

## Principal Investigator

**First Name:** Neeraj  
**Last Name:** Narula  
**Degree:** MD, MPH, FRCPC  
**Primary Affiliation:** McMaster University  
**E-mail:** [wonge12@mcmaster.ca](mailto:wonge12@mcmaster.ca)  
**Phone number:** 9055259140 x73884  
**Address:** 1280 Main Street West  
1280 Main Street West  
**City:** Hamilton  
**State or Province:** Ontario  
**Zip or Postal Code:** L8S4L8  
**Country:** Canada

## General Information

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

**First Name:** Neeraj  
**Last name:** Narula  
**Degree:** MD, MPH, FRCPC  
**Primary Affiliation:** Hamilton Health Sciences

**First Name:** Emily  
**Last name:** Wong  
**Degree:** BHSc  
**Primary Affiliation:** Hamilton Health Sciences

**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\\_-\\_wong\\_2021-4684.pdf](https://yoda.yale.edu/system/files/yoda_coi_-_wong_2021-4684.pdf)  
[https://yoda.yale.edu/system/files/yoda\\_coi\\_-\\_narula\\_2021-4684.pdf](https://yoda.yale.edu/system/files/yoda_coi_-_narula_2021-4684.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. [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 \(UNITI-1\)](#)
2. [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 \(UNITI-2\)](#)

3. [NCT01369355 - CNT01275CRD3003 - 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

Dominant Patient Reported Outcomes on Predicting Mucosal Healing in Crohn's Disease

### Narrative Summary:

Crohn's disease (CD) is a type of inflammatory bowel disease that is characterized by periods of relapse and remission. CD affects any area of the gastrointestinal tract but is more common in the ileum and colon (1). Three patient-reported outcomes (PROs) include: abdominal pain, number of daily soft/liquid stools and general well-being. PRO-based endpoints are now required for clinical trials for CD in place of CDAI-based endpoints (6). The primary objective of this study is to evaluate if dominant PROs at baseline, and their improvement at the end of induction therapy, can predict longer term clinical and endoscopic outcomes at week 52.

### Scientific Abstract:

#### Background

Patient reported outcomes (PROs) in Crohn's disease (CD) include abdominal pain (none/mild/moderate/severe) and number of daily liquid/soft stools, which are captured as part of the Crohn's Disease Activity Index (CDAI).

#### Objectives

This study aims to determine if dominant PROs at baseline, and their improvement at the end of induction therapy, can predict longer term clinical and endoscopic outcomes at week 52.

#### Study Design

The proposed study will be a post-hoc analysis of UNITI 1, 2, IM UNITI, EXTEND and CT-P13, which were all multicentre, randomized and double-blind trials. This post-hoc analysis aims to evaluate if dominant PROs at baseline, and their improvement at the end of induction therapy, can predict longer term outcomes at week 52.

#### Study Population

Participants with endoscopic data at baseline with at least one lesion as determined by baseline endoscopy and complete PRO data from the CDAI will be included in the analysis.

#### Outcomes

The primary outcome of the proposed study will be MH at week 52, defined as absence of mucosal ulcerations as determined by endoscopy. Secondary outcomes of interest include MH (defined as SES-CD < 3), clinical remission (CDAI < 150), and a combined definition of MH and dominant PRO resolution at week 52.

#### Statistical Analysis

Multivariable logistic regression models will be used to assess the relationship between baseline and post-induction PROs and outcomes. Known confounders will be adjusted for, including treatment allocation, disease duration, presence of baseline stricture and concomitant steroid use.

### 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 4 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 (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. Use of the MM-SES-CD in clinical trials may help establish more adequate balance between trial arms. Various cut-offs are currently being explored to categorize patients based on severity of MM-SES-CD. During the initial development of the MM-SES-CD, a cut-off score < 14 was proposed as a definition of remission/mild disease activity.

In addition to endoscopic disease activity, patient reported outcomes (PROs) are increasingly emphasized when evaluating treatments for CD. PRO-based endpoints are now required for clinical trials for CD in place of Crohn's Disease Activity Index (CDAI) based endpoints (6).

Several studies have identified a disconnect between the CDAI, PROs and objective measures of disease such as endoscopy (7). Recent post-hoc analyses have suggested that PROs at baseline and after the induction phase of treatment are not associated with one-year ER (8). However, PROs are subjective to each patient, and it is hypothesized that improvement in the most severe (dominant) PRO may have a prognostic role.

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

The primary objective of this study is to evaluate if dominant PROs at baseline, and their improvement at the end of induction therapy, can predict longer term clinical and endoscopic outcomes at week 52.

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

Other

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) is being requested. Data requested from the YODA Project (UNITI-1, UNITI-2, IM-UNITI) will be transferred to the Vivli platform for analysis.

#### Inclusion Criteria

Participants must meet the following criteria to be included in the analysis:

- 1) endoscopic data at baseline with at least one lesion as determined by baseline endoscopy, and
- 2) complete PRO data from the CDAI, and
- 3) at least one severely elevated PRO at baseline (i.e. at least one of AP ? 1 and SF ? 4)

#### Exclusion Criteria

Participants who have missing baseline endoscopic data, do not have endoscopic lesions at baseline, incomplete

PRO data as captured by the CDAI, or do not have at least one severely elevated PRO at baseline will be excluded.

