The Journal of Rheumatology 2021;48:1480–7
doi:10.3899/jrheum.201568
First Release July 15 2021

The Journal of Rheumatology

Patient Perspectives on Outcome Domains of Medication Adherence Trials in Inflammatory Arthritis: An International OMERACT Focus Group Study

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ABSTRACT. ***Objective.*** To describe the perspectives of patients with inflammatory arthritis (IA) on outcome domains of trials evaluating medication adherence interventions.

Methods. Adult patients (≥ 18 yrs) with IA taking disease-modifying antirheumatic drugs from centers across Australia, Canada, and the Netherlands participated in 6 focus groups to discuss outcome domains that they consider important when participating in medication adherence trials. We analyzed the transcripts using inductive thematic analysis.

Results. Of the 38 participants, 23 (61%) had rheumatoid arthritis and 21 (55%) were female. The mean age was 57.3 ± (SD 15.0) years. Improved outcome domains that patients wanted from participating in an adherence trial were categorized into 5 types: medication adherence, adherence-related factors (supporting adherence; e.g., medication knowledge), pathophysiology (e.g., physical functioning), life impact (e.g., ability to work), and economic impact (e.g., productivity loss). Three overarching themes reflecting why these outcome domains matter to patients were identified: how taking medications could improve patients' emotional and physical fitness to maintain their social function; how improving knowledge and confidence in self-management increases patients' trust and motivation to take medications as agreed with minimal risk of harms; and how respect and reassurance, reflecting health care that values patients' opinions and is sensitive to patients' individual goals, could improve medication-taking behavior.

Conclusion. Patients value various outcome domains related to their overall well-being, confidence in medication use, and patient–healthcare provider relationships to be evaluated in future adherence trials.

Key Indexing Terms: clinical trials, medication adherence, OMERACT, outcome and process assessment, qualitative research, rheumatic diseases

This project was supported by a 2020 Arthritis Australia Project Grant (Marion A Simpson Grant funded by the Estate of the Late Marion Alice Simpson).

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The authors declare no conflicts of interest relevant to this article.

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Accepted for publication May 10, 2021.

Optimal medication adherence is crucial for improved clinical and health outcomes.[1,2] Medication adherence is defined as "the process by which patients take their medication as prescribed."[3] For rheumatic diseases, however, up to 85% of the patients do not fully adhere to their medication regimen.[4,5,6] Although numerous clinical trials have been conducted in rheumatology to improve medication adherence and thereby clinical and health outcomes, few have demonstrated meaningful improvements.[7] Further, outcome domains and adherence measures included in studies on medication adherence are heterogeneous.[8,9,10,11] There is an urgent need for consensus on a minimum core domain set that matters to patients that should be measured in each adherence trial to reduce inconsistent and selective reporting and improve comparison of interventions.[12]

The Outcome Measures in Rheumatology (OMERACT) Adherence Working Group[13] is currently developing a core domain set for trials of medication adherence interventions in patients with rheumatic diseases.[14,15,16] The group consists of patients, healthcare professionals (HCPs), researchers, and other stakeholders. Their activities comprise the following: (1) a systematic literature review of outcome domains in medication adherence intervention trials in rheumatology[8]; (2) interviews with patients and caregivers to identify their views on core domains; (3) nominal group technique with patients and caregivers to prioritize outcome domains[17]; (4) an international modified Delphi study to define a preliminary core domain set; and (5) a consensus workshop to finalize a core domain set.[14] Within OMERACT, the patients' perspective is central in developing relevant information on core outcome domains as the ultimate aim is to improve outcomes for patients.[18] Hence, it is essential to study the patient perspective in depth to facilitate the development of a patient-centered core domain set for medication adherence interventions. This study aimed to describe the perspectives of patients with inflammatory arthritis (IA) on outcome domains of trials evaluating medication adherence interventions.

METHODS

Design and setting. We conducted focus groups with a descriptive explanatory design in Australia, Canada, and the Netherlands between September 2019 and February 2020.[19] Focus groups were chosen as this enables in-depth discussion between participants and comprehensive data collection.[20] Six patient research partners (PRPs) with IA were members of the Working Group and involved in the study design. COnsolidated criteria for REporting Qualitative research (COREQ) guideline was used to guide the methods and reporting.[21]

Participants. Adult patients (≥ 18 yrs) with IA (i.e., ankylosing spondylitis [AS], psoriatic arthritis [PsA], rheumatoid arthritis [RA], undifferentiated IA) who were taking ≥ 1 disease-modifying antirheumatic drug (DMARD) and were proficient in the local language (English or Dutch) were eligible to participate in this study.

