

**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 #: 2018-3121 )**

**Reviewers:**

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

**Review Questions:**

- |   |                            |
|---|----------------------------|
| 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                    |

**Decision:**

**Comments:**

No additional 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 #: 2018-3121 )**

**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:**

This is an interesting analysis to compare induction of remission and other measures of treatment response among patients with moderate-severe ulcerative colitis, comparing treatment with of infliximab and golimumab. Any observation of treatment response will depend upon the frequency of follow-up during the clinical trials. It would help to provide a bit more detail as to how this will be handled (particularly if the trials use different periods of followup: ie, q4weeks vs q6weeks, etc).

Moreover, I was surprised that the investigators are not taking advantage of time-to-event analyses, as opposed to using multivariable logistic regression, given the study question. Was there a particular reason why not? Hopefully, addressing these aspects of the proposal will strengthen the investigation.

## Principal Investigator

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**Country:** United States

## General Information

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

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**Last name:** Jairath  
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**First Name:** James  
**Last name:** Proudfoot  
**Degree:** MS  
**Primary Affiliation:** University of California San Diego, La Jolla, CA  
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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.

**How did you learn about the YODA Project?:** Scientific Publication

## Conflict of Interest

[http://yoda.yale.edu/system/files/coi\\_-\\_speed\\_of\\_onset\\_of\\_action\\_in\\_uc\\_-\\_jairathvp.pdf](http://yoda.yale.edu/system/files/coi_-_speed_of_onset_of_action_in_uc_-_jairathvp.pdf)  
[http://yoda.yale.edu/system/files/coi\\_-\\_speed\\_of\\_onset\\_of\\_action\\_in\\_uc\\_-\\_singhs.pdf](http://yoda.yale.edu/system/files/coi_-_speed_of_onset_of_action_in_uc_-_singhs.pdf)  
[http://yoda.yale.edu/system/files/coi\\_-\\_speed\\_of\\_onset\\_of\\_action\\_in\\_uc\\_-\\_proudfoot\\_j.pdf](http://yoda.yale.edu/system/files/coi_-_speed_of_onset_of_action_in_uc_-_proudfoot_j.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):**

1. [NCT00036439 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis](#)
2. [NCT00096655 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis](#)
3. [NCT00336492 - A Phase 3, Randomized, Open-label, Parallel-group, Multicenter Trial to Evaluate the Safety and Efficacy of Infliximab \(REMICADE\) in Pediatric Subjects With Moderately to Severely Active Ulcerative Colitis](#)
4. [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](#)
5. [NCT01551290 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Infliximab in Chinese Subjects With Active Ulcerative Colitis](#)
6. [NCT00488631 - A Phase 3 Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Golimumab Maintenance Therapy, Administered Subcutaneously, in Subjects With Moderately to Severely Active Ulcerative Colitis](#)

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

**Research Proposal****Project Title**

Speed of onset of infliximab and golimumab in patients with moderate-severely active ulcerative colitis: A Post-Hoc Analysis of RCTs

**Narrative Summary:**

Anti-tumour necrosis factor (TNF)-alpha therapy remains the cornerstone of management of patients with moderately-to-severely active ulcerative colitis (UC). With availability of other non-TNF-biologic and small molecule options, speed of drug onset has become an important consideration for selecting a biologic agent. In this study, we will evaluate the speed of action of infliximab (IFX) and golimumab (GOL) for induction of remission and response in patients with moderate-severe UC, through analyses of late stage (Phase III), placebo-controlled trials of IFX and GOL in UC. We have previously evaluated speed of onset of action for vedolizumab and tofacitinib.

**Scientific Abstract:**

**Background:** A rapid onset of action is an important characteristic of medical treatment for patients with moderate-severe UC. With increasing number of treatment alternatives, speed of onset of action has become an important factor to determine treatment.

**Objective:** To evaluate speed of action of infliximab (IFX) and golimumab (GOL) for induction of remission and response in patients with moderate-severe UC.

**Study Design:** Individual participant level pooled analysis of RCTs of infliximab (IFX) and golimumab (GOL) in patients with UC

**Participants:** Patients enrolled in phase III RCTs of IFX or GOL in moderate-severe UC, receiving active therapy with biologic agents

**Main Outcome Measures:** Change in clinical indices from baseline to end of induction. These include change in the mayo clinic score (MCS), stool frequency, rectal bleeding, mayo endoscopy score (MES), C reactive protein and calprotectin (where available).

**Statistical Analysis:** We will pool data of patients in active agent arms for IFX and GOL separately. A linear mixed model will be used to account for the correlation between repeated measures on individual patients that are clustered within studies and the time intervals of outcome assessment (defined as time elapsed since baseline assessment). The study will include fixed effects of drug treatment (infliximab, golimumab, placebo), time, treatment-time interaction, study, and additional patient-level covariates. The analysis will include random effects for patient

and patient-time interaction.

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

Anti-tumour necrosis factor (TNF)-alpha therapy remains the cornerstone of management of patients with moderately-to-severely active ulcerative colitis (UC). Three recombinant anti-TNF monoclonal antibodies are currently approved in the United States for clinical use in patients with active moderately-to-severely active UC: Remicade® (infliximab [IFX]), Humira® (adalimumab), and Simponi® (golimumab). Infliximab was the first approved of these agents based upon the Active Ulcerative Colitis Trials (ACT-1 and 2) (Clinicaltrials.gov numbers: NCT00036439 and NCT00096655). These trials recruited patients with moderately-to-severely active UC defined as a total Mayo Clinic score (MCS) of 6 to 12 points and a Mayo endoscopic sub-score (MES) of 2. Both studies had a similar design (ACT-1 was 54 and ACT-2 was 30 weeks in duration) with equal allocation of patients to treatment with placebo, IFX 5 mg/kg, or IFX 10 mg/kg. Infliximab was administered intravenously at week (W)0, W2, W6 and every 8 weeks thereafter.

