

**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 #: 2015-0677)

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:

Please note: investigators will not be able to extract a data set, only the summary results on their analyses on the 7 requested trials, which can then be pooled with other data summarized from the medical literature.

**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 #: 2015-0677)

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? | Yes, or it's highly likely |
| 4. Recommendation for this data request: | Not Approve |

Comments:

1. In the analysis plan, it is saying 2 independent investigators will assess the risk of bias. It does not clearly state how to deal with the discrepancies if the 2 investigators' assessments do not agree.
2. Also in the analysis plan, there are 5 items listed that would downgrade the studies in the analysis. Who would assess the items other than the first item? And, how?
3. Also in the analysis plan, a random effect model is mentioned, which variables will be considered random effect? How will interactions be handled?
4. Also in the analysis plan, it is mentioned that a two-sided p value less than 0.05 will be considered statistically significant. Not sure what statistical significance really means in this context.
5. Please note: these studies were not placebo-controlled during the induction phase and the primary outcome the researchers would like to examine is the rate of remission in the active group vs. placebo in induction (NCT00094458 and NCT00537316 do not have a placebo- control at all, and NCT00207662 does not have a placebo control in the induction phase)
6. A paper was published regarding the response of 'early' Crohn's disease patients using SONIC data (NCT00094458, C0168T67 / attached). It may be helpful.
7. Please note: investigators will not be able to extract a data set, only the summary results on their analyses on the 6 requested trials, which can then be pooled with other data summarized from the medical literature.
8. Please also include the revised proposal information you referenced in your email from January 13th

Principal Investigator

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2015-0677

General Information

Key Personnel (in addition to PI): **First Name:** Minhu
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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.

 [mao_ren_coi.pdf](#)

 [sbh_coi.pdf](#)

 [yc-coi.pdf](#)

 [chen_minhu-coi.pdf](#)

 [kobyashi_and_hibi_coi.pdf](#)

 [jian_zhang-coi.pdf](#)

 [zhao-coi.pdf](#)

 [coi-jing_guo.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

Associated Trial(s): [NCT00036439 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis](#)
[NCT00096655 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis](#)
[NCT00094458 - 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](#)
[NCT00487539 - A Phase 2/3 Multicenter, Randomized, Placebo-controlled, Double blind Study to Evaluate the Safety and Efficacy of Golimumab Induction Therapy, Administered Subcutaneously, in Subjects with Moderately to Severely Active Ulcerative Colitis](#)
[NCT00207662 - ACCENT I - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNF \$\alpha\$ Chimeric Monoclonal Antibody \(Infliximab, Remicade\) in the Long-term Treatment of Patients With Moderately to Severely Active Crohn's Disease](#)
[NCT00537316 - Efficacy & Safety of Infliximab Monotherapy Vs Combination Therapy Vs AZA Monotherapy in Ulcerative Colitis \(Part 1\) Maintenance Vs Intermittent Therapy for Maintaining Remission \(Part 2\)](#)

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

Research Proposal

Project Title

Meta-analysis: Duration of inflammatory bowel disease and its impact on efficacy of biologic drugs

Narrative Summary:

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory diseases of the gut, that can culminate in complications requiring abdominal surgery. Novel effective biologic therapies may change this natural history and there is some evidence that earlier use of biologic drugs is more beneficial than their introduction later after conventional drugs have failed. We aim to perform metanalysis of all trials of biologic drugs for CD and UC, to examine if response and remission rates achieved in patients with short-term disease is better than in long disease duration. If indeed so, it may provide important support for earlier use of biologic drug as a preferred therapeutic strategy.

Scientific Abstract:

Background: There is some evidence suggestive of a better response to anti-TNF treatment in patients with shorter Crohn's disease duration as compared with patients with longer disease duration. However, no systematic evaluation of this correlation has been performed, and data for ulcerative colitis (UC) is lacking.

Aim: The aim of the present study is to analyze if there is a correlation between the rate of response to biologic treatment and the duration of disease at treatment initiation.

Study design: A meta-analysis of all published randomized placebo-controlled clinical trials of anti-TNF and anti-integrin agents in IBD will be performed.