Eligible patients were invited to participate in a focus group. Patients were recruited either by clinicians (Australia, in 1 public hospital [Liverpool Hospital]), pharmacists (the Netherlands, in 1 specialized rheumatology clinic [Sint Maartenskliniek] and 1 academic hospital [Radboud University Medical Center, Radboudumc]) or through a research center (Canada, Arthritis Research Canada's Arthritis Patient Advisory Board). Interested patients received study information verbally or in writing and were asked to complete a questionnaire with demographic and clinical variables, including age, sex, level of education, type of IA, duration of arthritis, and current DMARDs. Characteristics of participants were shared with all sites to allow for purposive sampling to ensure a heterogeneous group of participants across all focus groups.

Data collection. A question guide was developed with OMERACT working group members, including PRPs, based on their expertise with medication adherence and outcome domain research, and translated from English into Dutch by researchers (CLB, BJvdB, MSV) from the Netherlands. The interview guide was pilot tested in each language on comprehensiveness and interpretation by a patient with IA who was using a DMARD.

Using the question guide, participants were encouraged to discuss outcome domains that are important to them when participating in a study evaluating an adherence intervention. Participants were given examples of adherence interventions to facilitate the discussion (e.g., counseling program, electronic reminders). Items included were as follows: "what do you expect to achieve if you take your medication properly," "which negative consequences do you foresee if you do not take your medication properly," "what do you hope to achieve if you take your medication properly," "what do you expect if you participate in an adherence intervention, both positive and negative," "how do we know that an intervention will work on adherence," and "what would be important to measure to see if it works on adherence?"

All focus groups were led by an experienced qualitative researcher; an assistant observed the discussion and took field notes. Focus groups were conducted in meeting rooms within a hospital or research institute and lasted approximately 2 hours. Discussions were audiotaped and transcribed verbatim. Participants were offered travel reimbursement and a stipend to attend the focus group.

Data analysis. Potential trial outcome domains that were important to patients were extracted from the transcripts and categorized. To identify outcome domains that were important to patients, inductive thematic analysis was applied in an iterative manner by constantly comparing the data and analysis.[22] First, 3 researchers (CLB, AK, SB) created a preliminary coding framework that was discussed with coauthors (BJvdB and AT) based on 1 transcript. Thereafter, the initial coding framework was applied to all transcripts, allowing for new categories and (sub)themes to be identified. CLB, AK, and SB read the transcripts to familiarize themselves with the data. Text fragments of meanings were identified and labeled with codes. These were grouped into categories and subthemes, and finally, overarching themes were explored. Each transcript was coded by 1 researcher and reviewed by a second experienced qualitative researcher (Australia: SB and AK; Canada and the Netherlands: CLB and BJvdB). Arbitrary codes were discussed until consensus was reached. Initial analysis of Dutch transcripts occurred in the local language. Identified categories and (sub)themes were translated into English (CLB). All results were merged and discussed until consensus was achieved on the final coding framework. Data were collected until data saturation, when no new themes emerged from subsequent focus groups.

Ethics. Ethical approval was obtained from local research ethics committees (Radboudumc, no. 2019-5525; South Western Sydney, local health district no. 2019/ETH12710; University of British Columbia, no. H19-04037). All patients gave written informed consent for participation.

RESULTS

Six focus groups were held (the Netherlands: n = 2; Australia: n = 3; Canada: n = 1), each with 4–10 participants. In total 38 patients participated, with RA (n = 23), AS (n = 11), and PsA (n = 8). Twenty-one (55%) were female and participants had a mean (SD) age of 57.3 (15.0) years. Patient characteristics are shown in Table 1.

Patients discussed 5 types of outcome domains that they considered important when participating in an adherence trial.

Table 1. Characteristics of participants.