In 2013, the United States Food and Drug Administration approved golimumab, another human monoclonal anti-TNF agent, for the treatment of patients with moderate-to-severe UC, largely based on the results of the Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment [PURSUIT], including the PURSUIT-subcutaneous induction [PURSUIT-SC; NCT00487539] and PURSUIT maintenance [PURSUIT-M; NCT00488631] trials. In these randomised, double-blind, placebo-controlled trials, treatment with subcutaneous [SC] golimumab induced clinical response, remission, and mucosal healing in larger percentages of patients with active UC than did placebo, and continued golimumab in patients who responded to induction therapy maintained clinical response through Week 54 [golimumab 50 or 100 mg] and achieved clinical remission and mucosal healing at Weeks 30 and 54 [golimumab 100 mg].

However, despite impressive results in the PURSUIT registration trials, uptake of GOL has been marginal in comparison to IFX. This may in part be related to a perception of an agent with slower onset of action.

The overall objective of this proposal is to evaluate the relative speed of onset of IFX and GOL through changes in clinical disease activity indices, after adjustment for relevant patient level covariates and other confounders. Our central hypothesis is that there is no difference in the speed on onset between these agents. The long-term goal of our program is to promote value-based care in UC, ensuring informed choice for patients and providers in an era of multiple available therapies for UC. The significance of this work lies in the fact that uptake of GOL has been marginal in comparison to IFX, in part based upon a preconception that a SC administered agent may be slower to work than a similar IV administered agent. The information generated through this study would be invaluable to inform both science, patient care, positioning of drugs in the therapeutic algorithm and treatment guidelines.

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

Specific aim #1: To evaluate and compare the speed of action of infliximab (IFX) and golimumab (GOL) as induction agents in patients with moderate-severe UC, through post-hoc analysis of phase III RCTs of IFX and GOL in UC.

Hypothesis: There is no difference in the speed of action of IFX versus GOL when measuring change in clinical disease activity indices, after adjusting for confounding variables including age, gender, baseline disease activity, concomitant aminosaliclates/corticosteroids/ immunosuppressive, disease extent

### **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:**

Data sources:

- Trials of GOL in UC (NCT00487539, NCT00488631)
- Trials of IFX in UC (NCT00036439, NCT00096655, NCT00336492, NCT01551290)

Inclusion criteria:

- Patients (adults or pediatric) with moderate-severe UC
- Treated with infliximab or GOL or placebo for induction
- Reported concomitant use of other medication for UC (aminosalicylates, immunosuppressives, corticosteroids)

**Exclusion criteria**

- Lack of information on use of 5-ASA at time of screening or first study-related visit
- Patients lost to follow-up or did not complete the induction phase of each trial

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

Primary outcome – change in the following clinical disease activity parameters and their components from baseline to the end of the induction period, adjusted for known confounders. These include MCS, stool frequency, rectal bleeding as well as CRP/calprotectin (if available).

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

Main predictor/independent variable will be use of GOL or IFX to the end of the induction period (yes vs no).

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

Key confounding variables of interest in our study are:

- o Biochemical measures of disease severity – baseline C-reactive protein as a categorical variable (<0.5mg/dl or ?0.5mg/dl), fecal calprotectin (where available, <150mcg/g vs. ?150mcg/g)
- o Co-interventions – concomitant use of immunosuppressives like azathioprine, 6-mercaptopurine or methotrexate (yes vs. no), aminosalicylates (yes vs. no) concomitant use of steroids (yes vs. no)
- o Factors known to modify pharmacokinetics of anti-TNF therapy – baseline albumin as a categorical variable (<3.5g/dl vs. ?3.5g/dl), sex (males vs. females)
- o Disease duration prior to trial entry, smoking status (yes vs no)

**Statistical Analysis Plan:**

A linear mixed model will be used to account for the correlation between repeated measures on individual patients that are clustered within studies and the time intervals of outcome assessment (defined as time elapsed since baseline assessment). The study will include fixed effects of drug treatment (infliximab, golimumab, placebo), time, treatment-time interaction, study, and additional patient-level covariates. The analysis will include random effects for patient and patient-time interaction. This model will be used to address determine the average rate of treatment effect for each drug, and the hypothesis that one drug may achieve a greater rate of treatment effect than the other drug.

**Project Timeline:**

Once study is approved and data access provided (assuming by May 2018), our key milestones dates are:

- o Project start date: June 1, 2018
- o Analysis completion date: August 31, 2018
- o Manuscript drafted: October 30, 2018
- o Manuscript submitted for publication: November 30, 2018
- o Date results reported back to YODA: November 30, 2018

**Dissemination Plan:**

We anticipate generation of one manuscript from this project. The target audience would be clinical gastroenterologists. Potentially suitable journals for this manuscript would be: American Journal of Gastroenterology, Clinical Gastroenterology and Hepatology, Alimentary pharmacology and Therapeutics or Inflammatory Bowel Diseases

**Bibliography:**

1. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2005 Dec 8;353(23):2462-76.
2. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology.* 2014 Jan;146(1):85-95