

## 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:** McMaster University

**First Name:** Emily  
**Last name:** Wong  
**Degree:** BHSc  
**Primary Affiliation:** McMaster University

**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\\_-\\_narula\\_4.pdf](https://yoda.yale.edu/system/files/yoda_coi_-_narula_4.pdf)

[https://yoda.yale.edu/system/files/yoda\\_coi\\_-\\_wong\\_3.pdf](https://yoda.yale.edu/system/files/yoda_coi_-_wong_3.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. [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 \(UNITI-2\)](#)
2. [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

Comparative Efficacy of Ustekinumab and Infliximab on One Year Outcomes Among Biologic-naïve Induction Responders in Crohn's Disease

### Narrative Summary:

Ustekinumab and infliximab are currently approved treatments for patients with Crohn's disease (CD). Ustekinumab is a monoclonal antibody targeted against the p40 subunit of the proinflammatory cytokines interleukin-12 (IL-12) and interleukin-23 (IL-23), which have been implicated in the pathogenesis of CD. Infliximab, which is an antibody that targets tumor necrosis factor alpha, and infliximab biosimilar CT-P13, were compared in the phase three trial NCT02096861. Data from the UNITI-2 and IM-UNITI trials are being requested to conduct a comparative efficacy analysis with data from the NCT02096861 trial among induction responders for one year outcomes.

### Scientific Abstract:

#### Background and Rationale

Head to head comparisons are required to understand how ustekinumab and infliximab compare in their ability to achieve one year clinical and endoscopic outcomes among CD patients who respond to treatment at the end of induction (week 6).

#### Objectives

This study aims to evaluate if differences exist between patients who responded to ustekinumab or infliximab at induction (week 6) and ability to achieve clinical and endoscopic outcomes at one year. These include objective markers of disease activity (e.g. fecal calprotectin), clinical remission, response, endoscopic response, and remission.

#### Study Design

This will be a post-hoc analysis of NCT02096861, UNITI-2 and IM-UNITI, which were multicentre, randomized, double-blind trials. UNITI-2 was an 8-week induction trial that included biologic naïve patients. If patients demonstrated a response, they were offered to continue in the maintenance study, IM-UNITI. This post-hoc analysis aims to compare if differences in treatment impact the ability to achieve clinical and endoscopic disease improvement at week 52 among induction responders.

#### Study Population

Patients were eligible for UNITI-2 if they had moderate-to-severe CD and if they failed conventional therapies but were never previously treated with biologics. Patients who did not respond at the end of UNITI-2 were offered open label ustekinumab and those who responded were re-randomized to placebo or continued ustekinumab. In this analysis, only those who receive ustekinumab 6mg/kg throughout will be included. Patients in NCT02096861 received infliximab at standard doses. For this analysis, patients with clinical response at week 6 (decrease in CDAI  $\geq 100$  points from baseline) and evidence of endoscopic disease activity at week 6 will be included.

#### Outcomes

The primary outcome of the proposed study will be clinical remission at week 52, defined as CDAI score of less than 150. Secondary outcomes of interest includes clinical response (decrease in CDAI from baseline  $\geq 100$ ), change in fecal calprotectin, change in C-reactive protein, endoscopic response at week 52 (decrease in SES-CD  $\geq 50\%$ ), and endoscopic remission (SES-CD  $< 3$ ).

#### Statistical Analysis

Descriptive statistics will summarize the proportion of patients achieving outcomes. Logistic regression will model the likelihood of achieving outcomes. Propensity score matching will be used if there are significant differences in baseline characteristics between treatment groups.

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

Ustekinumab is a monoclonal antibody targeted against the p40 subunit of the proinflammatory cytokines interleukin-12 (IL-12) and interleukin-23 (IL-23), which have been implicated in the pathogenesis of Crohn's disease (CD).(1) UNITI-2 (ClinicalTrials.gov number: NCT01369342) was a pivotal phase three double-blinded, placebo-controlled induction trial which randomized patients with moderate to severe Crohn's disease (CD) to receive placebo, weight-based ustekinumab 6mg/kg or standard dose ustekinumab for 8 weeks. Patients who did not respond were offered to continue with open label ustekinumab in IM-UNITI (ClinicalTrials.gov number: NCT01369355) and those who responded were re-randomized to placebo or continued to receive ustekinumab.

Infliximab, which is an antibody that targets tumor necrosis factor alpha, and infliximab biosimilar CT-P13 were compared in the phase three trial NCT02096861.(2) Patients were randomized in a 1:1:1:1 ratio to receive CT-P13 then infliximab, infliximab then CT-P13, infliximab throughout or CT-P13 throughout, with switching occurring at week 30. For the purposes of this analysis, infliximab and CT-P13 biosimilar will both be classified as infliximab.

