

**The YODA Project  
Research Proposal Review**

The following page contains the final YODA Project review  
approving this proposal.

**The YODA Project**  
**Research Proposal Review - Final**  
**(Protocol #: 2021-4778 )**

**Reviewers:**

- ☐ Nihar Desai
- ☒ Cary Gross
- ☐ Harlan Krumholz
- ☒ Richard Lehman
- ☒ Joseph Ross

**Review Questions:**

**Decision:**

- |   |                            |
|---|----------------------------|
| 1. Is the scientific purpose of the research proposal clearly described?  | Yes                        |
| 2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health? | Yes                        |
| 3. Can the proposed research be reasonably addressed using the requested data?  | Yes, or it's highly likely |
| 4. Recommendation for this data request:  | Approve                    |

**Comments:**

**The YODA Project  
Research Proposal Review**

Revisions were requested during review of this proposal.  
The following pages contain the original YODA Project review and  
the original submitted proposal.

**The YODA Project**  
**Research Proposal Review - Revisions Requested**  
**(Protocol #: 2021-4778 )**

**Reviewers:**

- ☐ Nihar Desai
- ☒ Cary Gross
- ☐ Harlan Krumholz
- ☒ Richard Lehman
- ☒ Joseph Ross

**Review Questions:**

**Decision:**

- |   |  |
|---|--|
| 1. Is the scientific purpose of the research proposal clearly described?  | No   |
| 2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health? | Yes  |
| 3. Can the proposed research be reasonably addressed using the requested data?  | Unsure, further clarification from requestor is needed |
| 4. Recommendation for this data request:  | Not Approve  |

**Comments:**

1. This is a useful project to leverage data from multiple RCTs to compare the efficacy of adalimumab, ustekinumab, infliximab, and vedolizumab on endoscopic outcomes at one year on each ileocolonic segment among patients with Crohn's Disease. Because these data all derive from different trials, and thus different trial populations, there is a risk of unmeasured confounding biasing the comparison. As in, some trials may be in younger patients, or sicker patients, or wealthier patients, etc. The investigators do not pre-specify the socio-demographic and clinical characteristics which will be used in their multivariable regression models to adjust for measured confounding. These should be clearly stated, including how missing data will be handled across the trials.
2. While endoscopic data may be available, it is unlikely that endoscopic images can be deidentified and made available to the investigators in a format which would allow researchers to use their scoring system.
3. Please note: in the Stelara studies, the endoscopic evaluation was done in a substudy and should be factored in the comparative analysis as well.
  - a. As a substudy, it is not clear there will be many placebo treated subjects to include in the analysis, and the concern of bias in the dataset is one that should be considered.
  - b. The substudy aspect is unique to UNITI and may lead to bias.
4. The researchers are asking for Induction and maintenance study results while the comparison is for the maintenance; please clarify rationale for requesting all 3 studies.
5. Overall, there are concerns of inability to eliminate bias in this comparative study. Please clarify the methods that will be applied to account for variability between the study designs, patient characteristics, timing of EH assessment and other aspects of the trial to minimize bias in the data before comparisons are made.

## Principal Investigator

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## 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\\_2021-4778\\_-\\_wong.pdf](https://yoda.yale.edu/system/files/yoda_coi_2021-4778_-_wong.pdf)  
[https://yoda.yale.edu/system/files/yoda\\_coi\\_2021-4778\\_-\\_narula.pdf](https://yoda.yale.edu/system/files/yoda_coi_2021-4778_-_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. [NCT01369329 - CNT01275CRD3001 - 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 - CNT01275CRD3002 - 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 - CANTO1275CRD3003 - 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 Effectiveness of Biologics for Endoscopic Healing of the Ileum and Colon 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) Healing of ulcers is an important treatment target in CD, and is defined as endoscopic healing (EH). Biologics are medications used to treat patients with moderate to severe CD. However, the comparative effectiveness of approved biologics for CD for achieving segment-specific EH has not been reported. The primary objective of this study is to compare the efficacy of four approved biologics for CD on endoscopic healing of the ileum and individual segments of the colon at week 52.

### Scientific Abstract:

#### Background

EH is an important goal of treatment in CD. Biologics approved for CD are required to demonstrate the ability to heal ulcers in the ileum and colon. There is growing evidence to suggest EH may not be linear across ileocolonic segments and the relative efficacy of biologics for segment EH has not been reported.

#### Objectives

This study aims to compare the efficacy of adalimumab, ustekinumab, infliximab, and vedolizumab on endoscopic outcomes at one year on each ileocolonic segment.

#### Study Design

The proposed study will be a post-hoc analysis of VERSIFY, UNITI, EXTEND, and CT-P13, which were all multicentre, randomized and double-blind trials. This post-hoc analysis aims to evaluate the relative efficacy of four biologics approved for use in CD on endoscopic outcomes for each ileocolonic segment.