Participants: Patients included in RCTs of anti-TNFs or anti-integrin drugs for IBD

Main outcomes measures: The primary outcome will be the rate of induction of remission in patients with less than 3 years disease duration (short disease) and those with more than 3 years duration (long disease). Secondary analyses will investigate short and long disease duration-associated rate of response to induction, rate of response and remission at end of maintenance phase (week 24-56 as per the specific trial) and colectomy rate (in UC only). All analyses will be performed separately for UC and CD. An additional exploratory analysis will compare outcomes in patients with very-short disease <1 year and all others

Statistical analysis: This will be a meta-analysis. Protocolized data extraction will be done and data will be pooled using a random effects model. We will perform risk of bias assessment, and express outcomes by odds ratios

Brief Project Background and Statement of Project Significance:

Background : The chronic relapsing-remitting course of Crohn's disease (CD), with ensuing bowel damage, is believed to be responsible for a possible reduced rate of response to anti-TNF in patients with long disease duration, as reported in some studies. However, no systematic analysis of all available clinical trials was hitherto performed to examine the correlation of CD duration with response to anti-TNF, or with the response to any biologic drug in general. Moreover, only scant data is available pertaining to such possible correlation in ulcerative colitis (UC). This comprises a knowledge gap in our understanding of optimal therapeutic strategies, and in particular, the role of early institution of biologic drugs, presumably using this early phase of disease as a window of opportunity whereby response to therapy will be optimal and will facilitate arresting disease progression and altering its natural history. Thus, the hereby proposed meta-analysis will provide important and novel systematic insight about the correlation between IBD disease duration and response to biologic therapy. Such information may prove to have important and wide impact on the choice of therapeutic strategies for IBD patients and in particular for decisions regarding top-down versus step-up approaches.

1. Schreiber S, et al. Increased response and remission rates in short-duration Crohn's disease with subcutaneous certolizumab pegol: an analysis of PRECiSE 2 randomized maintenance trial data. *Am J Gastroenterol* 2010; 105:1574–1582

2. Schreiber S, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med* 2007 ; 357 : 239 – 50.

3. Ananthakrishnan AN, Binion DG: Editorial: improved efficacy of biological maintenance therapy in "early" compared with "late" Crohn's disease: strike while the iron is hot with anti-TNF agents? *Am J Gastroenterol* 2010, 105:1583-1585.

4. Colombel JF et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010, 362:1383-1395.

5. Schreiber S et al. Subgroup analysis of the placebo-controlled CHARM trial: increased remission rates through 3 years for adalimumab-treated patients with early Crohn's disease. *J Crohns Colitis* 2013, 7:213-221.

Specific Aims of the Project:

The aim of the present study is to perform a meta-analysis of all CD and UC randomized placebo-controlled clinical trials using infliximab, adalimumab, golimumab, certolizumab as well as vedolizumab and etrolizumab. The primary outcome will be the rate of remission of the active arm over the placebo arm at the end of induction (week 4-14) in patients with short disease duration <3years compared to patients with longer duration of disease. Additional outcomes will be the rate of response (defined as per the particular study) at the end of induction, rate of response at the termination of the maintenance phase of the trial (when applicable) and rate of remission at the end of the maintenance phase of the study when applicable). All outcomes will be analyzed separately for CD and UC. An additional outcome for UC patients will be the rate of colectomy for patients with short and long-durion. An additional analysis will be employed for these above outcomes, stratifying the patients by very short disease duration of <1 year compared to all others, to better define the window of opportunity for maximal rate of response to therapy.

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 that confirms or validates previously conducted research on treatment effectiveness
Summary-level data meta-analysis
Summary-level data meta-analysis will pool 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:**

A search of the medical literature will be conducted using MEDLINE (1976 to November 2015), EMBASE and EMBASE Classic (1977 to November 2015), the Cochrane central register of controlled trials and the Cochrane IBD Group Specialized Trials Register and clinical trials registries (Clinicaltrials.gov, clinicaltrialsregister.eu). RCTs examining the effect of anti-TNF? (infliximab, adalimumab, certolizumab, golimumab) or anti-integrin therapies (vedolizumab, etrolizumab) in adult patients over the age of 16 years with active IBD will be eligible for inclusion. All these agents will hereafter be collectively designated as 'biologics'. The control arms will be required to receive placebo. Trials of CD for indications other than luminal disease will be excluded. Non-adult population trials (age<16 years) will be excluded.

