

## Principal Investigator

**First Name:** Philip

**Last Name:** Robinson

**Degree:** MBChB PhD FRACP

**Primary Affiliation:** University of Queensland

**E-mail:** [philip@brisbanerheumatology.com.au](mailto:philip@brisbanerheumatology.com.au)

**Phone number:** +61 4 59 482 682

**Address:** Suite 5, Level 6, St Andrew's War Memorial Hospital, 457 Wickham Terrace, SPRING HILL 4000, Australia

Royal Brisbane Hospital

**City:** HERSTON

**State or Province:** QUEENSLAND

**Zip or Postal Code:** 4006

**Country:** AUSTRALIA

**SCOPUS ID:** 55425572000

## General Information

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

**First Name:** Peter

**Last name:** Nash

**Degree:** MB BS FRACP

**Primary Affiliation:** University of Queensland

**SCOPUS ID:** 8548178700

**Are external grants or funds being used to support this research?:** No external grants or funds are being used to support this research.

**How did you learn about the YODA Project?:** Colleague

## Conflict of Interest

[https://yoda.yale.edu/system/files/peter\\_coi\\_0.pdf](https://yoda.yale.edu/system/files/peter_coi_0.pdf)

[https://yoda.yale.edu/system/files/coi\\_philip\\_v2.pdf](https://yoda.yale.edu/system/files/coi_philip_v2.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

1. [NCT01453725 - P07642 - A Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Effect of Golimumab Administered Subcutaneously in Subjects With Active Axial Spondyloarthritis \(Also Known as MK-8259-006-02\)](#)

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

## Research Proposal

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## Project Title

Assessment of treatment outcome with golimumab in nr-axSpA by baseline CRP

### Narrative Summary:

TNF inhibitors have been trialled in non-radiographic axial spondyloarthritis (nr-axSpA), a type of inflammatory arthritis that affects the spine and sacroiliac joints, and found to be effective. Just like in ankylosing spondylitis a blood marker of inflammation called C-reactive protein (CRP) has been found to predict response to treatment with TNF inhibitors. The published manuscript on the trial of golimumab in nr-axSpA reports response by positive CRP or negative CRP. The aim of this research is to analyse the trial in more detail to determine what the cut-points is for response to enable doctors to use this information in their clinical practice to better select patients for treatment.

### Scientific Abstract:

#### Background:

Golimumab has been trialled in the study in question and found to be effective in patient with non-radiographic axial spondyloarthritis. Studies on golimumab and other TNF inhibitors have shown TNF to be a important response criteria (1-4). However the clinical trial data does not specify response rates beyond positive and negative. The purpose of the study is to explore the response rates with differing levels of CRP. This will enable clinicians to make chooses about therapy for patients knowing their likely response rate based on their actual CRP level.

#### Objective:

To determine the ASAS40 response rate (and other secondary outcomes) in patients with non-radiographic axial spondyloarthritis by different CRP levels.

#### Study Design:

A secondary analysis of the primary trial results to determine the ASAS40 response rates (and other secondary outcomes) by different CRP levels. The individual patient level data will be divided into the CRP groups and the primary and secondary outcomes analysed.

#### Participants:

All participants in the primary clinical trial.

#### Main Outcome Measure(s):

Primary outcome: ASAS40 at 16 weeks by different CRP levels.

Secondary outcomes: Other secondary outcomes measured in the trial at 16 weeks by different CRP levels (both dichotomous and continuous).

#### Statistical Analysis:

Descriptive statistics and logistic regression.

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

Non-radiographic axial spondyloarthritis (nr-axSpA) is an inflammatory arthritis affecting the spine and sacroiliac joints. Effective therapies are available, including golimumab, which is part of the anti-tumour necrosis factor (TNF) class. Previous work has demonstrated that predictors of response to anti-TNF agents include a raised CRP. However the level of raised CRP that predicts a response to golimumab has not been determined.

This project is significant because often patients with nr-axSpA have low positive CRP levels and the level at which patients will respond to anti-TNFs like golimumab is not know. This work has the potential to provide significant guidance to practising clinicians on when it is best to commence agents like golimumab with the expectation that they will respond. Therefore this work can provide guidance to clinicians on when golimumab use would be of limited value and when it would be of good value to the patient (and secondarily to the payer).

