

**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 #: 2016-0698 )**

**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 YODA Project**  
**Research Proposal Review - Revisions Requested**  
**(Protocol #: 2016-0698 )**

**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 investigators state that they will be conducting a summary-level meta-analysis, and are requesting the CSRs. However, their analytic plan calls for analysis of patient-level factors such as severity, pain intensity, and treatment type. It would be helpful to clarify whether they plan to analyze patient-level data. It is unclear which trials are being included in the meta-analysis.

## Principal Investigator

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**State or Province:** Merseyside  
**Zip or Postal Code:** L18 2EL  
**Country:** United Kingdom

## 2016-0698

### General Information

**Key Personnel (in addition to PI):** **First Name:** Sarah  
**Last name:** Nolan  
**Degree:** MSc  
**Primary Affiliation:** University of Liverpool

**First Name:** Andreas  
**Last name:** Goebel  
**Degree:** MD  
**Primary Affiliation:** University of Liverpool

**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):** [NCT00299546 - 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 and Previously Treated with Biologic Anti](#)  
[NCT00269867 - A Placebo-Controlled, Double-Blinded, Randomized Clinical Trial of Anti-TNF Chimeric Monoclonal Antibody \(cA2\) in Patients With Active Rheumatoid Arthritis Despite Methotrexate Treatment](#)

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

## Research Proposal

### Project Title

Placebo response in rheumatoid arthritis

#### Narrative Summary:

We plan to perform a systematic review and meta-analysis of placebo response in rheumatoid arthritis - in other words whether those who are taking an inactive placebo treatment in a clinical trial rather than an active experimental treatment receive any benefit in terms of their rating of pain intensity on a visual analogue scale. The work will follow the same design of our previous work in complex regional pain syndrome:

Mbizvo GK, Nolan SJ, Nurmikko TJ, Goebel A. Placebo responses in longstanding Complex Regional Pain Syndrome: a systematic review and meta-analysis. *The Journal of Pain*, 2015; Feb;16(2):99-115.

#### Scientific Abstract:

Background: Previous work has demonstrated a lack of placebo response in for pain in complex regional pain syndrome, despite common anecdotal existence of such an effect which is often accounted for in study design. We wish to investigate whether placebo responses exist in other conditions in which such a response is commonly expected.

Objective: The aim of the project is to conduct a systematic review and meta-analysis of placebo pain responses in participants with rheumatoid arthritis recruited into placebo-controlled biologics trials.

Study Design: Systematic Review and Summary Level Meta-Analysis

Participants: Participants with rheumatoid arthritis, randomised to the placebo arm of a biologic trial of at least 4 weeks duration

Main outcome measure: Our primary endpoint will be 'placebo response,' defined as the mean change in pain intensity (measured on the VAS 0-100mm) from baseline to post-treatment.

Statistical Analysis: We will calculate a mean difference and standard error of mean difference for change in pain intensity from baseline for each trial We will then synthesise the individual effect sizes at the specified times of interest (early, short-term and long-term response) via meta-analysis using the method of inverse-variance.

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

Following on from our previous work which demonstrated a lack of placebo response for pain in complex regional pain syndrome, despite common anecdotal existence of such an effect which is often accounted for in study design (Mbizvo et al. 2015), we wished to extend our hypothesis to rheumatoid arthritis, a condition for which placebo response is also often anecdotally expected.

#### Specific Aims of the Project:

The aim of the project is to conduct a systematic review and meta-analysis of placebo pain responses in participants with rheumatoid arthritis recruited into placebo-controlled biologics trials.

**What is the purpose of the analysis being proposed? Please select all that apply.** Summary-level data meta-analysis

Summary-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:

- RCTs for the treatment of rheumatoid arthritis in adults diagnosed according to the American College of Rheumatology (ACR) revised 1987 criteria or 2010 criteria (reference);
  - o We will not exclude any trials based on severity of disease, duration of disease or previous biologic treatment.
  - o Trials of all sample sizes will be included
  - o Trials including mixed populations (i.e. participants with rheumatoid arthritis and participants with other conditions) will be included if information could be extracted for the subgroup with rheumatoid arthritis.
- Single-blinded (participants) or double-blinded (participants and investigators) trials;

