Rheumatoid Arthritis Working Group

Prepared for the 11th Annual PRO Consortium Workshop (April 22-23, 2020), which was cancelled due to COVID-19

PRO CONSORTIUM
CRITICAL PATH INSTITUTE

Background

Rationale for Rheumatoid Arthritis (RA) Working Group (WG)

- PRO Consortium member representatives and FDA advisors identified RA as a priority area with an unmet need for a fit-for-purpose PRO measure, as defined by the FDA, for use in evaluating clinical benefit in RA clinical trials.

Goal of the RA WG

- To qualify a PRO measure that assesses RA-related fatigue and supports product labeling claims of treatment benefit.
- In the Scoping Stage Summary Document submitted to FDA in September 2011, the RA WG proposed that the most important unmet measurement needs in RA trials were standardized PRO instruments assessing RA-related symptoms and RA-defining decrements in physical function. FDA, in its response in December 2011, acknowledged that "the PRO measures currently used in RA patients could be improved to meet current standards for measurement. We agree to participate in the qualification process for both PRO instruments you have proposed provided that instrument development includes involvement of representatives from the rheumatology academic community including OMERACT and ACR."
- In May 2012, a few members of the RA WG met with RA patients and clinical experts to assess interest in a joint development activity. Experts and patients were eager to participate in an activity, which would include representatives from FDA, clinical societies, and other key stakeholders. Subsequently, PRO Consortium leadership, supported by the RA WG, organized a consensus development workshop to identify a path forward (see History).

Concept of Interest

- Fatigue severity

Target Population

- Patients 18 years and older with rheumatoid arthritis

Targeted Labeling Language

- Patients treated with [*Drug X*] reported an improvement of fatigue if limited by fatigue at the start of the trial.
- Patients treated with [*Drug X*] reported a delayed worsening of fatigue if limited by fatigue at the start of the trial.
- Patients treated with [*Drug X*] reported a delayed onset of fatigue if not limited in fatigue at the start of the trial.

Milestones

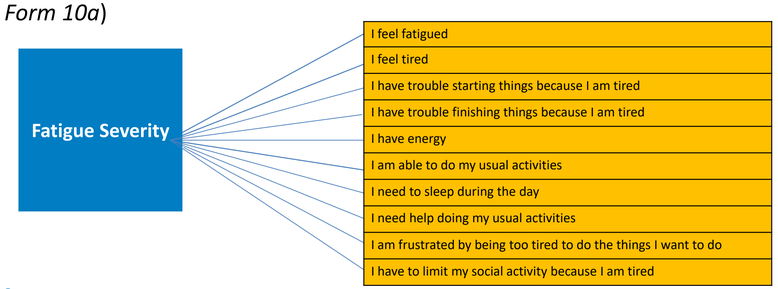
Milestone	Target Date	Completed Date
Letter of Intent submission to FDA		JUN 2016
Initial Briefing Package submission to FDA		AUG 2017
Qualification Plan submission to FDA		MAR 2019
Received Qualification Plan Determination Letter from FDA		SEP 2019
Full Qualification Package submission to FDA	Q4 2020	

Highlights

Example Endpoint Model for Treatment of RA

Endpoint Hierarchy	Endpoint Concept(s)	Endpoint Type
Primary (Composite endpoint for indication [i.e., Treatment of RA])	**American College of Rheumatology (ACR) criteria** • Patient assessment of pain • Inflammation (CRP or ESR) • Signs (swollen joint count, tender joint count) • Disease activity • Patient assessment of physical function	 • PRO • Biomarker • ClinRO • ClinRO and PRO • PRO
Secondary	Fatigue severity	• PRO

Hypothesized Conceptual Framework (based on the *PROMIS® Fatigue Short Form 10a*)



