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Development of a patient-centered core domain set for prospective observational longitudinal outcome studies in rheumatoid arthritis: an OMERACT initiative

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ABSTRACT

Objectives: To identify patient-centered core domains for prospective longitudinal observational studies (LOS) in rheumatoid arthritis.

Methods: Our working group held a virtual meeting in November 2020 to review data from a literature review and patient qualitative interviews, and to discuss strategies to move forward on domain identification and selection using the OMERACT 2.1 domain selection process.

Results: Important candidate domains and subdomains were identified including in the areas of life impact. Consensus was reached on moving forward with a Delphi process.

Conclusions: The meeting provided future directions to identify and select a core set of domains for use in LOS.

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The 'Outcome Measures in Rheumatology' (OMERACT) initiative has developed strategies to improve outcome measurement through a data-driven, consensus process involving relevant stakeholder groups [1]. OMERACT strives to standardize outcomes for rheumatic diseases with an initial focus on randomized controlled trials (RCTs) [2,3]. However, RCTs are usually of short duration, have defined

inclusion criteria for participants, and are conducted in controlled settings, all of which potentially limit generalization to broader communities of patients [4].

On the other hand, pragmatic, real-world evidence in non-randomized studies, can be complementary to RCTs by focusing on judgments about the population, intervention, comparison, and outcomes, in real-world settings [5]. Prospective longitudinal studies (LOS) can determine the effectiveness of interventions, identify rare adverse events not seen in RCTs, and most importantly, evaluate outcomes over a long-term. Due to the differences between RCTs and LOS, core outcome domains and instruments developed for RCTs of

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patients with RA may not capture concepts that are relevant to patients and providers over a longer term.

In an effort to standardize outcomes in LOS, we established the Patient Outcomes in Longitudinal Observational Studies (POLOS) Working Group and held a Special Interest Group (SIG) at OMERACT 2016, with the goal to identify patient-centered outcome domains to be used in longitudinal studies of patients with rheumatic diseases [7–9]. At that meeting, a decision was made to initially focus efforts on RA [6]. Our working group includes clinicians, researchers, fellows, patients, and industry representatives. At OMERACT 2018, we presented preliminary results of a systematic review of existing registries and LOS of patients with RA, which shows that patient-reported outcomes are not consistently reported and set the agenda for next steps [6].

The POLOS SIG met virtually in 2020 to discuss work to date and develop a framework for moving forward toward Core Domain Set development and endorsement. The purpose of this manuscript is to describe the discussion and working plan resulting from this meeting.

Materials and methods

The POLOS SIG virtual session took place November 11, 2020 at 14:00 central standard time, over Zoom. It lasted 60 minutes (15 minutes presentation, 45 minutes discussion). Registration was open to all OMERACT members. Discussions were led by a moderator (MSA), with questions posed via chat. A summary of the work conducted to date was presented, including the systematic review of registries previously published, and an overview of domains and subdomains identified from qualitative interviews of patients with RA and caregivers [6,10]. The presentation was followed by a guided discussion pertaining to the future direction and strategies to prioritize candidate domains following OMERACT methods [11]. Finally, polling (through Zoom) was conducted to reach consensus (simple majority) on specific methodological issues.

Results

Forty-six individuals (10 clinicians, 1 fellow, 13 researchers, 14 patients, 11 other/no response) participated in the virtual SIG.

Systematic review of the literature

We discussed the results of the systematic review on outcomes in LOS in RA [6]. Eighty-eight registries were identified worldwide. We found that LOS frequently collected disease activity, physical function, and a limited number of specific symptoms such as pain.

However, only 42% of LOS collected health-related quality of life data. Of these, only 33% ascertained mental health, and 23% social health. In previous discussions at OMERACT 2016, the participants at the SIG agreed that mental and social domains were among the most important aspects of long-term well-being for people with RA [7].

Qualitative interviews

We presented a summary of the results from individual qualitative interviews of patients with RA and related caregivers. These findings have not yet been published (manuscript being submitted). Patients with RA for at least five years were recruited from rheumatology clinics. This duration of disease was chosen to include patients with long-term experience of living with RA. Seven patients agreed to have a caregiver interviewed. Caregivers were interviewed on their own. Themes to identify candidate domains and subdomains for interviews were discussed at our SIG meeting in 2016, and followed the OMERACT Filter 2.1 framework [12]. These included: overall life impact, symptoms and physical function, social function/participation, work and related activities, financial status, mental well-being, and concerns with therapy. Participants were interviewed by an investigator in each country using broad open-ended questions exploring these themes. We included patients from 3 continents, predominantly women ($n = 23$, 83%) older than 50 years of age ($n = 21$, 72%) with long-standing RA. Three researchers (MSA, LC, MALO), working independently in pairs (two researchers assigned to each transcript), reviewed all transcripts and identified candidate domains and subdomains that were categorized into the core areas proposed by OMERACT including pathophysiological manifestations, life impact, resource use, and contextual factors [12,13]. The final classification was agreed upon by consensus. A sample of pertinent candidate domains for each core area is shown in Table 1.

Notable findings included:

- i Considerable importance on the impact of social and mental aspects on overall quality of life.
- ii Within physical function, there was an emphasis on complex activities (e.g., cooking, housework) versus simple activities such as lifting a cup or carrying a bag; while the latter are commonly included in instruments measuring physical function, they seemed less relevant to patients.
- iii In addition to identifying specific task or activities hindered by physical mobility, participants also noted quality of mobility in general (e.g., slow, clumsy, dependent).
- iv Some candidate domains, such as work participation, were identified as affecting multiple core areas (physical, mental, social and financial).

Table 1
Identified domains and subdomains from the qualitative interviews.

