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[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 \(Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease\)](#)

[NCT00207662 - C0168T21 - ACCENT I - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNFα Chimeric Monoclonal Antibody \(Infliximab, Remicade\) in the Long-term Treatment of Patients With Moderately to Severely Active Crohn's Disease](#)

[NCT00207766 - C0168T26 - ACCENT II - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNF Chimeric Monoclonal Antibody \(Infliximab, Remicade\) in the Long Term Treatment of Patients With Fistulizing CROHN'S Disease](#)

[NCT01190839 - REMICADECRD3001 - Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing REMICADE \(Infliximab\) and Placebo in the Prevention of Recurrence in Crohn's Disease Patients Undergoing Surgical Resection Who Are at Increased Risk of Recurrence](#)

[NCT00269854 - C0168T16 - A Placebo-Controlled, Dose-Ranging Study Followed by a Placebo-Controlled, Repeated-Dose Extension of Anti-TNF Chimeric Monoclonal Antibody \(cA2\) in the Treatment of Patients With Active Crohn's Disease](#)

[NCT00771667 - C0743T26 - A Phase 2b, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Ustekinumab Therapy in Subjects With Moderately to Severely Active Crohn's Disease Previously Treated With TNF Antagonist Therapy](#)

[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 \(UNITI-1\)](#)

[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 \(UNITI-2\)](#)

[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](#)

[NCT00265122 - C0379T07 - A Multicenter, Randomized, Phase 2a Study of Human Monoclonal Antibody to IL-12p40 \(CNTO 1275\) in Subjects With Moderately to Severely Active Crohn's Disease](#)

Principal Investigator

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Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.

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How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_coi_hzc_1.pdf

https://yoda.yale.edu/system/files/yoda_coi_var_0.pdf

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019-mosenia-final.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. [NCT00207662 - C0168T21 - ACCENT I - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNFα Chimeric Monoclonal Antibody \(Infliximab, Remicade\) in the Long-term Treatment of Patients With Moderately to Severely Active Crohn's Disease](#)
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5. [NCT00269854 - C0168T16 - A Placebo-Controlled, Dose-Ranging Study Followed by a Placebo-Controlled, Repeated-Dose Extension of Anti-TNF Chimeric Monoclonal Antibody \(cA2\) in the Treatment of Patients With Active Crohn's Disease](#)
6. [NCT00771667 - C0743T26 - A Phase 2b, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Ustekinumab Therapy in Subjects With Moderately to Severely Active Crohn's Disease Previously Treated With TNF Antagonist Therapy](#)
7. [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 \(UNITI-1\)](#)
8. [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 \(UNITI-2\)](#)

9. [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](#)

10. [NCT00265122 - C0379T07 - A Multicenter, Randomized, Phase 2a Study of Human Monoclonal Antibody to IL-12p40 \(CNTO 1275\) 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

Efficacy of Crohn's Disease Treatment Stratified by Disease Phenotype

Narrative Summary:

Crohn's Disease is a heterogenous disorder encompassing distinct clinical phenotypes which arise from different biological pathways. Preclinical and clinical studies suggest that the efficacy of different agents does vary by disease phenotype, including anatomical location. Although these data are commonly collected in clinical trials, they have not been uniformly analyzed by strata nor meta-analyzed across studies by phenotype. As such, clinicians are left to recommend treatments based on best guess of efficacy rather than high-quality evidence. Therefore, we propose to meta-analyze this existing trial data as an important first step towards realizing precision medicine for Crohn's Disease.

Scientific Abstract:

Background: Crohn's Disease is a heterogenous disorder encompassing multiple distinct clinical phenotypes which arise from different biological pathways. Clinical studies and experience suggest that the efficacy of different agents varies by phenotype including anatomical location, disease behavior, and prior medication failure. Although this data is commonly collected in clinical trials, it has not been uniformly analyzed or published. As such, clinicians are left to select between treatments based on best guess of efficacy rather than high-quality evidence, leading to suboptimal treatment, excess therapeutic risk, and increased healthcare costs.

Objective: To optimally position current therapy for Crohn's disease by quantifying treatment efficacy stratified by disease phenotype, including anatomic location, behavior, and prior medication use.

Study Design: Meta-analysis of randomized placebo-controlled clinical trials of therapeutic efficacy for Crohn's disease

Participants: Adult patients over the age of 18 with active Crohn's disease who received either placebo or molecularly-targeted therapy during trials of treatment induction or maintenance

Main Outcome Measure: Efficacy as measured by clinical response per study protocol, stratified by disease location, behavior, and history of prior medication use including anti-Tumor Necrosis Factor alpha failure

Statistical Analysis: Mixed-effects meta-analysis to assess therapeutic efficacy across phenotypic strata. Covariate significance testing and model sensitivity analysis will be performed.