#### Study Population

Participants with endoscopic data at baseline will be included in the analysis. For each segment assessed, patients with a segment SES-CD score of at least 3 will be included.

#### Outcomes

The primary outcome of the proposed study will be segment EH at one year, defined as segment SES-CD of 0 in the segment assessed. Secondary outcomes will use alternative definitions of EH, including absence of mucosal ulcerations (as defined by the SES-CD).

#### Statistical Analysis

Multivariable logistic regression models will be used to assess the likelihood of achieving segment EH at one year. Known confounders will be adjusted for, including, disease duration, concomitant corticosteroid use, and prior anti-TNF failure.

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

Crohn's disease (CD) is a type of inflammatory bowel disease that is characterized by periods of relapse and

remission and affects nearly 300,000 Canadians. CD affects any area of the gastrointestinal tract but is more common in the ileum and colon. Healing of ulcers is an important treatment target in CD, and is defined as endoscopic healing (EH). The Simple Endoscopic Score for CD (SES-CD) is a validated tool used to quantify mucosal inflammation in CD via endoscopy and is used to define EH. Biologics are medications used to treat patients with moderate to severe CD. To obtain regulatory approval, biologics must demonstrate the ability to heal ulcers in clinical trials of CD. Biologics approved for CD include adalimumab, ustekinumab, infliximab, and vedolizumab. Previous studies have demonstrated EH is not linear across the segments of the colon and the ileum and may be more difficult to achieve in the ileum and rectum. However, the comparative effectiveness of approved biologics for CD for achieving segment-specific EH has not been reported.

### Specific Aims of the Project:

The primary objective of this study is to compare the efficacy of four approved biologics for CD on EH of each ileocolonic segment at one year. The specific hypothesis to be tested is different biologics have varying degrees of effectiveness in the ileum and colon.

### 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:

#### Study Design

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

#### Inclusion Criteria

Participants must have endoscopic data at baseline. For each segment analyzed, patients must have a SES-CD of at least 3 in the segment to be included in the analysis.

#### Exclusion Criteria

Participants who have missing baseline endoscopic data will be excluded. For segment-specific analyses, participants with a segment SES-CD score less than 3 will not be included.

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

#### Outcome Measures

Patients with 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, and week 52. In EXTEND, patients underwent ileocolonoscopy at baseline, week 12, and week 52. In CT-P13, patients underwent ileocolonoscopy at baseline, week 14, and week 52. In CT-P13, ileocolonoscopy was performed at baseline and week 54. Therefore, the outcome of 'one year' includes week 52 and week 54 (in the case of CT-P13).

#### Primary Outcome

The primary outcome of the proposed study will be segment EH at one year, defined as SES-CD of 0 in the segment.

#### Secondary Outcome

The secondary outcomes of interest include segment EH (defined as absence of mucosal ulceration), at one year.

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

The independent variable in this study will be biologics at baseline (adalimumab, ustekinumab, infliximab, and

vedolizumab), which will be determined based on the randomization arm assigned to the participant.

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

N/A

**Statistical Analysis Plan:**

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

The SES-CD is an endoscopic scoring tool used in clinical trials to quantify endoscopic burden in CD. Each of the five ileocolonic segments are scored using four parameters, which are each scored from a scale of 0-3, for a total segment SES-CD score totalling 0-12. The primary outcome (segment SES-CD of 0) will be determined based on the total segment SES-CD score. Additionally, one of the parameters of the SES-CD measures the size of ulcers (0: none, 1: small, 2: large, 3: very large). The secondary outcome (absence of mucosal ulcerations) will be determined based on this parameter. Participants with missing outcome data will be analyzed on an intention-to-treat basis (e.g. those with missing endoscopic data at one year will be assumed to not have achieved endoscopic healing (EH)).

Multivariable logistic regression models will be used to assess the relationship between treatments and segment EH at one year. Adjustment for known confounders, including disease duration, concomitant corticosteroid use, and prior anti-tumor necrosis alpha failure will be performed. Planned exploratory analyses will stratify patients based on previous biologic exposure among other factors that are known predictors for the outcomes of interest. Sensitivity analyses will be conducted with alternative definitions of endoscopic healing (absence of mucosal ulcerations). 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: November – December 2021.

Date to Complete Analysis: December – January 2022.

Date to Draft Manuscript: January – February 2022.

Date to Submit Manuscript: February– March 2022.

**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 MA, Prideaux L, Allen PB, Moore G. Mucosal healing in Crohn's disease: a systematic review. *Inflamm Bowel Dis*. 2013;19(2):429-44.
2. Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc*. 2004;60(4):505-12.
3. Narula N, Wong ECL, Aruljothy A, Dulai PS, Colombel JF, Marshall JK, et al. Ileal and Rectal Ulcer Size Affects the Ability to Achieve Endoscopic Remission: A Post hoc Analysis of the SONIC Trial. *Am J Gastroenterol*. 2020;115(8):1236-45.