

## Principal Investigator

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## General Information

### Key Personnel (in addition to PI):

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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.

**How did you learn about the YODA Project?:** Colleague

## Conflict of Interest

[https://yoda.yale.edu/system/files/yoda\\_coi\\_2021-4602\\_-\\_wong.pdf](https://yoda.yale.edu/system/files/yoda_coi_2021-4602_-_wong.pdf)  
[https://yoda.yale.edu/system/files/yoda\\_coi\\_2021-4602\\_-\\_narula.pdf](https://yoda.yale.edu/system/files/yoda_coi_2021-4602_-_narula.pdf)

## 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

1. [NCT00094458 - C0168T67 - 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 Therapy \(Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease\)](#)
2. [NCT01369329 - CNTO1275CRD3001 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease Who Have Failed or Are Intolerant to TNF Antagonist Therapy \(UNITI-1\)](#)
3. [NCT01369342 - CNTO1275CRD3002 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease \(UNITI-2\)](#)
4. [NCT01369355 - CNTO1275CRD3003 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-](#)

[group. Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Subjects With Moderately to Severely Active Crohn's Disease](#)

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

## Research Proposal

### Project Title

Modified Multiplier SES-CD (MM-SES-CD) on Predicting Endoscopic Remission in Crohn's Disease

### Narrative Summary:

The Simple Endoscopic Score for Crohn's disease (SES-CD) is a validated tool used to quantify mucosal inflammation and assumes each parameter across all ileocolonic segments have equal prognostic value for achieving mucosal healing (MH). However, there is growing evidence to suggest components of the SES-CD vary in prognostic value for predicting MH. The Modified Multiplier SES-CD (MM-SES-CD) differentially weights components of the SES-CD to reflect the relative importance of each parameter on disease prognosis. The primary objective of this study is to determine the minimally clinically important change in MM-SES-CD from baseline to post-induction endoscopy that can predict week 52 MH.

### Scientific Abstract:

#### Background

The SES-CD is a validated tool used to quantify mucosal inflammation. There is growing evidence to suggest that individual parameters of the SES-CD have varying degrees of prognostic value for predicting MH. The MM-SES-CD differentially weights various components of the SES-CD to account for the relative importance of each parameter on disease prognosis.

#### Objectives

This study aims to determine the minimally clinically important change in MM-SES-CD from baseline to post-induction endoscopy that can predict MH at week 52.

#### Study Design

The proposed study will be a post-hoc analysis of the UNITI clinical trial programmes (i.e. UNITI 1, 2 and IM UNITI), VERSIFY, EXTEND and SONIC, which were all multicentre, randomized and double-blind trials. This post-hoc analysis aims to determine the optimal MM-SES-CD cut-off for predicting MH at week 52.

#### Study Population

Participants with endoscopic data available at baseline and post-induction and have at least one lesion as determined by baseline endoscopy will be included in the analysis.

#### Outcomes

The primary outcome of the proposed study will be MH at week 52. Secondary outcomes of interest include corticosteroid-free remission (CSFREM) at week 52.

#### Statistical Analysis

Possible cut-off values at the end of induction will be evaluated for predicting MH and CSFREM at week 52. The accuracy of cut-offs will be evaluated using the area under the curve (AUC) of the receiver operative characteristic (ROC). Sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) will be calculated.

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

Crohn's disease (CD) is a type of inflammatory bowel disease characterized by periods of relapse and remission.(1) Mucosal healing (MH) is an important treatment target in CD, which is often defined as Simple Endoscopic Score for Crohn's Disease (SES-CD) < 3.(2) The SES-CD is a validated tool used to quantify mucosal inflammation and was developed as a simpler alternative to the Crohn's Disease Endoscopic Index of Severity (CDEIS), as the complexity of the CDEIS precludes its routine use in clinical practice.(3) The SES-CD is comprised of four endoscopic parameters (presence and size of ulcers, proportion of surface covered by ulcers, proportion of affected surface and presence and severity of stenosis) measured in each of the five ileocolonic segments (ileum,

ascending colon, transverse colon, descending colon and rectum), and disease severity can be categorized using the sum SES-CD score as mild (SES-CD 3-6), moderate (7-15) and severe (>16).(3)

At the time of SES-CD development, each of the four parameters per segment was assigned a uniform score of 0-3, with a higher score indicating greater disease burden. Therefore, this assumes that each parameter across all five ileocolonic segments have equal prognostic value for achieving MH. However, there is growing evidence to suggest this may not be true. For example, in a post-hoc analysis of data from the SONIC trial, participants with deep and large ileal and rectal ulcers at baseline were 69% and 74% less likely to achieve MH compared to those with smaller ileal and rectal ulcers, respectively. This trend was more pronounced when these ulcers were compared to superficial and smaller ulcers. Further, the overall healing rate in the ileum was found to be significantly lower than in the colon.(4) These findings may suggest that individual parameters of the SES-CD have varying degrees of prognostic value for predicting MH.

The Modified Multiplier Simple Endoscopic Score for Crohn's disease (MM-SES-CD) was developed using post-hoc data of the UNITI and EXTEND clinical trial programmes and demonstrated significantly better accuracy than the SES-CD for predicting MH at week 52.5 As its name suggests, the MM-SES-CD differentially weights various components of the SES-CD to account for the relative importance of each parameter on disease prognosis.5 For example, the presence of an ileal stricture as scored by the SES-CD (0=none, 1=single passable, 2=multiple passable, 3=non-passable) would be multiplied by 4 to obtain the corresponding score using the MM-SES-CD. Use of the MM-SES-CD in clinical trials may help establish more adequate balance between trial arms. However, the evolution of MM-SES-CD scores and its relative performance compared to SES-CD scores on predicting MH have not been investigated.

