Core Outcome Sets Specifically for Longterm Observational Studies: OMERACT Special Interest Group Update in Rheumatoid Arthritis

Maria A. Lopez-Olivo, José B. Negrón, Richard J. Zogala, Loreto Carmona, Karla Criner, Niti Goel, Laura Gonzalez-Lopez, Francesca Ingegnoli, Amye Leong, Lyn March, Beverly Shea, Vibeke Strand, Peter Tugwell, Tiffany Westrich-Robertson, Natalia V. Zamora, Robin Christensen, and Maria E. Suarez-Almazor

ABSTRACT. ***Objective.*** This is an update from the Outcome Measures in Rheumatology (OMERACT) Core Outcomes in Longterm Observational Studies Special Interest Group with a focus on rheumatoid arthritis.

Methods. Preliminary data and proposed next steps were outlined and discussed by participants.

Results. Domains identified after initial steps (systematic review and qualitative research) were pain, physical functioning, participation (i.e., work, social), longterm symptoms, fertility/family planning, emotional well-being, coping, financial status, and adverse events including death.

Conclusion. The group agreed conceptually that short-term core outcomes could be different from longer term ones. Participants emphasized the importance of analyzing the need for core domains specifically for longterm longitudinal observational studies. (First Release March 1 2019; J Rheumatol 2019;46:1164–7; doi:10.3899/jrheum.181076)

Key Indexing Terms:
OBSERVATIONAL STUDIES REGISTRIES RHEUMATOID ARTHRITIS
OUTCOME ASSESSMENT OMERACT

From the Section of Rheumatology and Clinical Immunology, University of Texas MD Anderson Cancer Center; Department of Medicine-Immunology, Allergy & Rheumatology, Baylor College of Medicine, Houston, Texas; Kezar Life Sciences, San Francisco; Healthy Motivation, Santa Barbara; Division of Immunology and Rheumatology, Stanford University, Palo Alto, California; Division of Rheumatology, Duke University School of Medicine, Durham, North Carolina; International Foundation for Autoimmune and Autoinflammatory Arthritis, St. Louis, Missouri, USA; Global Alliance for Musculoskeletal Health of the Bone and Joint Decade, Truro, Cornwall, UK; Instituto de Salud Musculoesqueletica, Madrid, Spain; Universidad de Guadalajara, Guadalajara, Mexico; Division of Clinical Rheumatology, G. Pini Hospital, Università degli Studi di Milano, Milan, Italy; Institute of Bone and Joint Research, Sydney Medical School, University of Sydney, Sydney, Australia; Division of Rheumatology, Department of Medicine, and School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa; Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada; Instituto de Rehabilitacion Psicofisica, Buenos Aires, Argentina; Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital; Department of Rheumatology, Odense University Hospital, Odense, Denmark.

The Parker Institute is supported by grants from The Oak Foundation.

M.A. Lopez-Olivo, MD, PhD, Section of Rheumatology and Clinical Immunology, University of Texas MD Anderson Cancer Center; J.B. Negrón, MSc, Instituto de Salud Musculoesqueletica; R.J. Zogala, MD, Section of Rheumatology and Clinical Immunology, University of Texas MD Anderson Cancer Center; L. Carmona, MD, PhD, Instituto de Salud Musculoesqueletica; K. Criner, MD, Department of Medicine-Immunology, Allergy & Rheumatology, Baylor College of Medicine; N. Goel, MD, PhD, Kezar Life Sciences, and Division of Rheumatology, Duke University School of Medicine; L. Gonzalez-Lopez, MD, MSc, PhD, Universidad de Guadalajara; F. Ingegnoli, MD, PhD, Division of Clinical Rheumatology, G. Pini Hospital, Università degli Studi di Milano; A. Leong, MBA, Healthy Motivation and the Global Alliance for Musculoskeletal Health of the Bone and Joint Decade; L. March, MBBS, MSc, PhD, FRACP, FAFPHM, Institute of Bone and Joint Research, Sydney Medical School, University of Sydney; B. Shea, PhD, Division of Rheumatology, Department of Medicine, and School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, and Clinical Epidemiology Program, Ottawa Hospital Research Institute; V. Strand, MD, MACR, FACP, Biopharmaceutical Consultant, Portola Valley, California, USA; P. Tugwell, OC, MD, FRCPC, Division of Rheumatology, Department of Medicine, and School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, and Clinical Epidemiology Program, Ottawa Hospital Research Institute; T. Westrich-Robertson, BS, International Foundation for Autoimmune and Autoinflammatory Arthritis; N.V. Zamora, MD, Instituto de Rehabilitacion Psicofisica; R. Christensen, MSc, PhD, Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital, and Department of Rheumatology, Odense University Hospital; M.E. Suarez-Almazor, MD, PhD, Section of Rheumatology and Clinical Immunology, University of Texas MD Anderson Cancer Center.

