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

Conflict of Interest

http://yoda.yale.edu/system/files/ogdie_yoda_coi_form.pdf
http://yoda.yale.edu/system/files/mease_yoda_coi.pdf
http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_orbai_2015_1.pdf
http://yoda.yale.edu/system/files/lihi_yoda.pdf
http://yoda.yale.edu/system/files/coi_-_wang.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. NCT00265096 - A Multicenter, Randomized, Double-blind, Placebo controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered Subcutaneously in Subjects with Active Psoriatic

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

Research Proposal

Project Title

Construct and Content Validity of Instruments Used in Clinical Trials of Psoriatic Arthritis

Narrative Summary:

The goals of this study are to 1) examine the correlation among outcome measures used in clinical trials of psoriatic arthritis and 2) determine how these measures track together over time and treatment. These studies are a part of an Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) - Outcome Measures in Rheumatology (OMERACT) working group initiative to update the core set of measures that are recommended for use in clinical trials of psoriatic arthritis.

Scientific Abstract:

Background: The Outcome Measures in Rheumatology (OMERACT) - Psoriatic Arthritis Working Group is in the process of updating the core set of outcome measures to be included in the clinical trials of PsA.
Objective: The broad objective of this study is to examine the psychometric properties of existing instruments used in clinical trials of PsA. Specifically, we aim to examine their construct and content validity.
Study Design: Series of cross-sectional studies using data from clinical trials for PsA in the past five years.
Participants: Patients enrolled in eligible clinical trials of PsA
Main Outcomes: We will examine construct validity of the instruments by assessing the convergent and divergent relationships among instruments used in these clinical trials. Next, the set of instruments that best explains "response" will be examined by defining response in two ways (separately analyzed): Minimal Disease Activity and patient global assessment at the final visit.
Statistical Analysis: Correlation among of outcome measures will be examined using a correlation matrix in which the correlation coefficient between each pairwise comparison is reported. Instruments reporting similar outcomes should have high correlation whereas those report different outcomes should have lower correlation. To address content validity, we will use a multivariable prediction modeling approach to find the model that maximizes the $R2$ value. This set of instruments will be considered to best explain "minimal disease activity" and "patient global assessment" (modeled separately).

Brief Project Background and Statement of Project Significance:

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis affecting up to one third of patients with psoriasis. Psoriatic arthritis is a clinically heterogeneous disorder with distinct manifestations including peripheral arthritis, spondylitis, enthesitis, and dactylitis, in addition to skin and nail features. Nearly one half of patients will have erosions, approximately one quarter within the first 6 months of disease onset (Eder 2013). Furthermore, patients with PsA have lower health related quality of life (HRQoL) independent of skin psoriasis (Husted 2013). The heterogeneity of clinical manifestations complicates assessment of PsA outcomes and broadens its impact on daily life.

Over the past two decades, our knowledge about PsA and available therapies to treat PsA has evolved. However, the tools available to measure therapeutic responses have not adapted quite as rapidly. PsA outcome measures are largely adopted from rheumatoid arthritis (RA). Similar to RA, randomized controlled trials (RCTs) of PsA focus on peripheral arthritis as the primary outcome. Other PsA specific manifestations (for example spondylitis, dactylitis, enthesitis, skin disease) are often assessed as secondary outcomes (Gladman 2007). The existing PsA

core domain set for clinical trials was endorsed at the Outcome Measures in Rheumatology Clinical Trials (OMERACT) meeting in 2006 and contains the following domains for inclusion in PsA clinical trials: pain, joints, function, skin, patient global assessment of disease activity and health related quality of life (Gladman 2007). There is a need for an updated PsA core set of domains and outcome measures, developed with patient input, to ensure a common standard in PsA clinical care and interventional trials (Tillett 2015).

We are now in the process of updating the 2006 PsA core domain set. The objectives of this process are to 1) increase patient involvement in the core sets and 2) incorporate the methodology outlined in the OMERACT Filter 2.0, adopted in 2014 (Boers 2014). A core outcome measurement set for PsA has not previously been endorsed, mainly due to the lack of a core domain set incorporating patient involvement and updated methodology. To this end, the OMERACT PsA working group intends to update the core domains measured in clinical trials to reflect the many ways in which patients experience psoriatic arthritis. Additionally, the working group seeks to identify appropriate instruments to measure the core domains. The objective of this study is to examine the psychometric properties of existing outcome measures used in RCTs of PsA.

Specific Aims of the Project:

1) Examine construct validity of outcome measures used in PsA RCTs by determining the convergent and divergent intra- and inter-domain correlation.
This Aim will address the correlation among change on individual instruments with change in instruments within the same domain (e.g. among measures of peripheral arthritis activity) and between domains (e.g. peripheral arthritis activity and patient global response).

2) Determine the combination of outcome measures that maximizes the explained variation in response.
This Aim will address content validity of using multiple instruments to assess different domains as they pertain to the concept of "response" and addresses the question, ""What set of instruments best explains the experience of response? " A prediction model approach will be used to determine which set of "predictors" (outcome measures in this case) is associated with the best prediction of either minimal disease activity or patient global assessment at study completion.

