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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: Critical Path Institute
How did you learn about the YODA Project?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/system/files/20191203121726686.pdf
https://yoda.yale.edu/system/files/coi-greene-12.2.19.pdf
https://yoda.yale.edu/system/files/jackson.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_-_robert_chapman.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_jdp.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. NCT01604343 - CNTO136ARA3002 - A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study of CNTO 136 (Sirukumab), a Human Anti-IL-6 Monoclonal Antibody, Administered Subcutaneously, in Subjects With Active Rheumatoid Arthritis Despite DMARD Therapy
2. NCT01606761 - CNTO136ARA3003 - A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study of CNTO 136 (Sirukumab), a Human Anti-IL-6 Monoclonal Antibody, Administered Subcutaneously, in Subjects With Active Rheumatoid Arthritis Despite Anti-TNF-Alpha 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

Justification of PROMIS (FACIT) Fatigue Short Form 10a scale for FDA Drug Development Tool Qualification in Rheumatoid Arthritis

Narrative Summary:

We propose a series of quantitative analyses using SIRROUND-D/SIRROUND-T data in support of the Center for Drug Evaluation and Research Clinical Outcome Assessment submission of PROMIS Fatigue in RA Drug Development Tool (DDT) qualification submission. Qualification would enable drug developers to issue labelling claims based on the patient reported outcome of fatigue and allow use of patient-reported fatigue as an endpoint measure in RA treatment trials. Using this data, we will examine and compare the psychometric characteristics, including score distribution and correlation, internal consistency, test-retest reliability, convergent and known groups validity, and responsiveness to change.

Scientific Abstract:

Background: Rheumatoid arthritis patients consider fatigue an important aspect of their disease, and therefore is an important outcome when evaluating intervention effectiveness. Clinical Outcome Assessments (COAs) measure patient symptoms and are used to determine if a drug has been demonstrated to provide treatment benefit. FDA qualification of COAs enable developers to issue labeling claims and allow use of these outcomes as an endpoint measure in trials. We propose the 10-item PROMIS Fatigue (comprised from FACIT Fatigue) to be qualified for use as a measure of fatigue in RA patients
Objective: We propose a series of analyses in support of PROMIS Fatigue in RA Drug Development Tool qualification
Study Design: Item responses and scores from the PROMIS Fatigue will be requested along with measures of RA disease severity, quality of life, and response across time for analysis of reliability and validity of the measure
Participants: Subjects from SIRROUND-D and SIRROUND-T trials who have FACIT-Fatigue scores at any time

Main Outcome: The PROMIS Fatigue item responses and scores will be analyzed across time and by groups with known differences in related outcomes
Statistical Analysis: Analyses include assessment of item/score distributions; examination of floor/ceiling effects; reliability via Cronbach's alpha and ICC for patients expected to have no change in score at two concurrent time points; validity via correlation with similar scores and sensitivity of scores across known classification groups using ANOVA and assessment of sensitivity to change using mixed models

Brief Project Background and Statement of Project Significance:

Rheumatoid arthritis (RA) is the most common form of inflammatory arthritis and is associated with fluctuating debilitating symptoms that confer considerable decrements to patients' longevity and quality of life. Patient and clinician input reveal that fatigue has been identified as a common, persistent, and disabling symptom in RA, and a high priority for RA patients seeking treatment. RA patients not only consider fatigue as one of the most important aspects of their disease experience, but as an important outcome when evaluating the effectiveness of interventions. Research examining the fatigue experience of RA patients suggests that RA-associated fatigue differs from "normal" fatigue, impacts multiple domains of patients' lives, and is under-recognized by clinicians. Patient-reported outcome (PRO) measures serve as the best method for assessing symptoms like fatigue, as its severity and impact are best known by the patient. Given the importance patients place on fatigue and its resolution as part of remission, the persistence of fatigue despite well-controlled disease activity as defined by traditional indicators, broader inclusion of fatigue measures is needed in RA clinical trials in order to better understand patients' responses to treatment. This includes determination of whether interventions can provide overall benefit to patients above and beyond the existing indicators for disease progression, symptom maintenance, and clinical remission. Precise and valid measurement of fatigue is required to fully evaluate the effects of RA interventions in clinical trials. Clinical Outcome Assessments (COAs) measure a patient's symptoms, mental state, or the effects of a disease or condition on how the patient functions, and can be used to determine whether or not a drug has been demonstrated to provide treatment benefit. We propose a series of quantitative analyses using SIRROUND-D and SIRROUND-T clinical trial data in support of the Center for Drug Evaluation and Research Clinical Outcome Assessment submission of PROMIS Fatigue in Rheumatoid Arthritis Drug Development Tool (DDT) qualification submission. The FDA's DDT qualification of the PROMIS Fatigue in Rheumatoid Arthritis would enable drug developers to issue labelling claims based on the patient reported outcome of fatigue and allow use of patient-reported fatigue as an endpoint measure in RA treatment trials.