Address correspondence to Dr. M.E. Suarez-Almazor, 1515 Holcombe Blvd., Unit 1467, Houston, Texas, USA. E-mail: msalmazor@mdanderson.org

Accepted for publication December 18, 2018.

The Outcome Measures in Rheumatology (OMERACT) initiative has designed strategies to improve and standardize how outcomes are reported in studies related to rheumatic diseases[1]. Initially, OMERACT created a framework for outcome measures applicable to randomized clinical trials (RCT) and longitudinal observational studies (LOS); the current OMERACT Filter 2.0 provided a broader framework that expands the core outcome set into core outcome domains (the "what") and core outcome instruments (the "how")[2]. A

working group was established in 2014 and presented at OMERACT 2016 as a special interest group (SIG) to identify, classify, and evaluate the need for domains relevant to patients that should be collected in longterm LOS to better characterize the essence of living with a chronic condition[3].

We report a summary of the 2018 SIG meeting in which preliminary results were presented to facilitate discussion. The aim was to propose and agree upon next steps needed to identify longterm domains for patients with rheumatic diseases. To limit the scope of the preparatory work, it was agreed that the SIG would initially target longterm outcomes in studies among people with rheumatoid arthritis (RA).

MATERIALS AND METHODS

The LOS Working Group's proposed protocol follows the OMERACT handbook methodology to develop a core domain set[4]. The first step, i.e., a review of the key areas of health to identify previously collected and reported domains in registries and LOS, is near completion. Qualitative interviews are also being conducted of patients and their caregivers or nearest support person, followed by surveys of patients, clinicians, researchers, and others to identify candidate domains. The second step involves the development of a conceptual framework and taxonomy for identification and classification of domains within the structure proposed by OMERACT, and it is ongoing[2]. This will be followed by a Delphi process to select domains and core contextual factors. The final step is to formulate a draft core domains set.

RESULTS

At the 2018 OMERACT meeting, the 1.5-hour SIG session was open to all conference attendees. There were 27 participants [4 patient research partners (PRP), 16 clinicians, 6 researchers, and 1 industry representative]. We presented results from the systematic review with an extensive discussion of the preliminary analysis[5,6]. During the meeting, we also presented an overview of another core set developed by the European League Against Rheumatism task force[7] for registries and prospective LOS in RA. Participants agreed this set lacked important domains with specific relevance to longterm outcomes that patients worry about. The last presentations reported the findings of preliminary patient and caregiver interviews. Participants noted the importance of conducting qualitative studies to achieve the expected aims.

Systematic review of RA patient registries and LOS. The objective of the systematic review was to identify registries and LOS including individuals with RA to identify what outcomes are systematically collected to create a list of outcomes important to researchers[5,6]. We have included registries and LOS reporting on patients with RA, evaluating clinical or patient-centered outcomes, with at least one publication written in English in the past 5 years. We identified 95 registries and LOS searching through Google (using the names of each United Nations member state) and registry databases [i.e., Agency for Health Care Research and Quality (AHRQ) Registry of Patient Registries[8] and ClinicalTrials.gov] using terms related to RA and LOS. The selection of registries and LOS, data collection, and quality appraisal are being performed by 2 independent reviewers, followed by consensus or third-party adjudication as needed. We retrieved information on the data collected by each registry/LOS by conducting searches of the Medline and EMBASE databases[5,6].

