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 #: 2016-0903)

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:

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 Yale University Open Data Access (YODA) Project
Yale University Center for Outcomes Research and Evaluation (CORE)
1 Church Street, Suite 200, New Haven, CT 06510

The YODA Project
Research Proposal Review - Revisions Requested
(Protocol #: 2016-0903)

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:

The authors explain that they have identified 17 RCTs described in full text articles that are eligible for inclusion. Since only 4 are available through the YODA project, are the other 13 being requested in parallel? Are these trials also available through data sharing platforms or are they being requested directly from biologic manufacturers? It would be useful if the proposal listed the 17 identified published trials, or at least clearly cited them.

Also, the proposal suggests that each of the 17 trials for which data are able to be obtained will be analyzed as prespecified (ie, stratified by concomitant use of high-dose steroids, low-dose steroids, or no steroids), and then those estimates will be used for a pooled meta-analysis. Please confirm that the plan is not to pool IPD from 17 trials within the data sharing platform for analysis.

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2016-0903

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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.

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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): 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
NCT00207662 - ACCENT I - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNFa Chimeric Monoclonal Antibody (Infliximab, Remicade) in the Long-term Treatment of Patients With Moderately to Severely Active Crohn's Disease
NCT00207766 - 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
NCT00004941 - A Placebo-controlled, Repeated-dose Study of Anti-TNF Chimeric Monoclonal Antibody (cA2) in the Treatment of Patients with Enterocutaneous Fistulae as a Complication of 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

Use of TNF antagonist therapies with or without steroids for induction in Crohn's disease: A Meta-analysis

Narrative Summary:
Biologic agents, such as TNF antagonists, and corticosteroids are highly effective for induction of remission in Crohn's disease (CD) and ulcerative colitis (UC). Examination of data from a recent randomized controlled trial of combination therapy in patients with active CD (COMMIT) suggests that the addition of corticosteroids to infliximab may result in higher remission rates. However this possibility has not been evaluated by a dedicated RCT. Our objective is to perform a meta-analysis of existing induction trials of biologic therapies to assess whether adjunctive therapy with corticosteroids results in greater efficacy than biological monotherapy.

Scientific Abstract:
Background: Biologic agents, such as TNF antagonists, and corticosteroids are highly effective for induction of remission in Crohn's disease (CD) and ulcerative colitis (UC). Examination of data from a recent randomized controlled trial of combination therapy in patients with active CD (COMMIT) suggests that the addition of corticosteroids to infliximab may result in higher remission rates. However this possibility has not been evaluated by a dedicated RCT.
Objective: perform a meta-analysis of existing induction trials of biologic therapies to assess whether adjunctive therapy with corticosteroids results in greater efficacy than biological monotherapy. A secondary objective is to compare the safety of the two strategies.
Study Design: Meta-analysis of randomized control studies (RCTs) that fit search criteria
Participants: Study subjects in previously performed RCTs, age>18 years
Main Outcome Measure(s): The primary analysis will be a pooled summary estimate of clinical remission on anti-TNF therapy stratified by corticosteroid exposure at baseline. Secondary outcome to be measured are luminal response and safety of the two strategies.
Statistical Analysis: Standard meta-analysis methods will be used. The test of heterogeneity will be performed using the chi-squared test and the I2 test. Stratified analyses and meta-regression will be performed to explore factors that may explain heterogeneity between studies. This includes potential confounding factors such as disease severity (ex. Higher CDAI, CRP levels) or concurrent immunomodulator use.

Brief Project Background and Statement of Project Significance:
Biologic agents, such as TNF antagonists, and corticosteroids are highly effective for induction of remission in Crohn's disease (CD) and ulcerative colitis (UC). Examination of data from a recent randomized controlled trial of combination therapy in patients with active CD (COMMIT) suggests that the addition of corticosteroids to infliximab may result in higher remission rates. However this possibility has not been evaluated by a dedicated RCT. Our objective is to perform a meta-analysis of existing induction trials of biologic therapies to assess whether adjunctive therapy with corticosteroids results in greater efficacy than biological monotherapy. A secondary objective is to compare the safety of the two strategies.

Specific Aims of the Project:
The primary aim of the project is to assess whether adjunctive therapy with corticosteroids results in greater efficacy than biological monotherapy. We have performed a systematic literature review and will now perform a meta-analysis of relevant data.

We hypothesize that patients with CD treated with anti-TNF agents will have a higher response rate if treated concomitantly with corticosteroids for induction of remission, without significant differences in the risk of adverse events.