### Specific Aims of the Project:

To determine the (1) ASAS40 response (primary outcome), and also examine secondary outcomes (2) ASAS20, (3) ASAS partial remission, (4) BASDAI50, (5) change in SPARCC MRI SI score, (6) change in BASDAI and (7) change in ASDAS in patients with nr-axSpA to golimumab by their baseline CRP.

### 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

## Research Methods

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

The data source would be the participants data from the clinical trial in question. All participants in the trial would be included in this analysis.

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

ASAS40 outcome measure will be the primary outcome measure used, this is a well recognised and widely used outcome measure in clinical trials of axial spondyloarthritis. The ASAS response criteria are used to assess improvement in axial spondyloarthritis in clinical trials. Each of four domains is scored by the patient on a visual analog scale ranging from 0 to 10. The four domains are as follows:

1. Patient global assessment of disease activity for the past week
2. Patient assessment of back over the past week
3. Function (BASFI)
4. Inflammation (severity and duration of morning stiffness)

An ASAS40 response is defined as an improvement of at least 40% and an absolute improvement of at least 1 unit (on a 0-10 scale) in at least three of four domains, with no worsening of the remaining domain. ASAS20 is the same but only a 20% improvement. ASAS partial remission, BASDAI50, Change in SPARCC MRI SI score and change in BASDAI are all widely used outcome measures in rheumatology, the character restriction prevents me from describing them fully.

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

CRP level:

- (a) <5 mg/L
- (b) 5-10mg/L
- (c) > 10mg/L

It will be defined as the measures CRP in the clinical trial in question both as dichotomous groups and as a continuous measure.

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

All variables were defined in the original study. The ASAS response criteria are used to assess improvement in axial spondyloarthritis in clinical trials. Each of four domains is scored by the patient on a visual analog scale ranging from 0 to 10. The four domains are as follows:

1. Patient global assessment of disease activity for the past week
2. Patient assessment of back over the past week
3. Function (BASFI)
4. Inflammation (severity and duration of morning stiffness)

An ASAS40 response is defined as an improvement of at least 40% and an absolute improvement of at least 1 unit (on a 0-10 scale) in at least three of four domains, with no worsening of the remaining domain. In each CRP group, there will be a proportion who reach the ASAS40 response, this is the main outcome measure. ASAS partial remission, BASDAI50, Change in SPARCC MRI SI score and change in BASDAI are measured and defined in the original study and I will be simply examining their relationship to dichotomous CRP groups and CRP as a continuous measure.

### Statistical Analysis Plan:

ASAS40 responses are defined as a composite (see above). Once each patient has had their ASAS response calculated (see above), then each CRP group will have a proportion that reach an ASAS40 response, this is the

primary outcome measure. The process will be completed for each outcome measure, ie. in each CRP subgroup the outcome measures will be examined, and descriptive analyses generated to try to make a comparison between different CRP subgroups. The study was not designed or powered to look at these subgroups so making formal statistical comparisons may be of limited value but logistic regression analysis will be used to examine for the relationship of CRP to these outcome measures.

Software Used:

R

**Project Timeline:**

From receiving the data it will take approximately 3-4 months to complete the analysis, another 1 month to draft the manuscript, and then submission after this. This project is part of a larger project to assess CRP responses across a number of biologics and so it may be the case that the analysis on this YODA data is completed prior to the other data being available and the aim is to include all data in the same manuscript. All manuscripts will be shared with YODA at the time of submission.

**Dissemination Plan:**

Posters at scientific meetings, will submit to the American College of Rheumatology annual scientific meeting and/or the European League against Rheumatism annual scientific meeting. Published in a peer reviewed scientific journal of high quality, depending on the final manuscript, the target journal will be *Annals of the rheumatic diseases*, *Arthritis & Rheumatology*, *Arthritis Care & Research*, *Rheumatology (Oxford)* or *Arthritis Research & Therapy*.

**Bibliography:**

1. Brown, M.A., et al., Evaluation of the effect of baseline MRI sacroiliitis and C reactive protein status on etanercept treatment response in non-radiographic axial spondyloarthritis: a post hoc analysis of the EMBARK study. *Ann Rheum Dis*, 2018. 77(7): p. 1091-1093.
2. Sieper, J., et al., A randomized, double-blind, placebo-controlled, sixteen-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis. *Arthritis Rheumatol*, 2015. 67(10): p. 2702-12.
3. Dougados, M., et al., Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol*, 2014. 66(8): p. 2091-102.
4. Sieper, J., et al., Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann Rheum Dis*, 2013. 72(6): p. 815-22.