	Total, n = 38	Group 1, Netherlands, n = 9	Group 2, Netherlands, n = 10	Group 3, Australia, n = 7	Group 4, Australia, n = 4	Group 5, Australia, n = 3	Group 6, Canada, n = 5
Sex, female	21 (55.3)	6 (66.7)	4 (40.0)	4 (57.1)	2 (50.0)	2 (66.7)	3 (60.0)
Age, yrs, mean ± SD	57.3 (± 15.0)	64.3 (5.3)	64.4 (19.8)	54.9 (9.7)	47.8 (13.5)	42.0 (6.6)	50.8 (16.3)
Educational level							
Low	7 (18.4)	2 (22.2)	4 (40.0)	–	1 (25.0)	1 (33.3)	–
Middle	13 (34.2)	3 (33.3)	3 (30.0)	3 (42.9)	1 (25.0)	1 (33.3)	2 (40.0)
High	14 (36.8)	4 (44.4)	3 (30.0)	2 (28.6)	2 (50.0)	1 (33.3)	3 (60.0)
Unknown	–	–	–	2 (28.6)	–	–	–
Type of IA[a]							
AS	11 (28.9)	1 (11.1)	2 (20.0)	2 (28.6)	2 (50.0)	3 (100.0)	1 (20.0)
PsA	8 (21.1)	1 (11.1)	6 (60.0)	–	–	–	1 (20.0)
RA	23 (60.5)	7 (77.8)	6 (60.0)	5 (71.4)	2 (50.0)	–	3 (60.0)
Disease duration, yrs, median (range)	10 (2–65)	20 (7–55)	12.5 (3–65)	10 (5–25)	14 (2–19)	5 (5–10)	8 (5–33)
DMARD use,[a] n (%)							
Adalimumab	9 (23.7)	3 (33.3)	4 (40.0)	1 (14.3)	1 (25.0)		
Certolizumab pegol	1 (2.6)					1 (33.3)	
Etanercept	5 (13.2)	2 (22.2)	2 (20.0)		1 (25.0)		
Golimumab	2 (5.3)	1 (11.1)			1 (25.0)		
Hydroxychloroquine	5 (13.2)			3 (42.9)			2 (40.0)
Infliximab	2 (5.3)		1 (10.0)	1 (14.3)			
Leflunomide	2 (5.3)			1 (14.3)	1 (25.0)		
Methotrexate	16 (42.1)	7 (77.8)	9 (90.0)	4 (57.1)	1 (25.0)	1 (33.3)	2 (40.0)
Secukinumab	3 (7.9)				1 (25.0)	2 (66.7)	
Sulfasalazine	4 (10.5)			1 (14.3)	1 (25.0)		2 (40.0)
Tocilizumab	3 (7.9)	1 (11.1)					2 (40.0)

Values are expressed as n (%) unless otherwise indicated. [a] Participants could report multiple answers and therefore the sum exceeds 100%. AS: ankylosing spondylitis; DMARD: disease-modifying antirheumatic drug; IA: inflammatory arthritis; PsA: psoriatic arthritis; RA: rheumatoid arthritis.

Some of these outcome domains were related to factors that might support adherence (placed in a category called "adherence-related factors"; e.g., medication knowledge, individualized support). Other outcome domains included improving medication adherence itself, and likely benefits of adherence such as improved pathophysiology (i.e., physical and psychological health), life impact (e.g., ability to work), and economic impact (e.g., productivity loss; Table 2).

We identified 3 overarching themes reflecting the reasons why these outcome domains matter to patients: protecting and enhancing emotional, physical, and social well-being; improving knowledge of and confidence in self-management; and respect and reassurance in care (Figure 1). Below we elaborate on these 3 overarching themes.

Protecting and enhancing emotional, physical and social well-being.

1. *Motivated to maintain function*. Patients valued health outcome domains in relation to a medication adherence trial as they felt embarrassed, humiliated, and exhausted with their pain and the lack of physical mobility that their condition caused. They also felt that their cognitive function deteriorated and was somewhat impaired; for instance, they felt depressed due to loss of physical function. Patients emphasized that taking medications could improve these aspects of their mental and physical fitness so that they were able to maintain their social function and ability to work.

- "It physically helps me, obviously, because it reduces my pain, my general well-being, everything. I'm a better person when I take that. My activities are normal like everybody else's. Mentally as well, I feel like okay, I'm on track." (F/30s/AS)
- "You have to follow a routine every day or every week or every month, take the medicine to make the goal, to improve your health or pain." (F/40/AS)

Patients felt vulnerable and feared being dependent on others for care and financial support. Although medication adherence was linked to improved health, patients emphasized that health outcome domains fluctuated, often related to the timing and frequency of medication use, and that other contextual factors aside from their medications also influenced physical and psychological function.

- "Adherence is part of your lifestyle and so, how do you measure somebody's lifestyle? You've got to look at the whole spectrum...You can't, you can't just hone in on adherence. You have to look at how was their lifestyle and see if there's some change that you could ascribe to the intervention that you're talking about. And that's fairly tricky." (F/34/RA)

2. *Addressing low morale*. Patients wanted an adherence trial to help them feel understood and supported because of the low morale they can experience from their medications. At times, some patients felt their medications were futile and left them depressed and anxious; they therefore lost the motivation and commitment to complete the recommended regime.