Brief Project Background and Statement of Project Significance:

Crohn's Disease (CD) is an idiopathic and morbid syndrome of gastrointestinal inflammation with rising global incidence[1] but lacking curative or preventative strategies. It is a heterogenous disease entity that encompasses multiple distinct clinical phenotypes which arise from different biological pathways. Although treatment options for

CD historically have been limited, recent decades have seen the advent of novel agents with well-defined molecular targets. At the present time, patient response to any of these treatments remains largely unpredictable. Therefore, the choice of treatment largely lies in other factors such as side-effect profile, cost, and convenience rather than of predicted efficacy.

Clinical experience, limited clinical trials[2], and preclinical models[3] all suggest that treatment response varies by disease phenotype. Although disease phenotypic classification – most commonly the Montreal Classification[4] -- is collected on an individual patient level in all modern trials, it has gone without dedicated subgroup analysis in most of the pivotal trials that led to FDA approval.

As a result, clinicians are presently unequipped to make high-confidence treatment recommendations to their patients who encompass the full phenotypic spectrum of Crohn's disease. This therapeutic imprecision invariably leads to suboptimal disease control, excess exposure to medication-related risks, and increased healthcare costs.

Therefore, we propose to meta-analyze pre-existing, high-quality, placebo-controlled clinical trial data in order to prioritize FDA-approved therapeutic candidates by disease phenotype and help advance precision medicine for this morbid disease.

Specific Aims of the Project:

Hypothesis: This study is an estimation study rather than one that aims to perform specific statistical hypothesis testing. However, as previously mentioned, the scientific hypothesis that motivates this study is that currently approved Crohn's treatments will differ in efficacy when assessed within specific subgroups.

Objective: To optimally position current therapy for Crohn's disease by quantifying treatment efficacy stratified by disease phenotype, including anatomic location, behavior, and prior medication use (including a history of anti-Tumor Necrosis Factor-alpha failure)

Aims: We plan to quantify treatment efficacy by stratification along the lines of disease phenotype, including anatomic location, behavior (e.g. structuring, penetrating), and history of prior medication failure.

A secondary, exploratory goal of this work would be to perform comparative effectiveness (e.g. ranking of efficacy for each given subgroup). Network meta-analysis may be more appropriate for this objective, but may be hampered by limited trial number and patient numbers. While we plan to explore the potential of this methodology to yield useful results, achieving the first goal alone would represent a more than satisfactory outcome of this study.

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

Preliminary research to be used as part of a grant proposal

Participant-level data meta-analysis

Participant-level data meta-analysis pooling data from YODA Project with other additional data sources

Research Methods

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

The source of the data will be from randomized, placebo-controlled, phase 2-4 clinical trials of biologics (anti-Tumor Necrosis Factor alpha, anti-alpha4 beta7-Integrin, and anti-IL12/23) approved for the treatment of Crohn's Disease. We have identified a candidate list of trials by comprehensive search of clinicaltrials.gov. In this application we are specifically requesting the pharmacological trial data corresponding those sponsors partnered with the YODA platform; other pharmacological trial data is simultaneously being requested from other platforms (e.g. CSDR, Vivli).

Inclusion criteria includes completed, randomized, placebo-controlled, phase 2-4 studies of efficacy in adults over the age of 18. Exclusion criteria includes poor study enrollment, premature trial termination, and studies/patients receiving non-FDA-approved doses or routes of administration.

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

The primary outcome measure will be treatment response as defined by the original study protocol. This will be dichotomized as a binary categorical variable for this study. The nearly all of the trials we have requested data from report this by an absolute or relative reduction in the Crohn's Disease Activity Index (e.g. "CDAI 150" defined as a CDAI score under 150, or "CR 70/100" defined by a 70 or 100 point reduction in CDAI score). We plan to pool these outcomes.

We are also requesting endoscopic scores and histologic results for each of the trials to the extent that they are available -- but if they are not we do not foresee any limitations to proceed with this analysis. We are requesting scores corresponding to the baseline time (prior to trial start) as well as at the time of the primary endpoint. We recognize that there are multiple endoscopic (e.g. CDEIS, SES-CD) and histologic (e.g. Geboes, Naini/Cortina, GHAS) scores; we will assess the available scores as they are made available to us and determine at that time whether or not the literature supports their comparability. These would be treated as binary categorical variables.

