

**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 #: 2017-2326)

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 #: 2017-2326)

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:

It would be useful to provide more information on the newly developed Global Patient-Reported Outcome Measure (G-PROM), including a reference publication or poster. How is the G-PROM created, scored, and validated? While the project is quite interesting and feasible, the protocol could be strengthened by providing more information on what information is accounted for in the G-PROM (beyond AEs, the DAS28, and the ACR20, 50 and 70), including how each of the efficacy and safety outcomes are weighted. Also, is the DAS28 the outcome used for the G-PROM, or the change from baseline in DAS28?

I applaud the intention of the proposed analysis, which is to help patients to understand the harms and benefits of each option for treating RA. However, this would depend on their personal objectives and weightings - in effect, each person should construct a personal PROM, which can be fluid rather than fixed over time. Please clarify the rationale for an aggregated G-PROM.

The third data source, currently listed as 'TBD', must be specified.

Principal Investigator

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General Information

Key Personnel (in addition to PI):

First Name: Christine
Last name: Ramsey
Degree: PhD
Primary Affiliation: Yale School of Medicine

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

Project Funding Source: Rheumatology Research Foundation

How did you learn about the YODA Project?: Colleague

Conflict of Interest

http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_fraenkel_updated.pdf
http://yoda.yale.edu/system/files/yoda_project_coi_ramsey.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. [NCT00264550 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNF \$\alpha\$ Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy](#)

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

Research Proposal

Project Title

Development of a Global Outcome Measure for Rheumatoid Arthritis Clinical Trials

Narrative Summary:

This project aims to develop a new outcome measure that encompasses both benefits and harms of treatment at the individual patient level. The result will be a ranking of all trial subjects by the desirability of their overall outcome from “Remission without AEs” to “No clinical improvement and a life threatening AE (or death)”. Between these two extremes are mutually exclusive hierarchical levels of clinical outcomes ordered in terms of their desirability. Using this global outcome measure, randomized controlled trials could then report the percentage of patients classified into each level; improving patients’ understanding of the likelihood of the total effects of treatment on their lives.

Scientific Abstract:

Background: Currently available outcome measures for patients with inflammatory arthritis do not provide patients with the information they need in order to make informed decisions. The results of randomized controlled trials are currently reported as either average improvement scores across study subjects, (e.g. DAS) or the percentage of patients attaining a specified amount of improvement (e.g., ACR 20, 50 and 70). The numbers of subjects experiencing specific adverse events (AEs) are reported separately. While based on sound scientific methods, this approach does not provide any information on the overall effect of treatment.

Objective: The aim of this project is to develop and assess the validity of a Global Patient-Reported Outcome Measure (G-PROM) to better quantify and compare the distribution of patients’ experiences on medications. The measure will combine the range of possible benefits and the full spectrum of harms of treatment at the individual patient level. The result will be a ranking of all trial subjects by the desirability of their overall outcome.

Design: We will obtain estimates for criterion validity using the raw data from three previously published RCTs.

Participants: Individuals with RA participating randomized controlled drug trials for RA.

Main outcome: A scale measuring desirability of patients’ overall outcome on RA medications that captures the total patient experience on medications.

Analysis: We will fit a separate ordinal regression models for each outcome of interest applying longitudinal and survival techniques

Brief Project Background and Statement of Project Significance:

Best practices for patients with rheumatoid arthritis (RA)(1) (and possibly psoriatic arthritis(2-4)), call for patients to be treated-to-target (TTT). Adherence to this strategy requires ongoing disease activity monitoring and adjustments in treatment plans (i.e., changes or addition of medications) to achieve and maintain low disease activity or remission. TTT strategies are in large part possible because of the numerous treatment options currently available for patients with inflammatory arthritis. An RA patient failing methotrexate (MTX) monotherapy now has numerous treatment options to choose from.

Currently available outcome measures for arthritis, however, do not provide patients with the information they need to make an informed choice about their treatment options. Specifically, the results of randomized controlled trials (RCTs) are currently reported as either average improvement scores or the percentage of patients attaining a defined response. The numbers of subjects experiencing specific adverse events (AEs) are reported separately. While based on sound scientific methods, this approach does not quantify what is most important to patients: their overall experience on treatment. In the words of a patient with RA: “Patients have no way to determine the potential net benefit for a given treatment, much less to compare across treatments. What patients want to know is: What are my odds of getting better while enduring the lowest possible level of side effects for each medication? How will I feel overall on medication A compared to medication B?” Simultaneously weighing the efficacy and AEs of multiple drugs is also challenging for physicians, and makes it difficult for them to effectively engage their patients in shared decision-making. Thus, there is a need for more informative benefit: risk evaluation measures in rheumatology.

Specific Aims of the Project:

Aim 1. To generate a list of descriptions for the outcomes associated with medications commonly used to treat RA.

This effort will be led by core patient partners (co-investigators) on this grant. We will use an iterative process to develop descriptions for outcomes including both benefits and AEs as experienced by RA patients.

Aim 2. To generate equivalence classes of global outcomes using trajectory mapping (TM). While it is clear that the G-PROM will range from a ranking representing the “maximum possible benefit and no experienced toxicity” to “no benefit and death or life threatening toxicity”, intermediate levels require empirical data. We will use TM to determine how combinations of varying levels of benefits and AEs (between the highest and lowest desirability of overall outcome anchors) should be ranked.

Aim 3. To obtain preliminary estimates of the validity of the G-PROM as an instrument for measuring global outcomes in comparative RCTs for RA. We will obtain estimates for criterion validity using the raw data from previously published RCTs(5-6).