- Parallel design trials of at least 4 weeks duration with at least one active treatment arm and a placebo arm;
- o Trials will be included in which active and placebo treatments are started as monotherapy among participants or if active and placebo treatments are added on to existing treatments such as methotrexate provided that doses of existing treatments remain fixed throughout the trial. If existing treatment doses do not remain fixed or it is not stated that an appropriate length of washout period of existing treatments

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

Our primary endpoint will be 'placebo response,' defined as the mean change in pain intensity (measured on the VAS 0-100mm) from baseline to post-treatment. To standardise to a single scale, we will assume a conversion to VAS (0-100mm) by multiplying VAS (0-10cm) pain scores by ten. Where the mean change from baseline is not reported as a summary measure, we will calculate the placebo response from data extracted for baseline and all post-treatment pain scores reported. Where data are reported only graphically, we will contact the corresponding author for numerical data. If this is unsuccessful, we will measure the placebo response from the available published graph by hand; where two authors (SN and GM) will perform extraction from graphs and compare results for accuracy.

We intend to perform separate meta-analyses to assess 'early response' (at four to six weeks), 'short-term response' (at around 12 weeks and at around 24 weeks) and 'long term response' (at around 48 to 52 weeks). Measurement times which fit approximate into these time frames (e.g. six months as approximately 24 weeks) will be included in analysis if appropriate.

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

We intend to perform several subgroup analyses at each specified time (early, short-term and long-term response) to assess the relationship between placebo response and potential confounding factors of interest, if data reported in included trials allows:

- Placebo monotherapy compared to placebo added on to treatments
- Previous use of biologics compared to biologic naive
- Disease severity: DAS score of 5.1 or more compared to DAS score of less than 5.1
- Disease duration: less than one year compared to one year or more
- Intravenous compared to subcutaneous route of intervention
- Baseline pain (VAS 0-100 mm scale): mild pain 0-30mm, moderate pain 31-70mm, severe pain 71-100mm

#### **Statistical Analysis Plan:**

We will calculate a mean difference and standard error of mean difference for change in pain intensity from baseline for each trial (see Appendix for details). We will then synthesise the individual effect sizes at the specified times of interest (early, short-term and long-term response) via meta-analysis using the method of inverse-variance. Pooled mean differences and 95% confidence intervals will be reported for each meta-analysis separately.

We will assess the level of heterogeneity present between trials by visual inspection of forest plots and formally according to the I<sup>2</sup> statistic (reference Higgins 2003) (the percentage of variability between trials which is due to statistical heterogeneity). A rough interpretation of this I<sup>2</sup> statistic is as follows:

- 0% to 40%: may not be important;
- 30% to 60% may represent moderate heterogeneity;
- 50% to 90% may represent substantial heterogeneity;
- 75% to 100% represents considerable heterogeneity.

Due to wide ranging inclusion of trials of different biologics, design and participant characteristics, we anticipate that heterogeneity is likely to be present between trials; therefore we will perform random-effects meta-analysis at each specified time.

If subgroup analysis is possible, we will also perform the subgroup analyses described above (see Primary Outcome and assessment of potential confounding factors) with random-effects meta-analysis we will perform a test of subgroup differences to examine the influence of different study and participant characteristics (see Appendix for statistical details of test of subgroup differences). To account for the subgroup analysis of multiple trial related factors, Pooled mean differences and 99% confidence intervals will be reported for subgroups over the separate time periods.

If reported data allows, we also intend to perform meta-regression to assess the effect of baseline pain and disease duration on placebo response on a continuous scale (reference)

We will perform our systematic review and meta-analysis in accordance to the guidelines of the Preferred Reporting of Items for Systematic Reviews and Meta-Analyses (PRISMA) (reference). All statistical analyses will be

performed in Stata statistical software version 11.2 (version tbc and reference)

**Project Timeline:**

Project started / searches conducted: September 2015

Data extraction / data request: First half of 2016.

Analysis and report writing: Second half of 2016 (dependent on data requests).

Aim to submit manuscript - at the latest the end of 2016.

**Dissemination Plan:**

Publication in a relevant clinical journal

Possible presentation at related conferences, if feasible.

**Bibliography:**

Mbizvo GK, Nolan SJ, Nurmikko TJ, Goebel A. Placebo responses in longstanding Complex Regional Pain Syndrome: a systematic review and meta-analysis. *The Journal of Pain*, 2015; Feb;16(2):99-115.

**Supplementary Material:**  [prospero\\_record.pdf](#)