We identified 2 major types of registry/LOS: those primarily collecting information on patients with RA irrespective of therapy (condition-based), and those collecting information primarily related to RA therapy (therapy-based; e.g., biologic registries). We used an AHRQ guide developed to appraise registries[9]; the majority (57%) consisted of condition-based registries/LOS (54 studies)[5,6].

Most registries (98%) reported the collection of at least 1 disease activity measure or composite index. The most commonly reported disease activity outcome across all continents was the Disease Activity Score at 28 joints (DAS28) or a derivation of this score such as DAS66 or DAS44. The most common patient-reported outcome was physical functioning with 69% of the condition-based registries and 49% of the therapy-based registries, followed by health-related quality of life, pain, sleep, fatigue, stiffness, and depression. Few registries/LOS reported collection of variables to determine socioeconomic status. Over two-thirds (68%) reported collection of comorbidities. Most registries reported at least 1 disease activity measure (94% for condition-based and 90% therapy-based registries/LOS). Safety measures were reported more frequently in therapy-based versus condition-based registries/LOS (100% vs 35%)[5,6].

1. Ongoing Activities

Qualitative interviews of patients with RA and their caregivers/nearest support person. We are conducting interviews to evaluate which specific longterm outcomes are important to patients with RA and how they affect their lives. We are including patients with disease duration of 5 to 15 years from onset of symptoms. The interviews are being conducted in Argentina, Australia, Italy, Mexico, Spain, and the United States. The specific themes being analyzed include symptoms, limitations, and other manifestations of RA that patients find to be most significant/limiting in their daily life. Caregivers will respond to the same questions as patients. To better understand patient perspectives, we are also interviewing the patients' primary caregiver. It has been shown that caregivers often adopt an advocacy role and can use their practical experience to provide insightful information of the disease manifestations to promote health and well-being[10]. This perspective is enriching when trying to understand feared longterm outcomes. The SIG meeting participants agreed that both voices were relevant to expand upon the patient's experience and worries.

Table 1 shows the several areas of interest identified in the interim content analysis of the first 17 patients interviewed and the experience a PRP shared as a moderator of patient discussions using Facebook.

Participants in the SIG emphasized the need to be cognizant of how longterm outcomes are collected, taking

Table 1. Preliminary qualitative findings. Summary of domains identified.

Topics Analyzed	Patients Interviewed, n = 17	Patient Partner Representative Shared Experience of Online Discussions in a Social Network
Social function and participation	Perform optimally societal roles	Concerns about overarching symptoms, physical functioning, pain changes over time (i.e., inflammatory vs mechanical: "damage pain will not go away")
Physical function and symptoms, daily activities	Concerns about their ability to independently perform physical activities (e.g., interference with eating, personal hygiene, and fear of becomomg bedridden)	
Fear of complications	Fertility/family planning, death, damage to vital organs (e.g., lung, heart, and kidney complications)	
Financial status		Concerns about financial problems
Psychological/emotional well-being	Concerns including emotional well-being (e.g., depression, self-esteem, and fears) and coping (e.g., sense of humor, dependence on physician)	Coping (differs with time)
Therapy-related	Adverse events	Longterm effect of treatments (i.e., treatment influences symptoms in the longterm, vision loss)