History

- As requested by FDA, the RA WG involved outside stakeholders in this qualification initiative. The PRO Consortium was uniquely positioned to initiate, organize, and convene a diverse group of key stakeholders for a face-to-face workshop.
- The RA WG held the workshop, titled "Toward Consensus Development: Qualifying Endpoint Measures for Rheumatoid Arthritis Clinical Trials," on August 28, 2012, in Silver Spring, MD.
- Along with RA WG members and C-Path personnel, participants included persons with RA and representatives from FDA, American College of Rheumatology (ACR), Outcome Measures in Rheumatology (OMERACT), European League Against Rheumatism (EULAR), and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMSD).
  - Objective: To identify RA-related symptoms and RA-defining decrements in physical functioning that could be investigated by the RA WG for use as PRO-based endpoint measures in clinical trials to support label claims.
  - Outcome: Fatigue was identified as the most commonly reported troublesome symptom that is not currently assessed by the ACR response criteria. Hence, the measurement of fatigue was selected as the focus for FDA qualification to support a secondary endpoint to document treatment benefit.
- Following the consensus development workshop, the WG has collaborated with OMERACT and PROMIS investigators, and with Drs. Bartlett and Bingham to review the literature and gather clinical experts' input to define fatigue and explore its measurement in patients with mild to severe RA.
- Based on the work of Kaiser and colleagues (2016), the *PROMIS® Fatigue Short Form 10a* was selected to move forward for qualification. It is comprised of 10 of the 13 items in the *FACIT-Fatigue*, which has been used extensively in RA research and RA clinical trials.
  (Kaiser K, Shaunfield S, Clayman ML, Ruderman E, Cella D. Content validation of the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale in moderately to highly active rheumatoid arthritis. *Rheumatology* 2016; 6:193. doi: 10.4172/2161-1149.1000193)

Working Group Activities

Completed Activities

- On July 20, 2015, the RA WG met with the FDA/NIH Interagency Clinical Outcome Assessment Working Group (ICOA WG); Dr. Clifton Bingham presented evidence from the observational research in which he and Dr. Susan J. Bartlett are assessing fatigue in RA.
- Drs. Bingham and Bartlett's data suggests that in a subset of RA patients, fatigue is unique (i.e., not part of other measured outcomes) and that its measurement will add value over and above existing outcome measures since it is a common and debilitating impact of RA.
- FDA recommended that the RA WG submit a revised Letter of Intent summarizing the key points presented by Drs. Bingham and Bartlett.
- RA WG submitted Initial Briefing Package to FDA in August 2017 in support of qualification of the *PROMIS® Fatigue Short Form 10a*. FDA responded with several comments and information requests in March 2018, which were addressed.
- Contract between C-Path and Northwestern University was executed in August 2018 to prepare the Qualification Plan.
- RA WG submitted the Qualification Plan to FDA in March 2019.
  - RA WG submitted a response to an information request to FDA in July 2019.

Challenges

- Due to the delays in progression of milestone achievements, several members have withdrawn from the RA WG due to a lack of funding from their respective organizations.
- Several measures have been used in clinical trials to measure fatigue in RA but none had led to fatigue-related label claims until 2019, when the FACIT-Fatigue (which includes the *PROMIS® Fatigue Short Form 10a)* was included in the product labeling for upadacitinib.
- Access to patient-level data may only be available via sponsor data-sharing portals.

Next Steps

- Submit Full Qualification Package for the *PROMIS® Fatigue Short Form 10a* for the assessment of clinical benefit in RA trials.

Working Group Participants

Company/Organization	Representative
AbbVie	Pankaj Patel, PharmD, MS; Namita Tundia, PhD
Boehringer Ingelheim	Tristan Gloede, PhD
Eli Lilly and Company	April Naegeli, DrPH, MPH (Co-Chair); Nicki Bush, MHS; Carol Kannowski PharmD, RPh ; Laure Delbecque, PhD
Merck KGaA (EMD Serono)	Christian Henke, PhD; Paul Kamudoni, PhD
GlaxoSmithKline	Brandon Becker, PhD, MPH
UCB Pharma	Ann-Christin Mörk, PhD
Affiliation	**Other Participants**
Patient Representative	Amye Leong, MBA
OMERACT	Lee S. Simon, MD; Vibeke Strand, MD
Johns Hopkins University	Clifton O. Bingham III, MD
American Institutes for Research	San Keller, PhD
McGill University	Susan J. Bartlett, PhD
Research Partner	**Research Team**
Northwestern University	David Cella, PhD; Robert Chapman, BA; George J. Greene, PhD; Kathryn Jackson, MS; Sally Jensen, PhD; John Devin Peipert, PhD