What is the purpose of the analysis being proposed? Please select all that apply.

Other

New Research question to develop an improved scale for measuring patients' outcomes on different RA treatments

Research Methods

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

To assess the validity of our newly developed Global Patient-Reported Outcome Measure, we will use data collected on approximately 1800 RA patients from three different multicenter, double-blind randomized controlled trials using different classes of drugs for which we have access to the raw data at the individual patient level.

Data source:

1. A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNF α Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy (NCT00264550)
2. Rheumatoid Arthritis: Comparison of active therapy in patients with active disease despite methotrexate therapy (RACAT)
3. TBD

Inclusions/Exclusion Criteria:

The sample for this study will include adults \geq 18 years with active RA who participated in one of the RCTs listed about (see Data Source).

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

Global Patient-Reported Outcome Measure. G-PROM class levels will be generate based on the following measures in the existing data at 24 weeks:

1. Adverse events (list all)
2. Disease Activity Score (DAS28)
3. American College of Radiology (ACR) responses: ACR20 ACR50 ACR70

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

- Treatment groups (MTX + placebo, golimumab, 100mg, golimumab, 50mg + MTX, golimumab, 100mg + MTX)
- Duration of RA at baseline (years)
- Use of Disease modifying anti-rheumatic drugs (DMARDS) at baseline (yes/no)
- DAS28 score at baseline
- Duration of treatment adherence (weeks)

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

The following measures are requested for each participant at baseline:

- Age (years)
- Sex (male/female)
- Race (Caucasian, African American, other)
- Ethnicity (Hispanic/non-Hispanic)
- Body Mass Index (continuous)
- Current smoker (yes/no)
- Positive for rheumatoid factor (yes/no)
- Time since RA diagnosis (years)
- Use of NSAIDs (yes/no, dose)
- Use of oral corticosteroids (yes/no, dose)

Duration of previous MTX use (years)

Methotrexate dose, mg/week

The following measures are requested for each participant at baseline and each follow-up point

- American College of Radiology (ACR) responses
- DAS28 score
- Adverse events (list all per patient)
- Patient global assessment of pain (0-10 cm, VAS)
- Patient global assessment of disease activity (0-10 cm, VAS)
- Physician global assessment of disease activity (0-10 cm, VAS)
- Health Assessment Questionnaire Disability Index (HAQ-DI)
- C-reactive protein concentration (mg/L)
- Sharp/van der Heijde Score (SHS)

Statistical Analysis Plan:

The data requested in this proposal will be used to address Aim 3 of the study described above (see Specific Aims and Research Methods). We will combine de-identified individual patient-level data on participants from each of the trials. The combined dataset will be stored on a secure data sharing platform. Using data collected on AEs and benefits in these trials, we will classify each patient using the G-PROM and generate a ranking of all trial subjects by their overall outcome score. We will then calculate the probability of a better ranking for a randomly selected subject from the intervention compared to the control arm. This probability is calculated by the number of between-treatment comparisons in which a subject has a higher score in the intervention compared to a subject in the control arm divided by total number of possible pairwise comparisons⁷. If there is no difference in the distribution of the scores, the probability is close to 50% (95% CI). We will then compare conclusions generated using the G-PROM to those reported in the original trial⁵⁻⁶.

To assess the concurrent validity of the G-PROM, we will examine associations between G-PROM rankings and disease activity measures at 14 weeks. We will also examine the association between duration of RA and number of disease modifying anti-rheumatic drugs (DMARDs) at baseline and G-PROM rankings. We expect that longer duration of disease and greater number of DMARDs at baseline will be associated with worse G-PROM ranking. We will assess predictive validity by comparing baseline and 24-week G-PROM rankings to disease at 24-weeks. Additionally, we will assess predictive validity by examining the association between G-PROM scores and the total number of weeks a participant remains on their assigned treatment (an indicator of symptom improvement and tolerance of side effects). We will fit separate ordinal regression models for each outcome of interest applying longitudinal and survival techniques when appropriate. Significant associations ($p < 0.05$) between G-PROM and each of these measures will be considered evidence for concurrent and predictive criterion validity. All analyses will be conducted using SAS software available on the secured data storing platform.

Project Timeline:

Project started / searches conducted: July 2017

Data extraction / data request: First half of 2018.

Analysis and report writing: Second half of 2018 (dependent on data requests).

Aim to submit manuscript – end of 2018/first half of 2019.

Dissemination Plan:

Publication in Arthritis Care and Research or other relevant peer-review journal

Presentation at American College of Rheumatology

Bibliography:

1. Singh JA, Saag KG, Bridges SL, et al. 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res* 2016;68:1-25.
2. Coates LC, Helliwell PS. Treating to target in psoriatic arthritis: How to implement in clinical practice. *Ann Rheum Dis* 2015.
3. Coates LC, Moverley AR, McParland L, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): A UK multicentre, open-label, randomised controlled trial. *Lancet* 2015;386:2489-98.
4. Gladman DD. Is it time for treat to target in psoriatic arthritis? *Lancet*;386:2450-2.
5. O'Dell JR, Mikuls TR, Taylor TH, et al. Therapies for Active rheumatoid arthritis after Methotrexate failure. *N Engl J Med* 2013;369:307-18.
6. Keystone EC., et al. "Golimumab, a human antibody to TNF- α given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate: The GO-FORWARD Study" *Annals of the rheumatic diseases* 68(2009):789-796.
7. Evans SR, Rubin D, Follmann D, et al. Desirability of outcome ranking (DOOR) and response adjusted for duration of antibiotic risk (RADAR). *Clin Infect Dis* 2015;61:800-6.