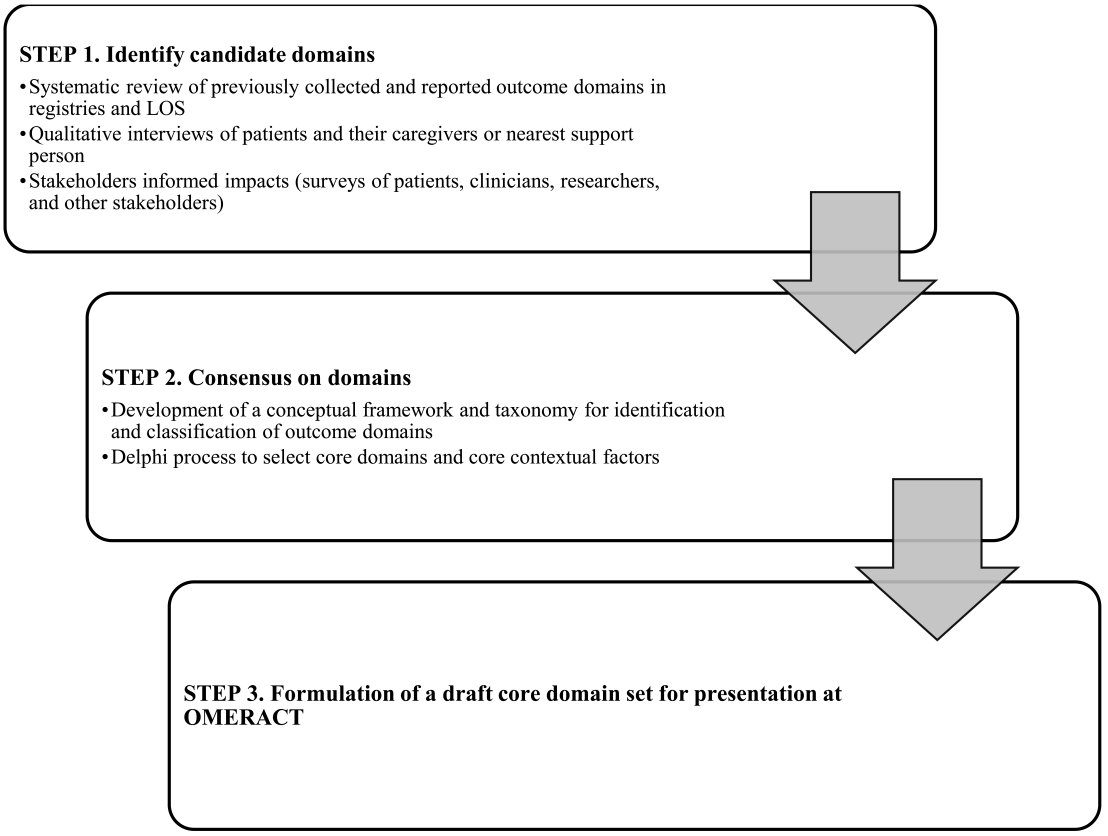

Figure 1. Study design. OMERACT: Outcome Measures in Rheumatology; LOS: longitudinal observational studies.

into account the stage of the patient's disease. Thus, participating patients mentioned an "identity crisis" occurring in patients within 5 years of diagnosis, with different concerns about their health compared to those patients with longstanding disease. There was further discussion on 3 different categories: patient-centered longterm effects, clinician-informed effects (identifying core areas such as life impact, pathophysiological, and adverse events), and other variables/domains needed for longterm observational studies (i.e., suspected mediators, covariates, and effect modifiers).

The domains resulting from these conversations will be mapped to the 4 core areas covered in the OMERACT core domain set (life impact, pathophysiological manifestations, death, and resource use).

2. Future Steps

Clinician-informed effects. Registry representatives, practitioners, and other health professionals will be interviewed in Spain, the United States, and Australia about important areas of concern such as life impact, pathophysiological manifestations, and resource use.

Consensus on domains. After identification of preliminary core domains, we will use Delphi consensus methods to agree on the preliminary inclusion of domains within the OMERACT onion model, assigning them to the inner, middle, and research core, respectively.

