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### General Information

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**Are external grants or funds being used to support this research?:** No external grants or funds are being used to support this research.

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## Certification

**Certification:** All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

**Data Use Agreement Training:** As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

**Associated Trial(s):** [NCT00094458 - Multicenter, Randomized, Double-Blind, Active Controlled Trial Comparing REMICADE® \(infliximab\) and REMICADE plus Azathioprine to Azathioprine in the Treatment of Patients with Crohn's Disease Naive to both Immunomodulators and Biologic](#)

**What type of data are you looking for?:** Individual Participant-Level Data, which includes Full CSR and all supporting documentation

## Research Proposal

### Project Title

Operating Characteristics of Centrally-Read Endoscopic Indices and a Novel Patient Reported Outcome Measure for Crohn's Disease

#### Narrative Summary:

Given the clinical importance of endoscopic disease activity in CD and potential to reduce placebo effect in clinical trials, it is important to understand operating properties of endoscopic indices and to use optimal outcome measures in clinical trials. Our primary objective is to assess the operating characteristic of (a) PRO2, (b) optimized CDEIS, and (c) optimized SES-CD using SONIC trial data. Operating characteristics will include reliability (inter- and intra-reliability of endoscopic scoring tools), sensitivity (responsiveness to treatment effect). We aim to evaluate these tools for possible outcome measurement as well as eligibility assessment for future clinical trials.

#### Scientific Abstract:

**Background:** Given the clinical importance of endoscopic disease activity in Crohn's disease (CD) and potential to reduce placebo effect in clinical trials, it is important to understand operating properties of endoscopic indices and to use optimal outcome measures in clinical trials.

**Objective:** To assess the operating characteristic of (a) PRO2, (b) optimized CDEIS, and (c) optimized SES-CD using the week 0, week 26, and week 50 SONIC study data.

**Study Design:** This study involves central adjudication of existing endoscopic images for disease activity scoring using optimized endoscopic indices (EIs). The reliability, responsiveness and operating characteristics of these optimized EIs will be explored in combination with existing clinical data. Additionally, the properties of a clinical index derived from existing CDAI data (PRO-2) will be analyzed using exploratory techniques.

**Participants:** Data from the completed SONIC trial that randomized 508 TNF and azathioprine-naive patients with moderate to severe CD to AZA monotherapy (n=170), IFX monotherapy (n=169), or IFX and AZA combination therapy (n=169). All data would be used for PRO2 analyses. For analysis of EIs, the subset of data where endoscopy video was collected would be used.

**Main Outcome Measures:** 1.) Reliability of central reader scoring of EIs 2.) Sensitivity/Responsiveness of EIs 3.) Correlation of EIs with other measures 4.) PRO2.

**Statistical Analysis:** Point estimates and 95% confidence intervals for reliability will be used. Analysis of additional outcome measures is described in detail in the SAP.

#### Brief Project Background and Statement of Project Significance:

Several endoscopic indices (EI) are currently available to assess disease activity in Crohn's disease (CD).[1-3] In response to a new regulatory decision that mandates the use of both patient reported outcomes (PROs) and endoscopic assessment as efficacy criteria in Inflammatory Bowel Disease (IBD) registration trials, Robarts adapted a 2-item PRO (PRO2) from the Crohn's Disease Activity Index (CDAI) as an interim measure, until a fully validated PRO can be developed.

The Crohn's Disease Endoscopic Index of Severity (CDEIS) [1] and the Simple Endoscopic Score for Crohn's Disease (SES-CD) [2] are commonly used EIs to assess disease activity. Both indices score endoscopic lesions in 5 colonic segments to obtain a composite score. A recent study identified common sources of disagreement among endoscopists when using these EIs, and created standardized rules to minimize variability in scoring these

problematic lesions [4]. These rules are termed the “optimized” EIs which further enhanced the reliability of these evaluative instruments. However, the operating properties of these optimized EIs and PRO2 are poorly defined. Understanding these properties is critical to the development of trials for the evaluation of new treatments for CD. Based on the clinical importance of endoscopic disease activity and the potential to reduce the placebo effect in clinical trials, it is imperative to understand the operating properties of the EIs to identify the optimal outcome measure. A subsequent post hoc sub-group analysis of SONIC attempted to address this question and demonstrated that week 26 mucosal healing and endoscopic response, defined as a decrease from baseline in SES-CD or CDEIS of at least 50%, identified those patients most likely to be in corticosteroid-free remission (CFREM) at week 50 [5]. Although these data established that EIs are responsive to clinical changes in CD, the degree of responsiveness has not been quantified and the responsiveness of optimized EIs have not yet been assessed. Additionally, the responsiveness of PRO2 has not been confirmed.

Accordingly, our aim is to determine the operating properties of central endoscopic scoring of optimized EIs and PRO2 for CD within a population of patients with moderate to severe CD. Since these patients received a treatment of known efficacy and demonstrated various degrees of improvement in disease status over the study period, EIs and PRO2 should reflect these changes. Recognizing that the validity of EIs also depends on their correlation with patient reported outcomes, we also aim to investigate the effect of co-primary end points, including EIs and PRO2, on the effect size estimates using the original study definitions. We anticipate this study will help to define the optimal endoscopic endpoints for use in clinical trials.

