

## Principal Investigator

**First Name:** Liana  
**Last Name:** Fraenkel  
**Degree:** MD, MPH  
**Primary Affiliation:** Yale University School of Medicine  
**E-mail:** [christine.ramsey@gmail.com](mailto:christine.ramsey@gmail.com)  
**Phone number:** 610-613-6745  
**Address:** 950 Campbell Avenue Bldg 35A

**City:** West Haven  
**State or Province:** CT  
**Zip or Postal Code:** 06516  
**Country:** USA

## General Information

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

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

**First Name:** Cynthia  
**Last name:** Frank  
**Degree:** RN, PhD  
**Primary Affiliation:** Yale University/ VA Connecticut Healthcare System  
**SCOPUS ID:**

**First Name:** David  
**Last name:** Broniatowski  
**Degree:** PhD  
**Primary Affiliation:** The George Washington University  
**SCOPUS ID:**

**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_form_for_data_requestors_fraenkel_updated.pdf)

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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):

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.

A scale measuring desirability of patients' overall outcome will generate more informative comparative benefit:risk data than current approaches. The G-PROM will 1) improve evidence-based, patient-centered, decision making, 2) allow investigators to conduct meaningful comparative studies, and 3) allow the FDA to evaluate medications without over-reliance on the judgment of expert panels to determine whether the benefits of proposed new medications outweigh their harms. The methods used will follow the ACR criteria guidelines to ensure eligibility of the final product for endorsement.

### **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:**

The data requested in these proposal pertain to Aim 3, assessing validity of the G-PROM developed in Aim 1 and Aim 2.

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 patient-level data.

Data source:

1. 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 (NCT00264550)
2. Rheumatoid Arthritis: Comparison of active therapy in patients with active disease despite methotrexate therapy (RACAT)
3. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment

Inclusions/Exclusion Criteria:

The sample for this study will include adults ? 18 years with active RA who participated in one of the RCTs listed

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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 these proposal pertain to Aim 3, assessing validity of the G-PROM currently being developed in Aim 1 and Aim 2 . Briefly, Aim 1 is a qualitative aim, involving the research team, rheumatologists recognized as experts in RA and an independent panel of 10 patients in an iterative process to generate and refine a list of outcomes based on patient-reported outcome measures already accepted by the FDA. For this project, we will include five benefit categories: Remission, ACR 70, ACR 50, ACR 20, and no improvement. Aim 2 will recruit approximately 400 participants with RA in a 2-stage process to complete an online survey to generate equivalency classes from the outcomes generated in Aim 1. We will examine five levels of benefit and an estimated 20 AEs (the exact number will be determined by Aim 1). Because of the exceedingly large sample size required to analyze these data in a single survey, we will perform the trajectory mapping procedure in two phases. In Phase 1, we will apply the TM technique to evaluate the overall structure of the AEs. This ranking will then be combined with the ranking over levels of benefit in order to create a partially-ordered hierarchy of side effect/benefit combinations. This is possible because levels of benefit [Remission, ACR 70, ACR 50, ACR 20 and no significant improvement (<

ACR 20)] are already ordered. In Phase 2, we will confirm that subjects are indifferent between profiles in the same equivalence class (or level), but have strong preferences for the better profiles across equivalence classes.

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 comparisons(7). 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 trial(5-6).

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 a 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

Aim 1: Generate a list of descriptions for the outcomes associated with medications commonly used to treat RA:  
July 2017 - December 2017

Aim 2: Generate equivalence classes of global outcomes using trajectory mapping:: Winter 2018

Aim 3: Obtain preliminary estimates of the validity of the G-PROM as an instrument for measuring global outcomes in comparative RCTs for RA:

Data extraction / data request: Fall 2017- Winter 2018

Analysis and report writing: Summer/fall 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:**

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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.