Despite the extensive clinical trial data available on individual treatments for CD, there is a need to better understand how these treatments compare in regards to long-term outcomes. Unfortunately, these comparisons are relatively limited in the literature due in part to varying outcome time points across different trials and differences in trial populations. The UNITI trials and NCT02096861 provide a unique opportunity to compare one year outcomes among induction (week 6) responders to ustekinumab and infliximab as outcome evaluations occurred at common time points. In the absence of robust head-to-head randomized clinical trials, this proposed analysis will help inform positioning of therapies in Crohn's disease.

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

This study proposes to compare the effectiveness of ustekinumab and infliximab on achieving clinical and endoscopic outcomes among patients who responded by the end of induction (week 6) from NCT02096861, UNITI-2 (ClinicalTrials.gov number: NCT01369342), and IM-UNITI (ClinicalTrials.gov number: NCT01369355). We hypothesize that both treatments are equally as effective in achieving clinical remission.

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

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

## **Research Methods**

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

Participants must meet all of the following criteria to be eligible for study inclusion(3):

1. ≥18 years of age
2. CD for a minimum duration of 3 months
3. Moderate-to-severe CD (defined as a Crohn's Disease Activity Index [CDAI] score 220-450)
4. Treatment failure or intolerance to immunomodulators and/or glucocorticoids (UNITI-2)

#### Exclusion Criteria

Participants who meet any of the following criteria are not eligible for study inclusion(1):

1. Bowel resection within 6 months
2. Received infliximab, adalimumab or certolizumab pegol ≥8 weeks before receiving study drug (UNITI)
3. Ongoing chronic or recurrent infectious disease
4. Previously received a biologic agent targeting IL-12 or IL-23 (UNITI)

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

#### Primary Outcome Measure

The primary outcome of this study, clinical remission, is defined as CDAI score < 150. The CDAI is comprised of 8 items assessing CD activity, including weight, sex, number of liquid/soft stools, abdominal pain, general well-being, use of anti-diarrheal drugs, presence of abdominal mass and hematocrit percentage. The total score ranges from 0 to 600, with a higher score indicating more severe disease activity.(4) In this study, CDAI scores at baseline, week 6 and week 52 will be reported and used to determine if clinical response (decrease in CDAI from baseline of at least 100) and clinical remission (CDAI less than 150) was achieved.

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

The independent variable in this study will be the treatment allocation of patients included in this analysis, which is defined by the treatment a patient was randomized to.

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

#### Secondary Outcome Measure

Secondary outcomes include change in objective markers of disease activity at week 6 and 52 (e.g. C-reactive protein and fecal calprotectin) and endoscopic remission at one year, which is defined as SES-CD score < 3. The SES-CD is an endoscopic scoring system of disease activity and extent, which is based on four endoscopic parameters. The rectum, sigmoid/left colon, transverse colon, right colon, and ileum are individually scored using this system.<sup>(5)</sup> In UNITI, a cohort of patients were enrolled in the endoscopic sub-study at baseline, with subsequent colonoscopies scheduled at week 8 and 52. In NCT02096861, all patients underwent a colonoscopy at baseline and those who remained in the study also had one at week 54. Patients with evaluable endoscopy data will be included in the endoscopic outcomes analysis at one year. In addition, subgroup analyses will be conducted among subpopulations with significant differences at baseline (e.g. patients with concomitant corticosteroid use and the outcome of corticosteroid-free clinical remission).

### **Statistical Analysis Plan:**

Descriptive statistics will be used to summarize baseline characteristics (e.g. disease activity and patient demographics) and dichotomous variables will be presented as proportions or percentages. Continuous variables will be reported as means or medians with corresponding standard deviations or interquartile ranges, respectively.

In this analysis, only those who receive ustekinumab throughout the entire UNITI study duration at a weight-based dose of 6mg/kg (which is the currently approved dosage) will be included. As both baseline populations may not be similar, we will employ propensity score matching in a 1:1 ratio with matching on relevant baseline covariates, such as concomitant corticosteroid use. Logistic regression will be used to model the likelihood of achieving outcomes. Models will be adjusted for baseline covariates with a p-value < 0.15 on univariate analysis.

Software Used:

STATA

### **Project Timeline:**

Date to Start Project: January – February 2022.

Date to Complete Analysis: February – April 2022.

Date to Draft Manuscript: April – May 2022.

Date to Submit Manuscript: May – June 2022.

### **Dissemination Plan:**

Analyses from this study may be shared to target audiences through presentations and abstracts. These may be submitted to 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 will be acknowledged in all study products, which will be shared at the time of submission.

### **Bibliography:**

1. Feagan, B. G. et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N. Engl. J. Med.* (2016) doi:10.1056/NEJMoa1602773.
2. Ye, B. D. et al. Efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn's disease: an international, randomised, double-blind, phase 3 non-inferiority study. *Lancet* (2019) doi:10.1016/S0140-6736(18)32196-2.
3. Feagan, B. G. et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N. Engl. J. Med.* (2016) doi:10.1056/NEJMoa1602773.
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5. Daperno, M. et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: The SES-CD. *Gastrointest. Endosc.* (2004) doi:10.1016/S0016-5107(04)01878-4.