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
New research question to examine treatment safety
Summary-level data meta-analysis will pool data from YODA Project with other additional data sources
Participant-level data meta-analysis
Participant-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 systemic review was performed of Medline, Central and Embase for all English language studies in adult patients with Crohn's disease studying the efficacy of either adalimumab, certolizumab pegol, golimumab, and infliximab. Abstracts were included in the search in addition to a hand search to identify randomized controlled trials (manuscripts and abstracts).

Inclusion criteria:
• Randomized, placebo-controlled trials in which patient level data (case report forms) is obtainable and information regarding length and dosing of concurrent steroids
• Adult patients with Crohn's disease
• Anti-TNF agent used includes any of Infliximab, adalimumab, certolizumab pegol, and golimumab
• Duration of 4-12 weeks for induction
• Data available for remission rates at a short time interval (i.e. between 4-12 weeks)

We have identified 17 full text articles that are eligible for our study. In order to meet the aim of our study, non-published patient level data must be obtained.

Main Outcome Measure and how it will be categorized/defined for your study:
The primary analysis will be a pooled summary estimate of clinical remission on anti-TNF therapy stratified by corticosteroid exposure at baseline. Patients with high dose concurrent steroid use (as defined in the inclusion criteria) will be analyzed separately from those with low concurrent steroid use. In this main analysis, all anti-TNF agents will be combined and will be evaluated based on remission at induction (between 4-12 weeks).

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
Many patients are treated with a weaning course of corticosteroids at the time of induction, so those patients who received the equivalent of >20mg daily of prednisone or equivalent during the first four weeks of induction treatment will be analyzed in the concomitant high-dose steroid therapy group. Those treated with <20mg daily of prednisone or equivalent during the first four weeks of induction will be analyzed in the concomitant low-dose steroid therapy group. Those who received no concurrent steroids will be analyzed in the no steroid group. Data will also be collected on patients in the placebo arms who received concomitant high dose steroids, low dose steroids, or no steroids, as per the definitions above.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
A secondary outcome that will be evaluated is luminal response. Response is measured differently between studies, but most commonly for CD will be based on a decrease in the Crohn's disease activity index (CDAI). Studies that report outcomes at weeks 4-12 will be combined irrespective of the duration of the induction period. To account for differences in steroid use between studies (i.e forced tapering, fixed dose, etc), the average daily dose of steroids used during the first four weeks of induction will be used to classify patients. An average daily dose of 20mg or more of prednisone will be considered high concurrent corticosteroid use. An average dose of less than 20mg of prednisone per day will be considered low dose. Safety will also be evaluated based on the same stratification and will include infusion/injection site reactions, malignancy, infections, and death.

Statistical Analysis Plan:
Standard meta-analysis methods will be used. The main analysis will be based on the intention-to-treat population from each study. The test of heterogeneity will be performed using the chi-squared test and the I2 test. The I2 test describes the percentage of variability in effect estimates that is due to heterogeneity rather than chance, wherein an I2 test greater than 50% suggests significant heterogeneity. A random effects model will be used assuming that heterogeneity will exist between studies; if the study data meet the criteria for homogeneity then a fixed effects model will be used. Stratified analyses and meta-regression will be performed to explore factors that may explain heterogeneity between studies. This includes potential confounding factors such as disease severity (ex. Higher CDAI, CRP levels) or concurrent immunomodulator use. Publication bias will be assessed using a funnel plot.

Sensitivity analyses (analyses to be run removing certain studies to see how it affects the results)
• Other sensitivity analyses may be run if there are outlier studies with unique design characteristics that appear to have a strong influence on the results (standard according to the Cochrane Handbook, section 9.7)

Subgroup analyses
• No concurrent immunomodulator versus immunomodulator-treated patients
• Individual anti-TNF agents will be compared with or without steroids, but not against each other

Project Timeline:
We have already performed a systematic literature review and have identified randomized control trials that fill our inclusion criteria. We have extracted all relevant published data but much data is still missing. Once access to study data is granted, we anticipate data extraction and analysis to take no longer than 2 months. Manuscript drafting will take another 1 month. Manuscript submission is aimed to take place no later than September 2016.

Dissemination Plan:
The results of this meta-analysis is anticipated to be of great interest to all IBD clinicians. A manuscript will be submitted about 3 months after data acquisition. As such, we plan to submit our manuscript to Gastroenterology, American Journal of Gastroenterology or Clinical Gastroenterology and Hepatology.

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