What is the purpose of the analysis being proposed? Please select all that apply.
Participant-level data meta-analysisParticipant-level data meta-analysis pooling 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:

Data will be requested from Phase III randomized clinical trials (RCTs) in PsA published in the past five years for the purpose of evaluating the measurement characteristics of instruments used to measure disease activity and treatment response. This includes the studies conducted for the following compounds: certolizumab pegol, golimumab, ustekinumab, apremilast, and secukinumab. Data from RCTs of the same medication will be pooled for analysis. Medications will be coded as A through E to avoid comparisons between medications. It is important to note that we are not comparing among therapies in any of the analyses. The reason to report these separately is that there may be clustering by trial or medication and stratification can help identify such differences.

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

For Aim 1, the goal of the study is to examine the construct validity by examining correlation among outcome measures for the various domains of disease activity, patient-reported measures and therapy response. The concept of construct validity is that an instrument measures what it is supposed to measure. We will establish construct validity by assessing convergent and divergent relationships of similar and dissimilar instruments pretreatment and post treatment separately.

For Aim 2: Content validity is the ability of an outcome measure (or set of outcome measures) to represent all facets of a condition. The PsA working group aims to measure as fully as possible patient response using available outcomes measures. We aim to determine the most complimentary group of outcome measures to best explain "response". Thus, we will examine two different parameters for response (two outcomes): 1) achievement of minimal disease activity (MDA) and 2) patient global assessment of disease at study completion.

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

All instruments (discussed in the 'variables of interest' section) will be mapped to one or more domains/constructs (e.g. peripheral arthritis, enthesitis, functional status, fatigue, etc). For instruments with multiple domains, their individual domains and summary component scores will be analyzed separately. These individual domain-scores will be used as the independent variables in the regression models in Aim 2.

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

The following measures will be included in the study in their original form (continuous or categorical):
Measures of peripheral arthritis activity: tender and swollen joint counts (28 joint count and 66/68 joint count)
Measures of radiographic damage (e.g. erosion score)
Laboratory measures of inflammation (e.g. C-reactive protein and sedimentation rate)
Physician assessment
Enthesitis (e.g. Leeds Enthesitis Index, 4-point enthesis index)
Dactylitis (e.g. count, severity, Leeds dactylics index)
Psoriasis (e.g. psoriasis area and severity index)
Nails (e.g. modified nail psoriasis severity index)
Global Assessments (skin, arthritis, and disease activity)
Stiffness (duration, VAS)
Depression scales
Pain (VAS)
Fatigue (e.g. FACET, SF-36)
Sleep
HRQOL (e.g. PsQOL, SF36)
Skin PRO (e.g. DLQI, PSI)
Function (e.g. HAQ, SF36 physical function)
Work Productivity (e.g. WPI, Work limitations questionnaire)

*A table containing all items to be included in the correlation matrix (when available) is attached in the supplementary table.

Statistical Analysis Plan:

We will first descriptively report the number and category of instruments in each clinical trial (anonymized). To address construct validity, we will create a correlation matrix containing all of the outcome measures. (examples in Choi 2009 and Strand 2011). Pearson's or Spearman's correlation coefficients will be calculated for each cell of the matrix (depending on the distribution of the measure). Intra-domain and inter-domain correlations will then be compared. Intra-domain correlation should be higher than inter-domain correlation for an individual outcome measure.

Responsiveness is the ability of an outcome measure to detect change over time. Correlation among change in the response measures will similarly be calculated. In addition, we will calculate standardized response means over all of the treatment groups (not comparing among therapies but combining all therapies). Confidence intervals will be generated using a bootstrapping method.

To address content validity, we will perform multivariable logistic and linear regression analyses with outcomes 1)MDA and separately, 2) the patient global assessment after treatment. Variance inflation factors will be used to assess for the degree of collinearity among outcome measures included in the models. Clustering by trial and/or medication will be accounted for in the models. The R squared value will be used to identify the best model for overall improvement. If there is significant missing data (or non-overlap of outcome measures), modeling will be performed in each study separately and compared across studies.(Choi 2009)

*More detail on the analysis can be found in the supplementary material.

Project Timeline:

September 2015 – Study start: Data cleaning and variable standardization
October 2015 – Data analysis/analysis completion
October/November 2015 – Presentation of results to PsA Working Group (including Patient Research Partners)
Jan 2016 - Manuscript drafted and prepared for submission in Feb 2016
Feb 2016 - Results reported back to YODA
March 2016 - Presentation at Nominal Group Technique Meeting for development of updated PsA Core Domain Set
May 2016 - Presentation of results at Outcome Measures in Rheumatology (OMERACT) conference and voting on updated PsA Core Domain Set

Dissemination Plan:

The target audience includes the Outcome Measures in Rheumatology conference participants, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis, Clinical Trialists, Pharmaceutical Companies, and the Food and Drug Administration.

The results will be presented as a critical part of the planned "Psoriatic Arthritis Workshop" at OMERACT in May 2016 (in Vancouver, CA) which will aim to update the PsA Core Measurement Set. This data will support OMERACT ratification of the updated Core Set.

The results will be published as a manuscript with goal submission in February 2016. Suitable journals include Arthritis and Rheumatology, Arthritis Care and Research, and the Journal of Rheumatology. The manuscript must be ready for inclusion in the OMERACT conference pre-reading materials by March 2016. A summary of the results will be reported and published in the OMERACT proceedings.

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Supplementary Material:

psa_instrument_assessment_yoda_suppl_methods_30july2015.docx