Core Area	Domain	Subdomains
Disease manifestations and abnormalities	Symptoms	Pain, fatigue, anxiety, depression, stress
	Comorbidities and organ damage	Joint damage, infections, fertility, consequences of surgery, adverse events of medications, organ damage
Life Impact	Physical	Grooming and dressing, housework, work, sexual life Quality of mobility (slowness, clumsiness)
	Emotional/mental	Distress, depression, anxiety, mixed moods
	Social participation	Work loss, absenteeism, presenteeism
		Community participation, family activities, losing friends Leisure activities (solitary or in group)
Death/Lifespan	Utility	Loss of income, increasing costs, future financial concerns related to ability to work
	Mortality	Overall mortality, disease-specific mortality, treatment-related mortality
Societal/Resources	Health care utilization costs	Out of pocket costs, costs of medical care, costs for other health needs (e.g. psychological support)
Contextual factors	Personal	Age, health literacy, financial dependence of others, coping, lifestyle risk factors
	Environmental	Insurance coverage, availability of medications, type of work, work adaptations, family support

- v Barriers to leisure activities were as important for group activities as for those performed alone (e.g., sports, crafts).
- vi Concerns about harms from medications and potential organ damage.

Consensus on methodology

Participants in the virtual SIG generally felt that the activities conducted to identify candidate patient-centered domains and subdomains through the systematic review and qualitative interviews were comprehensive. They agreed that the next step should be to prioritize candidate domains via the Delphi process, in preparation for voting at OMERACT 2022.

After discussion, it was agreed that Delphi participants should include: (a) principal investigators or corresponding authors of registries around the world identified through the systematic review, (b) members of the European League Against Rheumatism (EULAR) Registries and Observational Studies (RODS), and (c) OMERACT membership including patients, clinicians, researchers, and industry.

Participants at the SIG meeting were polled about methodology issues moving forward. The questions and responses are shown in Table 2. The first polling question was in relation to screening and selecting Delphi participants to those who conduct research or live with inflammatory arthritis; 70% of respondents agreed with filtering participants. Subsequent polling questions were regarding the content of the survey, with emphasis on the first round. Participants agreed that all subdomains identified in the qualitative interviews should be included in the first round, as opposed to lumping several themes together (e.g., considering together depression and sadness). They strongly felt that the first round should use wording as stated by the patients. Most participants preferred that candidate domains/subdomains be not categorized according to their respective core areas for the first round. However, if core areas were specified later on, the majority (59%) chose to have overlapping subdomains included under each core area. Most participants (67%) agreed that for specific items describing activities within candidate domains it would be best to prioritize complex tasks (e.g. shopping) vs. more simple tasks (e.g. carrying a bag). Finally, there was some discussion about inclusion of contextual factors in the initial Delphi survey. The majority felt that as there is another working group in contextual factors for rheumatic diseases studies in general, we should wait for the work of this group to inform us [14].

Table 2
Polling questions during SIG meeting.

Question	Yes, n (%) ^a
1 Do you agree with screening/filtering question for participants – Do you participate or use research on long-term studies of inflammatory arthritis or live with the disease?	26 (70)
1 Should we include in first Delphi round all areas identified by patients, or should we attempt to lump them? (Yes, is include all areas identified by patients)	29 (76)
1 Given that there is some overlap, should domains/subdomains be included in first Delphi round under core areas (e.g., depression as symptom and as mental impact)?	12 (32)
1 For some activities, should we prioritize complex vs. simple activities – lift a cup vs. eating, carrying a bag vs. grocery shopping?	22 (67)
1 If we categorize domains under core areas should we include overlapping domains more than once under each relevant core?	20 (59)
1 Should we include contextual factors in this initial Delphi survey?	14 (42)

^a Although there were 46 participants, not all 46 participants responded to each of these questions. Percentage estimated over denominator of those who responded.

Future steps

We are planning three Delphi rounds, to achieve an acceptable and parsimonious number of candidate core domains through the OMERACT consensus agreement process [13]. Selected domains and subdomains will be submitted for a final vote at OMERACT 2022, categorized into three groups: 1) core, 2) important but not core, and 3) research agenda [11,13].

Discussion

Our ultimate goal is to identify a core set of patient-centered domains that are relevant to patients with RA, and considered important for LOS [13]. Various stakeholder groups support this initiative. The qualitative interviews with patients and caregivers emphasized life impact themes, especially with respect to social participation, work, and mental well-being, but also emphasizing financial and healthcare burdens. Moreover, many of the areas identified by patients as relevant to them through interviews were seldom measured in LOS as shown in our systematic review. Finally, the SIG discussion established strategies to move forward with respect to the methods to reach consensus. Once a core set is approved by OMERACT, we will identify and select instruments to assess the core domains, that are valid, discriminative, and feasible to be recommended in observational research to assess the long-term effectiveness of interventions.

Declaration of Competing Interest

LC has not received fees or personal grants from any pharmaceutical companies, but her Institute performs contract work for pharmaceutical companies including Abbvie Spain, Eisai, Gebro Pharma, Merck Sharp & Dohme España, S.A., Novartis Farmaceutica, Pfizer, Roche Farma, Sanofi Aventis, Astellas Pharma, Actelion Pharmaceuticals España, Grünenthal GmbH, and UCB Pharma

LM – Honorarium for speaker fees in past 3 years from Pfizer, Abbvie, Eli Lilly, Novartis; grants from Janssen, Roche. All unrelated to this work. Member of OMERACT Exec which receives current educational grants from 9 companies.

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MSA – Past consultant for Pfizer, AbbVie, Eli Lilly, Agile Therapeutics, AMAG Pharmaceuticals, Gilead, Avenue Therapeutics, and ChemoCentryx, all unrelated to the topic of this paper. Member of Celgene advisory board. All activities unrelated to this work.

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