### **Specific Aims of the Project:**

Our goal is to assess the operating characteristics of PRO2, optimized CDEIS, and optimized SES-CD as outcome and eligibility criteria in clinical trials. To meet this goal, we will analyze the effects of different scoring tools, response and remission definitions on the estimates of effect size in the SONIC trial. Additional objectives are to confirm the intra- and inter-rater reliability for central reading of the optimized CDEIS and optimized SES-CD, and to examine the effects of various PRO2 and optimized SES-CD/CDEIS eligibility criteria on patient recruitment/trial feasibility.

Primary objective: To assess the operating characteristic of (a) PRO2, (b) optimized CDEIS, and (c) optimized SES-CD using the week 0, week 26, and week 50 SONIC study data.

Specific objectives include:

- a. To evaluate the intra-rater reliability of optimized CDEIS, SES-CD, and global assessment of endoscopic lesion severity (GELS).
- b. To evaluate the inter-rater reliability of optimized CDEIS, SES-CD, and GELS.
- c. To evaluate the sensitivity/responsiveness of the optimized CDEIS and SES-CD
- d. To explore outcome measurement and eligibility criteria definitions with optimized EIs and PRO2.

**What is the purpose of the analysis being proposed? Please select all that apply. Other**

## **Research Methods**

### **Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:**

Both data from the original SONIC study and new data based on expert endoscopist assessment of optimized EIs will be used.

For objectives a, b and c, related to operating characteristics of optimized EIs, only data from a subgroup of SONIC subjects would be used and combined with expert endoscopist assessments. It is expected that a subset of approximately 172 subjects had endoscopic lesions at baseline, and underwent repeat endoscopy at week 26.

For objective d, relating also to characteristics of PRO2, outcome data from all SONIC subjects would be used.

### **Main Outcome Measure and how it will be categorized/defined for your study:**

The main outcome measure will be CDAI from the original SONIC study.

The magnitude of treatment effect will be quantified using the optimized SES-CD, optimized CDEIS and GELS. These effect sizes will be compared with the estimates for the original CDAI-derived outcome measures (response and remission) in subjects, with and without objective evidence of inflammation at baseline (based on CRP), between study interventions (AZA monotherapy, IFX monotherapy, IFX and AZA combination therapy).

Correlations between changes in EIs, PRO2, CRP, and CDAI will be assessed. The relationship between clinical response (decrease in CDAI  $\geq$  100 points from baseline, decrease in CDAI  $\geq$  70 points from baseline), clinical remission (CFREM), deep remission (no endoscopic ulcers and normal CRP), and optimized EI (optimized SES-CD, optimized CDEIS), PRO2 will be assessed.

**Main Predictor/Independent Variable and how it will be categorized/defined for your study:**

Optimized SES-CD, Optimized CDEIS and GELS scoring will be defined based on the recent publication of created standardized rules to minimize variability in scoring of the original EIs[4]. Summarized rules for scoring are based on the January 31st, 2014 Delphi Consensus for Optimized SES-CD and Optimized CDEIS.

PRO2 will be derived from components of the existing SONIC study CDAI data.

**Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:**

Other variables of interest include CRP, treatment group assignment, corticosteroid use (for corticosteroid free remission), as defined in the original SONIC study.

If available, demographic data (age, gender, race, smoking status, duration of CD, location of disease, presence of fistula) would be valuable to describe the subset of ~172 with endoscopic data.

**Statistical Analysis Plan:****1) RELIABILITY OF CENTRAL READER SCORING OF INDICES**

Point estimates and 95% one-sided confidence intervals for inter-rater and intra-rater reliability for each of the scores will be estimated using a two-way random effects ANOVA model with interaction, with the endoscopy video and the reader/rater as factors and both considered as random effects. The confidence interval procedures proposed by Gilder et al. will be followed [6]. Study results will be interpreted according to the benchmarks set by Landis and Koch [7].

**2) RESPONSIVENESS** will be quantified by calculation of indices discussed by Deyo et al. [8] For videos read by multiple readers, responsiveness will be calculated using the average score of all readers. We will also explore the possibility of using mixed effects to account for repeated measures in estimating responsive indices. Two-sided 95% confidence intervals will be obtained for estimated indices. Our objection for pure hypothesis testing, as suggested by De Vet et al., [9] is aligned with popular guidelines such as CONSORT statement (Schulz et al.[10]) and recommendations by the APA Task Force on Statistical Inference [11]. Specifically, for each index (optimized SES-CD, optimized CDEIS, GELS, PRO2), we will calculate: Effect Size and Guyatt Responsiveness Statistic.

**3) OPERATING PROPERTIES OF CO-ENDPOINTS:** Pearson's correlation coefficient, regression analyses and additional pre-defined analyses will be done.

**4) ELIGIBILITY:** Exploratory subgroups will be based on various hypothetical PRO2 entry criteria, assessed as a discrete cut-offs and as a continuous (combined) measure and compared against optimized SES-CD and optimized CDEIS criteria.

**Project Timeline:**

Projected Start Date: 01-Sep-2015

Central Endoscopic Data Review Complete: 01-Sep-2015

Data mapping: 15-Sep-15

Data analysis: 16-Sep-15 to 30-Oct-15

Manuscript drafted: 01-Dec-15

Results reported back to YODA Project: 01-Dec-15

Manuscript first submitted for publication: 23-Dec-15

**Dissemination Plan:**

Dissemination Plan:

- Conference presentation: DDW, EUGW

- Peer-reviewed journal publication: Gastroenterology or Gut or similar.

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