks associated with this study. The primary risk relates to research MRI safety issues, such as burns and projectile-related injury. Standard-of-care MRI safety and screening practices will be performed by appropriately trained individuals/technologists at each site. The MRI scanner creates noise in the process of image acquisition. To mitigate this, study participants will be provided with hearing protection (ear plugs) per standard clinical practice.

Loss of confidentiality is another potential risk. This risk will be mitigated through the privacy and confidentiality measures described below.

While there are no known risks to noncontrast MRI during pregnancy, patients that are known to be pregnant or possibly pregnant will not be enrolled out of an abundance of caution.

Adverse events occurring during study participation will be documented by study personnel and reported to the IRB, as required.

13. RISK/BENEFIT ANALYSIS:

Overall, the proposed study has minimal risk, and the potential benefits of a future abbreviated clinical MRE examination that would allow more frequent, faster, potentially lower cost assessments are considerable. Thus, the risk/benefit ratio is favorable.

14. DATA SAFETY & MONITORING:

No DSMB will be assembled, as the proposed study is minimal risk, has no significant impact on patient care, and is not being used to make medical decisions. A study coordinator will be present for the duration of the participant's research MRI visit. Any adverse events that may occur will be documented by the coordinator and assessed by a study team medical doctor for severity and relatedness to the study. Investigators will closely monitor data and participants to immediately identify any potential risks and adverse events which will be reported to the IRB by the study team in a timely manner, as required.

15. PRIVACY and CONFIDENTIALITY:

All study data will be handled in a HIPAA-compliant manner. Paper records will be stored in secure, locked offices and cabinets. Electronic records will be password-protected. Study data will be entered into a HIPAA-compliant database, such as REDCap. Imaging data will be stored and reviewed on a HIPAA-compliant cloud platform; all PHI will be removed from imaging data except for date of encounter.

Study data, including images, will be stored beyond the study period, and they may be used for additional research investigations by the current study team. In addition, entirely deidentified study data may be made available to other investigators upon reasonable request. Finally, entirely deidentified study data may be made publicly available, as required by the funder. This information will be presented in the informed consent process.

Data Sharing

Imaging Data

To facilitate multi-site data sharing and analysis, a cloud-based HIPAA compliant platform will be utilized. This platform has been cleared by the U.S. Food and Drug Administration (FDA), and its use has been approved by the CCHMC Information Technology Security. Only study team members will have access to any data stored in this platform.

Clinical/laboratory Data

Limited (de-identified, with the exception of date of service) data will be shared with CCHMC for the purpose of data analysis.

Survey Data
Survey data will be shared with CCHMC for the purpose of data analysis.

16. COST OF PARTICIPATION:

Clinical MRE examinations will be billed to third-party payers (e.g., commercial insurance, Medicare). Research MRE examinations will be paid for by the research study (Helmsley Charitable Trust).

17. PAYMENT FOR PARTICIPATION:

Participants will receive a total of $100 for study participation to cover potential lost wages, costs of transportation/parking, time, etc. $80 will be paid for completing the research MRE and $20 will be paid for completing the survey.

18. REFERENCES

1. Mollard BJ, Smith EA, Dillman JR. Pediatric MR enterography: technique and approach to interpretation-how we do it. Radiology. 2015 Jan;274(1):29-43. doi: 10.1148/radiol.14122449. PMID: 25531478.

2. Dillman JR, Anupindi SA, Dane B. Proposal of an Abbreviated Noncontrast MR Enterography Protocol for Patients With Crohn Disease. AJR Am J Roentgenol. 2023 Dec 6. doi: 10.2214/AJR.23.30422. Epub ahead of print. PMID: 38054957.

3. Gandhi NS, Dillman JR, Grand DJ, Huang C, Fletcher JG, Al-Hawary MM, Anupindi SA, Baker ME, Bruining DH, Chatterji M, Fidler JL, Gee MS, Grajo JR, Guglielmo FF, Jaffe TA, Park SH, Rimola J, Taouli B, Taylor SA, Yeh B. Computed tomography and magnetic resonance enterography protocols and techniques: survey of the Society of Abdominal Radiology Crohn's Disease Disease-Focused Panel. Abdom Radiol (NY). 2020 Apr;45(4):1011-1017. doi: 10.1007/s00261-020-02407-8. PMID: 31982931.