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

The main predictor variable is receipt of the active drug vs placebo, also defined as a binary categorical variable.

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

The phenotypic data we seek are disease location, behavior, age of onset, and the presence of perianal disease as defined by the Montreal classification, history of prior inflammatory-bowel disease medications (including antiTNF-alpha) as well as reasons for treatment failure if available (e.g. primary or secondary loss of response, unacceptable side effects), concurrent medications at baseline (e.g. immunosuppressants, glucocorticoids, aminosalicylates, antibiotics), the presence of comorbid extraintestinal manifestations, demographics (age, gender, race/ethnicity, body mass index (or if unavailable, weight), duration of disease), smoking status at the time of the trial, history of prior intestinal surgery, history of prior C Difficile infection, and baseline inflammatory biomarkers (C-Reactive Protein, Fecal Calprotectin, Erythrocyte Sedimentation Rate, and Albumin as available).

The clinical phenotypes listed above would be identified on the basis of what was documented by the physician/site investigator.

The above list of covariates adequately defines the desired phenotypes. Interactions will be explored in regression analysis but no unsupervised learning is planned.

Statistical Analysis Plan:

Missing Values: For missing values corresponding to the primary endpoint we will perform non-responder imputation. For missing data corresponding to other variables we will perform group mean imputation. We will repeat the analysis using exclusion of missing data and perform sensitivity analysis to assess the robustness of our conclusions to these methods.

Statistical Procedure:

We will perform a mixed effects linear model meta-analysis and weight individual study effect sizes using the DerSimonian-Laird method. Treatment (active drug vs placebo), as well as aforementioned covariates (e.g. disease location, behavior, demographics (age, gender, race) and medication history including anti-tumor necrosis factor failure) will be treated as fixed effects. Individual studies will be treated as random effects. We will also explore network meta-analysis methods if the size of the available data will permit this.

Measures to Adjust for Multiplicity, Confounders, Heterogeneity:

We will assess study heterogeneity using Q and I-squared statistics. We will adjust for multiple testing using the Benjamin-Hochberg method to maintain a false discovery rate at the 0.05 level.

Sensitivity Analysis: We will assess the sensitivity of our model to intention-to-treat vs per-protocol analysis, inclusion vs exclusion of patients receiving non-FDA approved dosing, as well as statistical significance with and without multiple hypothesis correction. We will also test the sensitivity of our model using leave-one-out tests, and interactively perform the meta-analysis with n-1 studies to test if the result are influenced by one particular study.

QC Plan: We anticipate that many of the requested patient-level datasets have already undergone data-cleaning activities as a part of the study database lock process in the course of carrying out the trial. Our data-cleaning activities will focus on harmonizing the data between data-sets to facilitate meaningful meta-analytic cross-comparison and usage of the statistical software.

Programming Plans: We will be performing all data visualization and statistical analysis in the R programming environment. We will use the following statistical computing packages:

tidyverse

data.table

stringr

MICE

caret

lme4

metafor

plotly

DT

survminer

descTools

heatmap.2

lubridate

survival

RMarkdown

FrontierMatching

gemtc

netmeta

Project Timeline:

We will initiate analysis immediately upon receipt of the data. We will spend the first 3-6 months exploring the structure of the data and performing data cleaning and harmonization. We will spend the subsequent 3 months performing data analysis, visualization and interpretation. We anticipate requiring another 1-2 months to prepare a manuscript for submission. Overall, we anticipate an 8-12 month analytic period prior to journal submission.

Dissemination Plan:

We suspect that this analysis will have broad interest within the gastroenterology community. When the work is complete we will submit abstracts for presentation at national gastroenterology meetings as well as to gastroenterology journals with a wide readership base. Specific target journals would be *Gastroenterology*, the *American Journal of Gastroenterology*, and *Inflammatory Bowel Diseases*.

Bibliography:

1. Ng, S. C. et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* (London, England) 390, 2769–2778 (2018).
2. Sands, B. E. et al. Infliximab Maintenance Therapy for Fistulizing Crohn's Disease. *N. Engl. J. Med.* 350, 876–885 (2004).
3. Kiesler, P., Fuss, I. J. & Strober, W. Experimental Models of Inflammatory Bowel Diseases. *Cell. Mol. Gastroenterol. Hepatol.* 1, 154–170 (2015).
4. Satsangi, J., Silverberg, M. S., Vermeire, S. & Colombel, J.-F. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 55, 749–53 (2006).