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

#### Outcome Measures

Patients with PRO data as reported by the CDAI, ulcerations at baseline and endoscopic data available at baseline 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 CT-P13, patients underwent ileocolonoscopy at baseline, week 14 (end of induction) and 52. Therefore, outcomes will be evaluated at post-induction (week 8/12/14) and week 52.

#### Primary Outcome

The primary outcome of the proposed study will be MH at week 52, defined as absence of mucosal ulcerations as determined by endoscopy.

#### Secondary Outcome

The secondary outcomes of interest include MH (defined as SES-CD < 3), clinical remission (defined as CDAI < 150), and a combined definition of MH and dominant PRO resolution (defined as resolution of severely elevated SF or AP) at week 52. Sensitivity analyses will be conducted using alternative definitions of dominant PRO resolution.

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

The independent variable in this study will be dominant PROs at baseline and their improvement at post-induction (week 8/12/14). Severe AP is defined as a score of 3, on a scale of 0=none, 1=mild, 2=moderate and 3=severe. As no defined cut-off for severely elevated SF exists, a cut-off of ≥4 will be used to define severely elevated SF as this has been shown to correlate with elevated CDAI scores (9,10). At baseline, the most severe score for AP or SF will be defined as the dominant PRO. Participants with severe AP and SF will be classified as achieving dominant PRO resolution if both AP and SF have been resolved.

### **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.

Severe AP is defined as a score of 3, on a scale of 0=none, 1=mild, 2=moderate and 3=severe. As no defined cut-off for severely elevated SF exists, a cut-off of ≥4 will be used to define severely elevated SF as this has been shown to correlate with elevated CDAI scores (9,10). At baseline, the most severe score for AP or SF will be defined as the dominant PRO. Participants with severe AP and SF will be classified as achieving dominant PRO resolution if both AP and SF have been resolved. 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).

Multivariable logistic regression models will be used to assess the relationship between baseline and post-induction PROs and outcomes of interest. Adjustment for known confounders, including treatment allocation, disease duration, presence of stricture at baseline and concomitant corticosteroid use, will be performed. Planned exploratory analyses will stratify patients based on MM-SES-CD category, SES-CD category, and other factors that are known predictors for the outcomes of interest (e.g. prior anti-TNF failure, disease location, disease duration). Sensitivity analyses will be conducted with alternative definitions of dominant PRO resolution (e.g. those with severely elevated AP and SF at baseline will have achieved resolution if either AP or SF is resolved). Results will be presented as odds ratios with 95% confidence intervals and associated p-values. Data will be analyzed using Stata.

Software Used:

STATA

### **Project Timeline:**

Date to Start Project: June – July 2021.

Date to Complete Analysis: July – August 2021.

Date to Draft Manuscript: August – September 2021.

Date to Submit Manuscript: September – October 2021.

### **Dissemination Plan:**

Results arising from this study include presentations and abstracts to target audiences. These will be submitted to relevant conferences such as Canadian Digestive Diseases Week, Digestive Disease Week, and European Crohn's and Colitis Organisation. A manuscript will 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:**

1. De Cruz, P., Kamm, M. A., Prideaux, L., Allen, P. B. & Moore, G. Mucosal healing in Crohn's disease: A systematic review. *Inflammatory Bowel Diseases* (2013). doi:10.1002/ibd.22977
2. Vuitton L, Marteau P, Sandborn WJ, et al. IOIBD technical review on endoscopic indices for Crohn's disease clinical trials. *Gut* 2016;65:1447–55.
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
5. Narula N, Wong EC, Colombel JF, Sandborn WJ, Marshall JK, Daperno M, Reinisch W, Dulai P. Predicting endoscopic remission in Crohn's disease by the modified multiplier SES-CD (MM-SES-CD). *Gut*. 2021 Mar 24.
6. Williet N, Sandborn WJ, Peyrin-Biroulet L. Patient-reported outcomes as primary end points in clinical trials of inflammatory bowel disease. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2014;12(8):1246-56.e6.
7. Schoepfer AM, Beglinger C, Straumann A, Trummel M, Vavricka SR, Bruegger LE, et al. Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. *The American journal of gastroenterology*. 2010;105(1):162-9.
8. Wong ECL, Buffone E, Dulai PS, Marshall JK, Reinisch W, Narula N. End of Induction Patient Reported Outcomes Predict Clinical Remission but not Endoscopic Remission in Crohn's Disease. *Journal of Crohn's and Colitis*
9. Lewis JD, Rutgeerts P, Feagan BG, D'Haens G, Danese S, Colombel JF, et al. Correlation of Stool Frequency and Abdominal Pain Measures With Simple Endoscopic Score for Crohn's Disease. *Inflammatory bowel diseases*. 2020;26(2):304-13.
10. Feagan B, Sandborn WJ, Rutgeerts P, Levesque BG, Khanna R, Huang B, et al. Performance of Crohn's disease Clinical Trial Endpoints based upon Different Cutoffs for Patient Reported Outcomes or Endoscopic Activity: Analysis of EXTEND Data. *Inflammatory bowel diseases*. 2018;24(5):932-42.

### **Supplementary Material:**

[https://yoda.yale.edu/sites/default/files/extended\\_research\\_protocol.docx](https://yoda.yale.edu/sites/default/files/extended_research_protocol.docx)