Specific Aims of the Project:

Aim 1: Assess item and score distributions by calculating frequencies of each response and examining floor/ceiling effects. We hypothesize that item and score distribution will be similar across time and no response option will very rarely/frequently endorsed.

Aim 2: Assess reliability by calculating Cronbach's alpha (internal consistency) and the intraclass correlation (ICC) for patients expected to have no change in score at two concurrent time points (test-retest). We hypothesize that the measure will show high internal consistency (alpha > .7) and test-retest reliability (ICC > .7).

Aim 3: Assess validity by comparing against another known measure of fatigue (convergent validity) and examining sensitivity of scores across groups expected to differ in fatigue (known groups validity). We hypothesize that there will be high correlation between the two measures and a difference in score across known groups.

Aim 4: Assess sensitivity to change using repeated measures mixed effect models to estimate the effect size estimate of change, standardized response mean, standardized mean change difference and Guyatt's statistic to identify differences by known group. We hypothesize that we will see a change in score across time in patients whose clinical status has changed.

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

Evaluate the psychometric characteristics of the PROMIS Fatigue 10a in RA Population, in support of obtaining a DDT COA qualification of this measure of fatigue in rheumatoid arthritis patient population.

Research Methods

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

We will include all subjects from the SIRROUND-D and SIRROUND-T clinical trials who have PROMIS (FACIT) Fatigue 10a scores at any time point.

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

FACIT-Fatigue/PROMIS (FACIT) Fatigue 10a individual item responses and scores at each time point; scores will be calculated per the FACIT-Fatigue Subscale Scoring Guidelines (https://www.facit.org/FACITOrg/Questionnaires) and as PROMIS (FACIT) Fatigue 10a scores (http://www.healthmeasures.net/).

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

SF-36 Vitality score will be used as-is; change in score will be categorized using the minimally important difference thresholds for worsened/improved scores: -7.3 and 11.9 and -8.3 and 1.4, respectively (Nordin, 2016)
Crohn's Disease Activity Index (CDAI)will be categorized into groups: Remission (CDAI ?2.8), Low Disease Activity (2.8 < CDAI ? 10), Moderate (10 < CDAI ? 22), High (CDAI > 22) (Anderson 2012; Bingham, 2019)
American College of Rheumatology (ACR) response will be defined as (Felson et al, 1998; Furst et al, 2003):
ACR20: >= 20 % improvement in tender joint and swollen joint count and >= 20% improvement in 3 of the following 5 assessments: Participant's assessment of pain using VAS, Participant's global assessment of disease activity by using VAS, Physician's global assessment of disease activity using VAS, Participant's assessment of physical function as measured by HAQ-DI, and Serum CRP
ACR50: >= 50 % improvement in tender joint and swollen joint count and >= 50% improvement in 3 of the 5 assessments listed for ACR20
ACR70: >= 70% improvement in tender joint and swollen joint count and >= 70% improvement in 3 of the following 5 assessments listed for ACR20

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

Major Clinical Response (MCR) will be defined as participants achieving ACR70 Response for 6 continuous months (24 weeks) in the study period

Disease Activity Index Score 28 (DAS28) will be used categorized as:
Good responders: improvement from baseline greater than (>) 1.2 with DAS28 less than or equal to (<=) 3.2; moderate responders: improvement from baseline >1.2 with DAS28 >3.2 to <=5.1 or improvement from baseline >0.6 to <=1.2 with DAS28 <=5.1; non-responders: improvement from baseline <=0.6 or improvement from baseline >0.6 and <=1.2 with DAS28 >5.1. Score difference from baseline will also be calculated.

