Expanding the Measurement of Treatment Benefit in Rheumatoid Arthritis (RA): The Role of the Patient-Reported Outcome Consortium's RA Working Group

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Abstract

OBJECTIVES: To develop a patient-reported outcome (PRO) instrument that can be qualified by the Food and Drug Administration (FDA) for use in rheumatoid arthritis (RA) randomized controlled trials (RCTs) to support treatment benefit claims.

METHODS: On August 28, 2012, a consensus development workshop was held by the RA Working Group (WG) within the Critical Path Institute's PRO Consortium to identify RA-related PRO concepts to determine their potential role in the documentation of treatment benefit in RA RCTs. Key stakeholders participated in this one-day meeting, including RA patients, representatives from the FDA (Division of Pulmonary, Allergy, and Rheumatology Products [DPARP] and Study Endpoints and Labeling Development [SEALD], and others), experts from the American College of Rheumatology (ACR), European League Against Rheumatism (EULAR), Outcome Measures in Rheumatology (OMERACT), National Institutes of Health (NIH, NIAMS) and the pharmaceutical industry (RA WG members).

RESULTS: Over the course of the workshop, a consensus emerged that there are several outcomes important to RA patients not explicitly assessed by the ACR response criteria (i.e., fatigue, stiffness, and participation). Finally, consensus amongst the various stakeholders was reached that any new measure needs to provide information over and above what is currently captured by the traditional primary composite endpoints and the priority would be to focus on FDA qualification of a PRO measure evaluating RA-related fatigue.

CONCLUSION: The RA WG is initiating a collaboration with clinical experts through OMERACT to provide an operational definition of fatigue and to develop a conceptual framework to support its measurement in clinical trials. Following this preliminary step, qualitative and quantitative steps will be launched to develop the fatigue measure.

Background

Critical Path Institute (C-Path)[1]

- Established in 2005 by the University of Arizona and the US Food and Drug Administration (FDA)
- An independent, non-profit organization
- Dedicated to implementing FDA's Critical Path Initiative - A strategy for transforming the way FDA-regulated products are developed, evaluated, manufactured, and used
- Provides a neutral, pre-competitive venue for collaboration aimed at accelerated development of safe and effective medical products
- Primary sources of funding for C-Path's core operations:
  - government agency grants (e.g., FDA, Science Foundation Arizona)
  - foundation grants/contracts (e.g., Gates Foundation, PKD Foundation)
  - private philanthropy

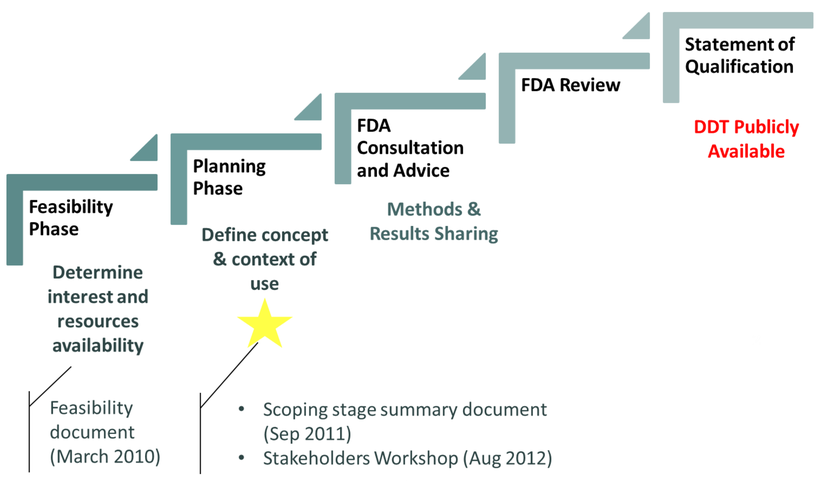
Patient-Reported Outcome (PRO) Consortium

- Formed in late 2008 by C-Path in cooperation with the FDA and the pharmaceutical industry
- Membership
  - Only available to medical product companies
  - 25 members in 2012
- Non-Voting Participants
  - Representatives of governmental agencies (e.g., FDA, NIH, EMA)
  - Clinical consultants, patients, academic researchers, and contract research organizations partnering in the development of the PRO instruments
- Goals
  - Enable pre-competitive collaboration that includes FDA input/expertise
  - Develop qualified, publicly available PRO instruments
  - Avoid development of multiple PRO instruments for the same purpose
  - Share costs of developing new PRO instruments
  - Facilitate FDA's review of medical products by standardizing PRO endpoints

Rheumatoid Arthritis Working Group (RA WG)

- Convened in early 2011 as one of the PRO Consortium's seven working groups
- Primarily composed of pharmaceutical industry experts in health outcomes
- Objective
  - To identify RA-related concepts best assessed through patient self-report that could be further investigated to determine their potential role in the documentation of treatment benefit in RA clinical trials

Figure 1. RA Working Group status on the Path to PRO Instrument FDA Qualification Process[2]



Stakeholder Workshop

Toward Consensus Development: Qualifying Endpoint Measures for Rheumatoid Arthritis Clinical Trials

- Origin
  - Expert outreach (2011)
    - Meeting with representatives from EULAR, ACR, OMERACT
    - Inform clinical experts and patients of the goals of the RA WG
  - FDA's response to Scoping Stage Summary Document (Dec 7 2011)
    - *"We acknowledge 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."*
  - OMERACT representation within the RA WG (Jan 2012)
  - OMERACT 11 (May 2012)
    - Presentation by the RA Working Group
    - Recommended holding a workshop involving all stakeholders
- Sponsored by RA WG member firms within C-Path's PRO Consortium
  - Most viable mechanism to quickly organize and host a neutral forum to engage appropriate stakeholders for information sharing and consensus development around a research agenda

Workshop Objectives

- To identify RA-related symptoms and RA-defining decrements in physical functioning that could be investigated by the RA Working Group for use as patient-reported endpoints in clinical trials to support label claims.
- Expected outcome was a research agenda aimed at collecting evidence for the FDA qualification of one or more PRO instruments that capture concepts that are relevant to patients with RA. Once qualified, the PRO instruments will contribute to the assessment of treatment benefit in RA drug registration trials.

