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 #: 2014-0291)

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 #: 2014-0291)

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:

We found the Methods used to describe your proposed research unclear. Specifically, you described the methods that will be used for the systematic review, but without providing explicit information on your plan for analyzing the clinical trial data that will then be used as part of your systematic review. Please provide more detail on the methods planned for the analysis of the 2 trials being requested. It would be helpful to provide a description of how the data for the 2 trials will be examined (including planned study sample and inclusion/exclusion criteria, main outcome measure definitions, other variables of interest, and the statistical analysis plan).

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Associated Trial(s):
A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Golimumab in the Treatment of Chinese Subjects with Ankylosing Spondylitis
A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Ankylosing Spondylitis

What type of data are you looking for?: Full CSR

Research Proposal

Project Title:
Comparative effectiveness of tumor necrosis factor alpha inhibitors in ankylosing spondylitis

Scientific Abstract:

Background: Five tumor necrosis factor-alpha inhibitors (TNFi) have shown considerable efficacy in placebo-controlled trials for the treatment of ankylosing spondylitis (AS) refractory to non-steroid anti-inflammatory drugs. However, to date, only one head-to-head trial was conducted to compare the efficacy and safety of infliximab and etanercept.
Objective: The aim of this study is to integrate available evidence and estimate the relative short-term efficacy of different TNFi in AS.
Study Design: Systematic review and meta-analysis
Participants: Adult patients with ankylosing spondylitis, treated with TNFi, in a randomized controlled trials.
Main outcome measures: change of BASDAI and BASFI at week 12 and at week 24.
Statistical analysis: Bayesian multiple treatment comparison

Brief Project Background and Statement of Project Significance:

Five tumor necrosis factor-alpha inhibitors (TNFi) have shown considerable efficacy in placebo-controlled trials for the treatment of ankylosing spondylitis (AS) refractory to non-steroid anti-inflammatory drugs. To date, only one head-to-head trial was conducted to compare the efficacy and safety of infliximab and etanercept. A comparison of effectiveness and safety of different TNFi is lacking. The aim of this study is to integrate available evidence and estimate the relative short-term efficacy of different TNFi in AS. The information on comparative effectiveness of TNFi in AS will help decision making in clinical practice.

Specific Aims of the Project:

Aim1. To compare the efficacy of TNFi in AS, using BASDAI change and BASFI change at week 12 and week 24 as primary end points.
Aim2. To compare the safety of TNFi in AS, using numbers of total adverse events, severe adverse events, severe infections, tuberculosis infection as secondary end points.

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Research Methods:

Searches: We conducted a systematic search of PubMed, EMBASE and Cochrane Database for published randomized control trials of TNFi in ankylosing spondylitis up to May 20th, 2014 in all languages, and supplemented it with manual searches of reference lists from previous systematic review articles.
Types of study to be included:
Inclusion criteria:
- Adult Patient fulfills the modified New York criteria for diagnosis of ankylosing spondylitis;
- intervention: TNFi; comparator: placebo or a different TNFi;
- Randomized controlled trials.
Exclusion criteria:
- Case series, case report;
- Abstract, unpublished data;
- studies on Axial SpA, if a subgroup analysis of AS was not reported.
Outcomes and data abstraction: the primary outcomes include mean difference of BASDAI and BASFI at week 12 and week 24. Secondary outcomes include ASAS 20, CRP, BASMI, and adverse events. Literature review and data extraction were done by two independent reviewers. Any disagreement was resolved by
discussion. Extracted data included study design, participant characteristics, and relevant outcomes.
Statistical analysis: Bayesian network meta-analysis will be carried out to synthesize the results from the studies. This will be implemented using Markov Chain Monte Carlo (MCMC), via the R package gemtc (http://cran.rproject.org/web/packages/gemtc/index.html). We assume consistency (i.e., indirect effects can be derived from differences in the corresponding direct effects) during modeling. The relative effect sizes are reported as posterior mean differences along with 95% credible intervals. Drug rankings are derived from the MCMC results by evaluating the rank of each drug at each MCMC iteration based on size of the effect of the drug compared to placebo, and evaluating the relative frequency of each ranking over the MCMC iterations.

Narrative Summary:

Tumor necrosis factor alpha inhibitors (TNFi) are mainstay treatment for ankylosing spondylitis. Five TNFi have been approved in the United States. However, a comparison of the efficacy and safety of these agents in ankylosing spondylitis is lacking. This study is to estimate the relative efficacy and safety of the five TNFi and help clinicians and patients in decision making.

Project Timeline:

Systematic review – the systematic review of randomized controlled trials of TNFi in AS has been completed.
Meta-analysis – preliminary analysis has been completed, awaiting for authors and/or sponsors providing missing data for final analysis.
Manuscript draft and submission for publication – anticipated in December 2014.

Dissemination Plan:

One journal article will be produced using the requested data (and with data obtained from literature and other sponsors). The target audiences are clinicians and clinical researchers.

Bibliography:

Giardina AR, Ferrante A, Ciccia F, et al. A 2-year comparative open label randomized study of efficacy and safety of etanercept and infliximab in patients with ankylosing spondylitis. Rheum Int 2010; 30:1437-40.

Migliore A, Broccoli S, Bizzi E, Laganà B. Indirect comparison of the effects of anti-TNF biological agents in patients with ankylosing spondylitis by means of a mixed treatment comparison performed on efficacy data from published randomised, controlled trials. J Med Econ 2012; 15:473-80.

Shu T, Chen GH, Rong L, et al. Indirect comparison of anti-TNF-α agents for active ankylosing spondylitis: mixed treatment comparison of randomized controlled trials. Clin Exp Rheumatol 2013; 31:717-22.