Rheumatoid Arthritis Working Group

Presented at the Ninth Annual PRO Consortium Workshop – Silver Spring, MD – April 25-26, 2018

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 treatment benefit in RA clinical trials

Goal of the RA WG

- To qualify a PRO instrument that assesses RA-related fatigue and supports product labeling claims of treatment benefit

In the Scoping Stage Summary Document submitted to the 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. The 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.)

Milestones

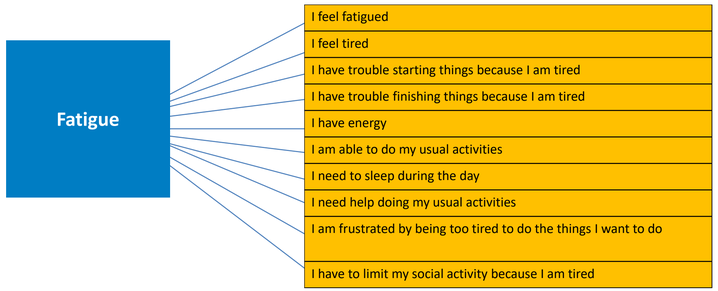
Milestone	Expected Date	Completed Date
FDA confirmed willingness to participate in the project		DEC 2011
Consensus development workshop		AUG 2012
Agreement to conduct preliminary work with OMERACT		JAN 2013
Begin work with OMERACT after agreements are signed		JAN 2014
Submit letter of intent to FDA: Qualification of a Patient-Reported Measure of Fatigue for Use in Assessing Treatment Benefit in Rheumatoid Arthritis Trials		JUN 2016
Vendor selection and contracting for continuation of Content Validity Stage		FEB 2017
Submit Initial Briefing Package		AUG 2017
Submit Qualification Plan (QP)	2018Q3	
Submit Full Qualification Package to FDA	TBD	

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 (Other treatment benefits)	Reduction in fatigue	• PRO

Hypothesized Conceptual Framework



History

- As requested by the 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 RA patients and representatives from the 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.
  - Workshop overview presented as a poster during 2013 ISPOR European Congress.
- 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.

Working Group Updates

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 his and Dr. Susan J. Bartlett's observational research regarding the importance of assessing fatigue in RA
- Drs. Bingham and Bartlett's data suggests that in a subset of RA patients, fatigue is unique and that its measurement may add value over and above existing outcome measures
- FDA recommended that the RA WG submit a revised Letter of Intent (LOI) summarizing the key points presented by Drs. Bingham and Bartlett
- Follow-up discussions were held with FDA COA Staff and Office of Biostatistics personnel
- Contract between C-Path and Dr. Bingham/Johns Hopkins University executed in February 2016 to develop supplementary evidence for the LOI
- Contract between C-Path and Northwestern University executed February 2017 to prepare Initial Briefing Package in support of qualification of the *PROMIS® Short Form Fatigue 10a*
- Submitted Initial Briefing Package to FDA in August 2017

Unique Issues for the Working Group

- Due to the delays in progression of milestone achievements, several WG members have withdrew 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 have led to fatigue-related label claims
- PROMIS Short Forms for Fatigue and the PROMIS T-score metric have potential in measuring fatigue in RA

Next Steps

- Submit Qualification Plan to FDA for the qualification of *the PROMIS® Short Form Fatigue 10a* for use in assessing treatment benefit in RA trials

Working Group Participants

Company/Organization	Representative
Boehringer Ingelheim	Tristan Gloede, PhD
Eli Lilly and Company	April Naegeli, DrPH, MPH (Co-Chair); Enkeleida Nikai, MSc, MB (Co-Chair): Carol Gaich, PharmD, RPh
Merck KGaA (EMD Serono)	Christian Henke; Paul Kamudoni, PhD
GlaxoSmithKline	Josephine Park, MHP, MBA
UCB Pharma	Kristina Harris, PhD
Nonmember Participants' Affiliation	**Name**
OMERACT	Vibeke Strand, MD; Lee S. Simon, MD
NIAMSD/PROMIS	James Witter, MD, PhD
Johns Hopkins University	Clifton O. Bingham III, MD
American Institutes for Research	San Keller, PhD
McGill University	Susan J. Bartlett, PhD
Patient Representative	Amye Leong, MBA
Contract Research Organization	**Research Team**
Northwestern University	David Cella, PhD; David Condon, PhD, MBA