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

The primary outcome will be the rate of remission of the active arm over the placebo arm at the end of induction (week 4-14) for IBD patients with short disease duration compared to patients with long duration of disease. Remission will be defined by the particular clinical score used by each of the designated RCTs included. Short disease duration will be defined as <3 years and compared to patients with longer duration of disease (>3 years). For all analyses, UC and CD will be analysed separately. An exploratory analysis will combine the UC and CD data for the same outcome measures.

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

The main predictor variable will be disease duration, Bearing in mind the chronic, life-long course of IBD, and because of variability in the definition of what comprises 'short-disease duration' in different published trials and expert opinions, ranging between 1-5 years since onset [Schreiber S, AJG 2010, Schreiber S, N Engl J Med 2007, Ananthakrishnan AN, AJG 2010, Colombel JF, N Engl J Med 2010], a disease duration of up to 3 years will be defined as a short disease and compared with the outcomes in patients with longer duration of disease. These time-points will be defined as the disease duration since the diagnosis of IBD at the time of enrollment into the particular RCT. See supplementray file for succinct tables with the desired data to be captured.

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

The additional variables used as secondary predictor will be an alternative definition of short/long disease duration dichotomy, namely disease duration defined as very short duration if less than or equal to one year and as long disease duration if longer than one year since the diagnosis of IBD, at the time of enrollment into the particular RCT.

Additional outcomes sought for comparison between short and long disease duration will be the rate of response (defined as per the particular study) at the end of induction, rate of response at the termination of the maintenance phase of the trial (when applicable) and rate of remission at the end of the maintenance phase of the study (when

applicable). An additional outcome for UC patients will be the rate of colectomy for patients with short and long-duration of disease. See supplementray file for succint tables with the desired data to be captured.

Statistical Analysis Plan:

Two investigators will independently assess the risk of bias as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins JPT et al, Cochrane handbook for systematic reviews of interventions: version 5.0.0, 2008). We will use the GRADE criteria to assess the overall quality of evidence used for specific outcomes. As we will include Evidence from randomized controlled trials all data will begin as high quality evidence. However, they can then be downgraded due to: (1) risk of bias from the studies, (2) indirect evidence, (3) inconsistency (unexplained heterogeneity), (4) imprecision in data, and (5) publication bias. Data will be pooled using a random effects model, to give a more conservative estimate of the likelihood of benefit of biologics in short-term disease, allowing for any heterogeneity between studies [DerSimonian R, et al, Control Clin Trials 1986]. As the outcomes are dichotomous data, we will use the Odds Ratio (OR) and extract a single data set from each study for further analysis. Pooled results will be expressed as odds ratio for the respective outcome for biologics versus placebo arm, for patients with short disease duration compared to those long duration of disease, with 95% confidence intervals (CI). Inconsistency will be quantified with a statistical test of heterogeneity. A two-sided p value less than 0.05 will be considered statistically significant. Stata version 14.0 will be used for all statistical analyses and to generate Forest plots of pooled RRs with 95% CIs, as well as funnel plots. The latter will be assessed for evidence of asymmetry using the using the Egger test, if sufficient (?10) eligible studies.

Project Timeline:

1st January – Complete submission of data requests to remaining companies' websites
31st March – Retrieval of all data. Data set locking
31st June – completion of analysis and manuscript drafting

Dissemination Plan:

If this systematic analysis indeed shows there is a tangible benefit for use of biologics early after disease onset rather than at later disease stages, this may comprise an important step forward in our therapeutic strategies aiming to optimize the therapy of IBD and to improve the care of patients with these chronic inflammatory conditions. The results of this study will be disseminated to patients and care-givers by variety of routes including disease-specific educational websites, publication in medical journals as well as in general press, and distribution to patients' societies.

Bibliography:

- 1.Schreiber S, et al. Increased response and remission rates in short-duration Crohn's disease with subcutaneous certolizumab pegol: an analysis of PRECiSE 2 randomized maintenance trial data. *Am J Gastroenterol* 2010; 105:1574–1582
- 2.Schreiber S , et al. Maintenance therapy with certolizumab pegol for Crohn?s disease . *N Engl J Med* 2007 ; 357 : 239 – 50.
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4. Colombel JF et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010, 362:1383-1395.
5. Schreiber S et al. Subgroup analysis of the placebo-controlled CHARM trial: increased remission rates through 3 years for adalimumab-treated patients with early Crohn's disease. *J Crohns Colitis* 2013, 7:213-221.

Supplementary Material:  [data_tables.docx](#)