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

The proposed study aims to determine the minimally clinically relevant change in MM-SES-CD from baseline to post-induction endoscopy that can predict MH at week 52. The relative performance of these changes will be compared to changes in the SES-CD.

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

Research on clinical prediction or risk prediction

## **Research Methods**

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

#### Study Design

This study will obtain participant-level data from the Yale University Open Data Access (YODA) Project and Vivli. Data from UNITI-1 (ClinicalTrial.gov number: NCT01369329), UNITI-2 (ClinicalTrial.gov number: NCT01369342), IM-UNITI (ClinicalTrial.gov number: NCT01369355), EXTEND (ClinicalTrial.gov number: NCT00348283), SONIC (ClinicalTrial.gov number: NCT00094458) and VERSIFY (ClinicalTrial.gov number: NCT02425111) is being requested. Data requested from the YODA Project (UNITI-1, UNITI-2, IM-UNITI and SONIC) will be transferred to the Vivli platform for analysis.

#### Inclusion Criteria

Participants must have endoscopic data available at baseline and post-induction and have at least one lesion as determined by baseline endoscopy.

#### Exclusion Criteria

Participants who have missing baseline or post-induction endoscopic data, or do not have endoscopic lesions at baseline, will be excluded.

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

#### Outcome Measures

Patients with ulcerations at baseline and endoscopic data available at baseline and end of induction will be included. A cohort of patients in UNITI were enrolled in the endoscopic sub-study and underwent ileocolonoscopy at baseline, week 8 (end of induction) and 52. In EXTEND, patients underwent ileocolonoscopy at baseline, week

12 (end of induction) and 52. In SONIC, ileocolonoscopy was performed at baseline and week 26. In VERSIFY, ileocolonoscopy was performed at baseline and subsequently at weeks 14, 26 (primary study) and 52 among the sub-study cohort. Therefore, endoscopic data will be collected at: 1) end of induction will be obtained from UNITI and EXTEND, 2) week 26 from SONIC and VERSIFY and 3) baseline and week 52 from all trials.

#### Primary Outcome

The primary outcome of interest is MH at week 52, defined as SES-CD <3. Sensitivity analyses will be conducted using alternative MH definitions (e.g. SES-CD of 0), and endoscopic response, (e.g. SES-CD reduction ?50%).

#### Secondary Outcome

The secondary outcome of interest is CSFREM at week 52, defined as Crohn's disease activity index score <100 and absence of corticosteroid use.

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

The independent variable in this study will be MM-SES-CD cut-offs at the end of induction, as described in the Statistical Analysis section. The MM-SES-CD differentially weights components of the SES-CD, and the sum score will be calculated at baseline and end of induction. Absolute and relative cut-offs at the end of induction will be generated based on these scores.

#### Statistical Analysis Plan:

Descriptive statistics will be used to summarize baseline characteristics (e.g. disease activity and patient demographics) as well as outcomes among patients with baseline endoscopic disease activity. Dichotomous variables will be presented as proportions or percentages. Continuous variables will be reported as means with standard deviations or medians with interquartile ranges.

Possible cut-off values at the end of induction (i.e. week 8 or 12) will be evaluated for predicting MH and CSFREM at week 52, which includes: mucosal healing (absence of ulcerations), absolute value of MM-SES-CD ranging from < 50 to < 1 points, absolute value of SES-CD ranging from < 10 to < 1 points, absolute decrease in MM-SES-CD from baseline ranging from 0 to 50 points (only among those with a baseline value higher than the cut-off), absolute decrease in SES-CD from baseline ranging from 0 to 10 points (only among those with a baseline value higher than the cut-off), relative change in SES-CD from baseline (0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%) and relative change in MM-SES-CD from baseline (0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%). Participants with missing outcome data will be analyzed on an intention-to-treat basis (e.g. those with missing endoscopic data at week 52 will be assumed to not have achieved MH).

The accuracy of the various cut-offs will be evaluated using the area under the curve (AUC) of the receiver operative characteristic (ROC) and defined as poor (AUC: 0.5–0.7), fair (0.7–0.8), good (0.8–0.9) and excellent (0.9–1.0). AUCs will be compared using the concept of generalized U-statistics, as described by DeLong et al.(5) Sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and associated 95% confidence intervals will also be calculated. Cut-offs with an AUC of at least 0.70 will be considered and the optimal cut-off will be selected among those with a high PLR and low NLR. Bootstrap resampling on 10,000 samples will be done to validate the chosen cut-off.

Sensitivity analyses will be conducted on subpopulations (e.g. participants on active treatment only and participants who did not cross-over to a different treatment arm during the trial). To account for multiple hypotheses testing, the statistical significance level will be set at 0.025. Data will be analyzed using Stata.

Software Used:

STATA

#### Project Timeline:

Date to Start Project: April – May 2021.

Date to Complete Analysis: May – August 2021.

Date to Draft Manuscript: August – September 2021.

Date to Submit Manuscript: September – October 2021.

#### Dissemination Plan:

Results arising from this study may be through presentations and abstracts to target audiences. These may be submitted to relevant conferences such as Canadian Digestive Diseases Week, Digestive Disease Week, and European Crohn's and Colitis Organisation. A manuscript may also be submitted for publication. The YODA Project and Vivli will be acknowledged in all study products, which will be shared prior to submission.

### **Bibliography:**

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3. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc* 2004;60:505–12.
4. Narula, N. et al. Ileal and Rectal Ulcer Size Affects the Ability to Achieve Endoscopic Remission. *Am. J. Gastroenterol.* (2020). doi:10.14309/ajg.0000000000000617
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6. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837–845.