Formulation of a draft core domain set. Once the relevant domains are identified, we will formulate a core domain set that will be placed according to the onion model. Then the set will be submitted to the Technical Advisory Group and for final vote at an OMERACT meeting.

DISCUSSION

The first aim of this initiative has been to identify reported outcomes in international RA patient registries/LOS through a systematic review. We found that there are differences in the methodology reported, with few registries publishing a protocol for data collection. We also found significant heterogeneity in data collection and variability in the instruments used to define various domains. The most commonly reported outcomes included disease activity, physical functioning, pain intensity, and mortality.

Ongoing qualitative research reveals which specific outcomes are critical for patients with RA in the longterm. Preliminary identified domains currently included in the core set for RCT are physical functioning, pain, and adverse events including mortality. Those identified by participants not routinely included in RCT and not part of RA core sets are participation (i.e., work and social), longer-term life events such as fertility/family planning, emotional well-being, coping, and financial status.

The duration of longterm followup has not been specifically defined by our group, and will be discussed and defined by consensus as we continue to gather information from participants. At face value we considered as longterm those registries or studies planning to collect data on each individual participant for a minimum of 2 years.

We will continue to expand on our work identifying variables relevant to patients with RA through our systematic review of registries, qualitative work, and surveys. Our overarching goal is to achieve a core set of critical outcomes specifically to collect in registries/LOS of patients with RA through domain definition, prioritization, and final OMERACT consensus.

ACKNOWLEDGMENT

We thank the patient research partners and the participants for their valuable input at the OMERACT 2018 meeting.

REFERENCES

1. Boers M, Tugwell P, Felson DT, van Riel PL, Kirwan JR, Edmonds JP, et al. World Health Organization and International League of Associations for rheumatology core endpoints for symptom modifying antirheumatic drugs in rheumatoid arthritis clinical trials. J Rheumatol Suppl. 1994 Sep;41:86-9.
2. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. J Clin Epidemiol 2014;67:745-53.
3. Zamora NV, Christensen R, Goel N, Klokker L, Lopez-Olivo MA, Kristensen LE, et al. Critical outcomes in longitudinal observational studies and registries in patients with rheumatoid arthritis: an OMERACT special interest group report. J Rheumatol 2017;44:1894-8.
4. Boers M, Kirwan JR, Tugwell P, Beaton D, Bingham CO III, Conaghan PG, et al. The OMERACT Handbook. [Internet. Accessed January 14, 2019.] Available from: https://omeract.org/resources
5. Zamora NV, Lopez-Olivo MA, Christensen R, Goel N, Kristensen LE, Strand V, et al. Environmental scan of rheumatoid arthritis patient registries around the world: an OMERACT initiative [abstract]. Arthritis Rheumatol 2016;68 Suppl 10:abstract 1221.
6. Zogala R, Criner K, Lopez-Olivo MA, Zamora N, Rai D, Pratt G, et al. Patient-reported outcome measures used in rheumatoid arthritis cohorts and registries around the world: An environmental scan from the outcome measures in rheumatology critical outcomes in longitudinal observational studies working group [abstract]. Arthritis Rheumatol 2018:2480.
7. Dixon WG, Carmona L, Finckh A, Hetland ML, Kvien TK, Landewe R, et al. EULAR points to consider when establishing, analysing and reporting safety data of biologics registers in rheumatology. Ann Rheum Dis 2010;69:1596-602.
8. Agency for Healthcare Research and Quality. Registry of patient registries. [Internet. Accessed September 11, 2018.] Available at https://patientregistry.ahrq.gov
9. Registries for evaluating patient outcomes, 3rd edition: a user's guide. Gliklich RE, Dreyer NA, Leavy MD, editors. Rockville, MD: Agency for Healthcare Research and Quality; 2007.
10. Kelland K, Hoe E, McGuire MJ, Yu J, Andreoli A, Nixon SA. Excelling in the role of advocate: A qualitative study exploring advocacy as an essential physiotherapy competency. Physiother Can 2014;66:74-80.