Table 2. Five types of outcome domains of a medication adherence trial that were important to patients.

Domain	Outcomes Extracted From Focus Groups
Medication adherence	Timing, dosing, accuracy of injection technique
Adherence-related factors (i.e., upstream factors that can influence the behavior of adherence, and could be measured at the conclusion of a trial to explain adherence levels)	Medication knowledge Medication adherence knowledge Medication beliefs Medication concerns Support from healthcare professional Family support Community support General emotional support Memory/forgetfulness Medication effectiveness Medication side effects Self-efficacy
Pathophysiology	Physical Physical functioning (e.g., ability to exercise, drive, picking up things, bending over, tying shoelaces) Range of motion Mobility Disease activity Pain Inflammation Organ function Biomarkers Fitness Sexual function Psychological Well-being Fatigue Anger/irritability Depression Helplessness Satisfaction Morale Confidence Medication side effects Side effects (weight gain, dry nails, hair loss, changes in mood, stomach cramps, cancer, cataracts, diabetes)
Life impact	Quality of life Ability to work Sleep disruption Social roles (relatives, parenting, grandparenting) Independence
Economic impact	Cost of disease and treatment (individually and for healthcare and society) Healthcare utilization Productivity loss

- "I think psychological is the biggest block to most people, your situation being one of them... You know I have to take this medication for how long? Am I gonna be on it for life? What's it gonna do for me?" (F/48/RA)
- "I think the last thing is just ways to overcome any initial negative morale, so if you've been taking medication consistently and it doesn't work, what then?" (M/30/AS)

Patients were not keen to discuss their disease and medications with their relatives for fear of judgment, lack of knowledge, and the absence of acceptance.

3. *Balance between medication necessity beliefs and concerns*. When participating in an adherence trial, patients wanted assistance with being able to better balance the perceived necessity of taking medication against concerns they had. Concerns related to medication use affected their confidence in therapy. Patients felt that medication adherence was needed to achieve a normal life, but they also expressed negative opinions as medication use induced anxiety about long-term safety and feared addiction to chemical products. Patients indicated that a positive attitude toward medications increased motivation to take them.

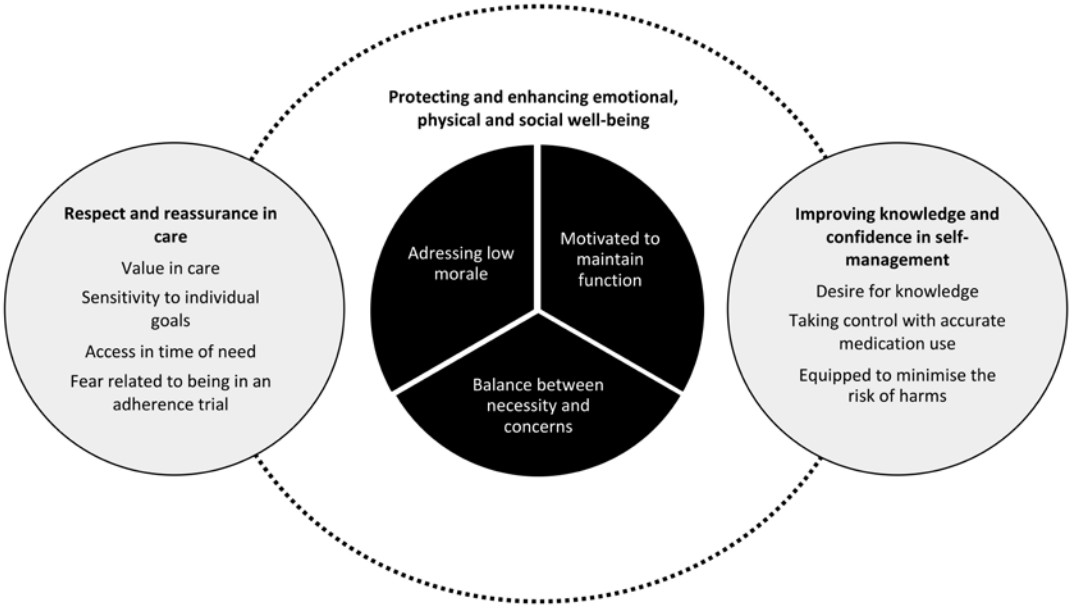

Figure 1. Schematic presentation of overarching themes reflecting reasons why outcome domains of medication adherence trials matter to patients. In the setting of an adherence trial, patients were most concerned with outcome domains related to their overall well-being. In addition, patients valued improved knowledge and confidence in self-management as well as respect and reassurance in care in relation to participation in adherence trials.