EuroQol Health State Visual Analogue Scale (EQ VAS) can be used as a quantitative measure of health outcome, used as a linear response ranging from 0-100; differences in score will be calculated at each time point where available.

Statistical Analysis Plan:

We will assess item response distributions by calculating the n and % of each response option, graphically examining/identifying the item response distribution and examining floor/ceiling effects, where “floor” is the worst health option (i.e., greater fatigue) and “ceiling” is the best health option (i.e., less fatigue). We will identify the likelihood of a ceiling for an item effect by identifying those items in which a large percentage of the participants have selected the best health option. For negatively worded items (HI7, AN2, AN3, AN4, AN8, AN14, AN15, AN16), a ceiling effect is likely to occur if a large percentage of participants select response category 1 (Not at all), and a floor effect is likely to occur if a large percentage of participants select response category 5 (Very much); for positively worded items (AN5, AN7), a ceiling effect is likely to occur if a high percentage of participants select response category 1 (Very much), and a floor effect is likely to occur if a high percentage of participants select response category 5 (Not at all). We will assess score distribution using mean/standard deviations and graphically examining the score distribution.
We will calculate Spearman’s rank correlations for each pair of items and create scatter plots of responses to each item pair to graphically display item relationships and identify potential non-linear relationships.
Internal consistency will be assessed via calculation of Cronbach’s alpha coefficients. Only participants who

complete all 10 items will be included in the Cronbach's alpha calculation. In addition, the Cronbach's alpha-if-item-deleted analyses will be programmed to include only participants with complete data for each item under investigation. Therefore, there will not be any missing item data when calculating Cronbach's alpha. Values of Cronbach's alpha > 0.7 are generally considered acceptable for group comparisons, and values > 0.9 are generally accepted to represent "excellent" internal consistency (Nunnally, 1978).

Test-retest reliability will be assessed via calculation of intraclass correlation coefficient, ICC(absolute) (Qin et al., 2018), between consecutive time points for subjects having "high agreement" in SF-36 Vitality scores at these time points, based on the most conservative (smallest) MID for worsened and improved score for SF-36 Vitality and MAF (-7.3 and 11.9 and -8.3 and 1.4, respectively) which provides a range of non-important differences (Nordin, 2016). Similarly, as a secondary analysis, patients with a "non-significant" change score on the EQ VAS, determined as a score <0.5 SD from mean change will be selected and intraclass correlation coefficient, ICC(absolute), will be calculated between consecutive time points.

The extent to which PROMIS-Fatigue scores are related to scores measuring similar concepts (convergent validity) will be assessed via calculation of the Pearson correlation coefficient between scores from the PROMIS Fatigue and the SF-36.
Sensitivity of PROMIS Fatigue Short Form 10a scores to differences between participants in distinct CDAI groups (known groups validity) will be assessed via calculation of mean and standard deviation of Fatigue score and comparison of mean scores across groups using a one-way ANOVA.
Responsiveness to change will be measured using repeated measures multilevel mixed effects models, grouping subjects based on their response to treatment (via ACR improvement levels and change in SF-36 based on MID thresholds mentioned above). Effect size estimate of change, standardized response mean, standardized mean change difference, and Guyatt's statistic will be used to evaluate responsiveness. As secondary analyses, models will be repeated using DAS28 categories of change and EQ VAS thresholds of change mentioned above.
Software Used:
RStudio

Project Timeline:

This project will begin immediately after data has been obtained. Analysis will be completed roughly one month after data have been obtained and results will be reported back to the YODA project at that time. Results will be added to the Final Qualification Package for the FDA which will be drafted approximately two months after analysis completion. The completed qualification package will be submitted in early 2020 with final qualification dependent on FDA review. Should the project timeline exceed 12 months, a project extension will be requested.

Dissemination Plan:

Results of this analysis will be reported in the FDA's DDT Final Qualification Package for consideration for qualification of the PROMIS Fatigue Short Form 10a in Rheumatoid Arthritis.

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