Workshop Format

Structure

- Agenda developed in collaboration with C-Path PRO Consortium, FDA, OMERACT representatives, and RA WG co-chairs
- Format of the workshop:
  - Presentations of existing evidence and current state and opportunities for measuring treatment benefit in RA
    - Presenters identified
  - Presentations followed by general discussion facilitated by moderator
    - Comparable to focus group
    - Moderator provided *a priori* questions identified by RA WG
    - Final discussion comprised measurement gaps and consensus on the path forward for RA WG

Key Stakeholders

- 11 from FDA Center for Drug Evaluation and Research (CDER)
  - Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
  - Study Endpoints and Labeling Development (SEALD) Staff
  - Planning and Informatics
- 2 Patient representatives
- 8 Experts identified by respective professional organization leadership
  - American College of Rheumatology (ACR)
  - European League Against Rheumatism (EULAR)
  - Outcome Measures in Rheumatology (OMERACT)
- 2 National Institutes of Health (NIAMS/NIH)
- 16 RA WG members

Workshop Outcomes

Context of use

- Operationalize the recruitment of patients across the spectrum of disease with mild to severe RA
- Measure should have discriminatory power (i.e., able to differentiate between an active treatment and placebo) and not be limited by floor or ceiling effects

Concepts of measurement

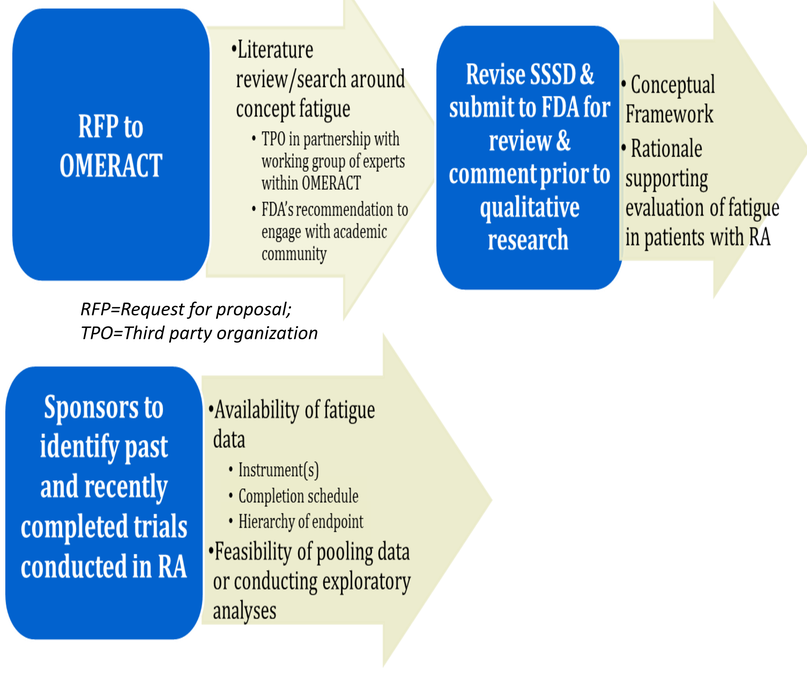
- RA-related symptoms discussed
  - Fatigue
  - Stiffness
    - Important concept that requires further investigation
    - Agreement that not a top priority for the RA WG at this time
- Decrements in Physical Function
  - Not comprehensively captured by the Health Assessment Questionnaire-Disability Index (HAQ-DI)
  - Patient Reported Outcomes Measurement Information System (PROMIS) Physical Function and PROMIS HAQ-DI being investigated
  - Agreement to remove this concept from RA WG research agenda
- Participation/Productivity
  - Important concept of measurement to pursue qualification of PRO instrument in future

Consensus

- Most important unmet need in RA
  - Fatigue
    - Qualification as secondary endpoint
- Modifications to ACR response criteria out of scope
  - Demonstrated ability to document treatment benefit in a broad range of heterogeneous patients
  - Experts acknowledged limitations of PRO components

Workshop Outcomes (cont.)

Figure 2. Path Forward for RA WG



Conclusions

- Sponsorship of the workshop by C-Path's PRO Consortium enabled multiple stakeholders the opportunity to engage in an information sharing discussion to identify RA-related concepts best assessed through PRO measures that could be further investigated to determine their potential role in the documentation of treatment benefit in RA clinical trials
  - This level of stakeholder participation could not have been accomplished by one industry member alone
- The RA WG is moving forward in a collaboration with clinical experts through OMERACT to focus on development and FDA qualification of a measure of fatigue to support a secondary endpoint to document treatment benefit.

References

[1] Coons SJ, Kothari S, Monz BU, Burke LB. The Patient-Reported Outcome (PRO) Consortium: filling measurement gaps for PRO end points to support labeling claims. Clin Pharmacol Ther 2011 Nov;90(5):743-8.
[2] FDA's Guidance for Industry: Qualification Process for Drug Development Tools (draft - October 2010)

Disclosures

Conflicts of Interest

- None to declare

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