· "For me, understanding generally how it works in the body is a good motivating factor 'cause I would know why I'm taking it and maybe, side effects, risks, expected duration of prescription. Because I was afraid of having to take this the rest of my life, so kind of like a psychological counseling to alleviate concerns with having to take the medication." (M/76/PsA)

Improving knowledge of and confidence in self-management

1. *Desire for knowledge*. Patients valued increasing their medication knowledge as a result of participating in an adherence trial. They indicated that sufficient knowledge increased trust and confidence in their medication, enabled them to make deliberate therapy choices, and increased motivation to take medication as prescribed. In terms of being provided information about medications, patients wanted to be given accurate information at the time of diagnosis and regularly throughout the disease process, regarding the expected effectiveness of their medications. They also wanted information on a variety of treatment options to compare and choose from.

· "I'd want to know the benefits of taking the medication... What I mean is, what are the potential things to be aware of that may affect your consistency in how you take medication and ways to manage that?" (M/30/AS)

2. *Taking control with accurate medication use*. Patients strongly preferred to make their own decisions and therefore wanted an adherence trial to help them take better control of their disease, especially when it came to medications.

· "The intervention could help me walk through a solution of how do I stay on track with my medications and keep my disease under control while I keep going through, you know, what I do in life." (F/48/RA)

Patients acknowledged that long-term medication use is challenging, and they struggled to fit it into daily life. Patients valued the feeling that the medication was the best possible that would make them believe they were getting maximum benefits. Patients admitted to being less adherent with medications and blood test monitoring due to forgetfulness and/or busy lifestyles and were willing to get help to take their medications as prescribed. Patients wanted to be aware of what could affect medication adherence and the options to manage difficulties with adherence.

· "The question I think that a lot of patients have is if you miss a dose or if you stop taking it, like how quickly after that would you feel the effects of not taking it ...." (M/40/AS)

If patients were not adhering to their medications, they felt it would be important to know why this was occurring. Some patients experienced their overall well-being improving when they were nonadherent with their medications, thereby questioning the need for therapy, whereas others felt their disease progressing, emphasizing the need of being adherent.

· "My results are better without them, in some respects, when I've been a bit sloppy with my medications. Which is quite strange, because then you start questioning are my medications really working? And then you start thinking well, what if I didn't need to take this or that?" (M/50/RA)

3. *Equipped to minimize the risk of harms.* Patients felt it was empowering to better understand unintended effects (e.g., side effects) of their medications in the setting of an adherence trial as this could affect their medication-taking behavior. They wanted to know short- and long-term side effects with regard to likelihoods and severity, as well as how to identify side effects.

· "My experience with RA is I've had more problems from side effects than I have from the disease itself." (F/50/RA)

· "It would be good to know more about the likelihood of those things happening and how would you spot that? So yes, lymphoma is a risk, what are the signs of lymphoma? Because when it was happening to me, I didn't even connect it with the medication." (F/50/RA)

Patients preferred to know the actions that they need to take in the case of side effects, for example, by taking medications at night. Knowing about side effects could increase anxiety for some patients, and some preferred the option of not receiving information about possible side effects.

· "I just disregard [the potential side effects of medications] because I think I'll probably get them anyway, so I'd rather not know." (F/70/RA)

Respect and reassurance in care

1. *Value in care.* Patients valued HCP support to address adherence-related factors as part of an adherence intervention. They wanted their opinions to be acknowledged and felt ignored when objective tests conflicted with their subjective experiences.

· "One of the negative things would be judgment. When you have those times where you go, 'it's not working, I'm not right.' And they'll say, 'but your blood looks good,' and you go, 'but I'm telling you, it's not right.' I guess you just want it to be a safe place where you can say, 'yeah, I've had it, I don't want to do injections anymore. When can I stop?'" (F/40/RA)

They wanted to feel able to ask questions, and to feel safe when disclosing nonadherence to their HCPs.

· "I hid from my doctor and the medications for like 6 months because I was scared of them. But it was really important to me when I came back to my doctor with the tail between my legs, and like 'I'm sorry' that I was met without judgment for doing that." (F/56/RA)

2. *Sensitivity to individual goals*. When discussing outcome domains that were important to them, patients felt that HCPs were often focused on numbers, laboratory values, pain, and inflammation, which were not the most important things to patients. Fatigue was an example of something that influences daily function but was not addressed by their HCP.

· "Just communication with nurses would be sufficient for me when I feel bad…At one point I knew it was because of the medication while they said you can do whatever you want. But I'm not going, I know my own body. I said it is because of that. It felt undermining when they said it isn't." (F/67/RA)

Patients wanted their HCPs to enable them to achieve their unique role in society, and to understand individual goals, social expectations, and employment needs. In the setting of an adherence trial, patients wanted the adherence intervention to help them achieve goals that were important to them, and also for the intervention to be relevant and tailored to their individual issues. They indicated that the support one person needed could be very different from another individual (e.g., needing reminders, a phone contact for advice or injection support) and could change over time.

· "You also want to be able to achieve, just in general, your lifestyle goals because everyone's different in terms of what they want to be able to do in their own life." (M/30/AS)

3. *Access in time of need*. HCP and family support was an important outcome of an adherence trial to patients so they could access assistance in times of need, eliminating delays in care from someone with the knowledge and skills to offer the appropriate support. Patients felt secure having someone to call between appointments for medication advice when required, and for emotional support during difficulties with their medications.

· "I think the relationship is super important and when I was first diagnosed…Having that person there… knowing that there was somebody at the clinic that you could ask. Right, I think that's important." (M/40/AS)

4. *Fears related to being in an adherence trial*. Patients discussed potential disadvantages of participating in an adherence trial. Some patients feared acknowledging medication nonadherence in a trial might adversely influence their access to treatment outside the trial. They wanted to be able to have access to adherence interventions when required, at convenient times and places.

DISCUSSION

Overall, patients discussed that medication nonadherence could directly affect social participation and quality of life. As a result, patients valued improving adherence, which was supported by improving adherence-related factors such as medication knowledge, beliefs and concerns, and family and HCP support. These findings are in line with other quantitative and qualitative studies that raise similar influences on medication adherence in rheumatology, such as how the disease affects a normal life span,[23,24] knowledge,[25] beliefs and concerns,[26,27,28,29] family support,[28] and HCP support.[28,30] While emotional, physical, and social outcomes emerged as relevant outcome domains from the patient perspective, most medication adherence studies report numerical health outcome domains such as joint counts, inflammatory markers, and bone turnover markers.[8] Patients also discussed the importance of addressing outcome domains related to self-management capabilities and the patient–HCP relationship. These outcome domains have not been comprehensively evaluated in trials.[8] Not measuring what patients consider important could lead to medication adherence interventions that comprise little support and potentially limited effectiveness from the patient perspective.

Our findings indicate that how patients feel and can function are ultimately what matters most to them. However, participants pointed out that understanding this in the context of an adherence trial is not straightforward. The benefit of medication can be influenced by the timing in relation to the drug, and other external factors (e.g., recent fall, weather). Thus, it is important to acknowledge the methodological limitations when measuring health outcome domains.

Adherence was an important outcome for many participants as this relates to their overall well-being. Some interesting comments from patients also included education on barriers for adherence and how to overcome them, the importance of checking what individual barriers were in order to understand the results of a trial, and that the need for adherence support differs greatly between one patient to another. Measuring and

reporting adherence as an outcome is required to aim for a patient-centered approach to adherence trials.[31]

Some limitations should be acknowledged. First, the Canadian focus group included participants from a patient advisory board, who had greater awareness of trial design and the topic of medication adherence. Nevertheless, similar themes were identified across groups. Moreover, data analysis occurred in the local language and Dutch transcripts were not translated into English. However, results were carefully combined and discussed by multiple researchers to ensure that findings adequately captured all aspects. Last, selection bias may have occurred through self-selection of interested participants as well as recruitment from 3 countries.

To date, medication adherence interventions in rheumatology lack standardized, comparable outcome domains. Patients value various outcome domains related to their overall well-being, confidence in medication use, and patient–HCP relationships to be evaluated in future adherence trials. These results are a helpful step to guide researchers to measure relevant and consistent outcome domains. The next step is to generate broader consensus among international patients and other stakeholders in the development of a core domain set of patient-valued outcome domains for trials of medication adherence interventions.

ACKNOWLEDGMENT

We thank all participants for sharing their perspectives in this study. We thank the larger working group members of OMERACT for their contribution to the overall body of work, as well as the PRPs for their input (Michael Gill and Ina Campbell).

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