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Patient perspectives on outcome domains of medication adherence trials in inflammatory arthritis: an international OMERACT focus group study

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Conflict of interest

All authors declare to have no relevant conflict of interest.

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Running head

Outcomes in adherence studies

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 years) with IA using disease-modifying anti-rheumatic drugs (DMARDs) from centres across Australia, Canada, and the Netherlands participated in six focus groups to discuss outcome domains of medication adherence trials that they consider important. We analysed 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 categorised into five 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 matters to patients were identified. First, how taking medications could improve patient's emotional and physical fitness to maintain their social function. Second, how improving knowledge and confidence in self-management increase patient's trust in and motivation to take medications as agreed with minimal risk of harms. Finally, how respect and reassurance, reflecting healthcare that values patient's opinions and is sensitive to patient's individual goals could improve medication taking behaviour.

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

Introduction

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 medications as prescribed" (3). For rheumatic diseases, however, up to 85% of the patients do not fully adhere to their medication regimen (4-6).

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). Furthermore, outcome domains and adherence measures included in studies on medication adherence are heterogeneous (8-11). There is an urgent need for consensus on a minimum core domain set that matters to patients which should be measured in each adherence trial to reduce inconsistent and selective reporting and improve comparison of interventions (12).

The Outcome Measures in Rheumatology Adherence Working Group (OMERACT-Adherence Group) (13) is currently developing a core domain set for trials of medication adherence interventions in patients with rheumatic diseases (14-16). The group consists of patients, healthcare professionals, researchers and other stakeholders. Their activities comprise: (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 prioritise outcome domains (17), (4) an international modified Delphi study to define a preliminary core domain set, and (5) a consensus workshop to finalise 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-centred core domain set for medication adherence interventions. This study aimed to describe the perspectives of patients with inflammatory arthritis on outcome domains of trials evaluating medication adherence interventions.

Materials and 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 with inflammatory arthritis were members of the Working Group and involved in the study design. Consolidated criteria for reporting qualitative research (COREQ) were used to guide the methods and reporting (21).

Participants

Adult patients (≥18 years) with inflammatory arthritis (i.e., ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, undifferentiated inflammatory arthritis) who were at least one disease-modifying anti-rheumatic drug (DMARD) and with proficiency 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 one public hospital (Liverpool Hospital)), pharmacists (the Netherlands; in one specialised rheumatology clinic (Sint Maartenskliniek) and one academic hospital (Radboud university medical center)) or through a research centre (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, gender, level of education, type of inflammatory arthritis, 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 working group members of OMERACT, including patient research partners, based on their expertise with medication adherence and outcome domain research, and translated from English into Dutch by researchers (CB, BvdB, MV) from the Netherlands. The interview guide was pilot tested in each language on comprehensiveness and interpretation by a patient with inflammatory arthritis 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. counselling program, electronic reminders). Items included "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 made 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 outcome domains of trials that were important to patients were extracted from the transcripts and categorised. 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, three researchers (CB, AK, SB) created a preliminary coding framework which was discussed with co-authors (BvdB and AT) based on one transcript. Thereafter, the initial coding framework was applied to all transcripts, allowing for new categories and (sub)themes to be identified. CB, AK and SB

read the transcripts to familiarize themselves with the data. Text fragments of meanings were identified and labelled with codes. These were grouped into categories and sub-themes and finally overarching themes were explored. Each transcript was coded by one researcher and reviewed by a second experienced qualitative researcher (Australia SB and AK, Canada and the Netherlands CB and BvdB). 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 (CB). All results were merged and discussed until consensus was achieved on the final coding framework. Data was collected until data saturation, when no new themes emerged from subsequent focus groups.

Ethics

Ethical approval was obtained from local research ethics committees (Radboud university medical center Nijmegen, the Netherlands no. 2019-5525; South Western Sydney Local Health district no. 2019/ETH12710; University of British Columbia, Vancouver, Canada 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 rheumatoid arthritis (n=23), ankylosing spondylitis (n=11), and psoriatic arthritis (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 five types of outcome domains that they considered important when participating in an adherence trial. 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, individualised 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 three 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 three overarching themes.

Protecting and enhancing emotional, physical and social well-being

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 lack of physical mobility that their condition caused. They also felt that their cognitive function deteriorated and was somewhat impaired, for instance, feeling depressed due to loss of physical function. Patients emphasised 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 wellbeing, 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 emphasised 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)

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 motivation and commitment to complete the recommended regime.

"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 judgement, lack of knowledge, and the absence of acceptance.

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 also expressed negative opinions as medication use also induced anxiety about long-term safety and feared addiction to chemical products. Patients indicated that a positive attitude towards medications increased motivation to take them.

"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 counselling to alleviate concerns with having to take the medication." (M/76/PA)

Improving knowledge of and confidence in self-management

Desire for knowledge

Patients valued increasing their medication knowledge as a result of participating in an adherence trial. Patients 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. When provided with information about medications, patients wanted to be given accurate information at the time of diagnosis and regularly throughout the disease process of 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)

Taking control with accurate medication use

Patients wanted an adherence trial to help them to take better control of their disease, especially when it came to medications as patients strongly preferred to make their own decisions.

"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 being on what they felt was the best medication to them in order to obtain the maximum benefits from treatment. 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 impact medication adherence and 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 non-adherent with their medications, 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)

Equipped to minimise 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 behaviour. 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 rheumatoid arthritis 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 it [AK: 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

Value in care

Patients valued healthcare professional 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 bloods look 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 non-adherence to their healthcare providers.

"I hid from my doctor and the medications for like six 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)

Sensitivity to individual goals

When discussing outcome domains that were important to them, patients felt that healthcare providers were often focussed on numbers and laboratory values, pain and inflammation, which were not the most important things to them. Fatigue was an example of something that influences daily function, and this was not addressed by their healthcare provider.

"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 healthcare providers to enable them to achieve their unique role in society, 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 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)

Access in time of need

Healthcare professional 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)

Fears related to being in an adherence trial

Patients discussed potential disadvantages of participating in an adherence trial. Some patients feared acknowledging medication non-adherence 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 non-adherence 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 healthcare professional support. Findings are in line with other quantitative and qualitative studies which 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 (26-29), family support (28), and healthcare professional 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 patient-healthcare provider 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 they feel and can function are ultimately what matters most to patients. 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, the 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 wellbeing. 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 and another. Measuring and reporting adherence as an outcome is required to aim for a patient-centred 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. Lastly, selection bias may have occurred through self-selection of interested participants as well as recruitment from three countries.

To date, medication adherence interventions in rheumatology lack standardized, comparable outcome domains. Patients value various outcome domains to be evaluated in future adherence trials related to their overall well-being, confidence in medication use and patient-healthcare provider relationships. 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.

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Tables and figures

Table 1: Characteristics of participants

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

Figure 1: Schematic presentation of overarching themes reflecting reasons why outcome domains of medication adherence trials matters 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.

Table 1: Characteristics of participants

Characteristics	**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**
Gender, female n(%)	21 (55.3)	6 (66.7)	4 (40.0)	4 (57.1)	2 (50.0)	2 (66.7)	3 (60.0)
Age (years), 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 n(%)							
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 inflammatory arthritis* n(%)							
Ankylosing spondylitis	11 (28.9)	1 (11.1)	2 (20.0)	2 (28.6)	2 (50.0)	3 (100.0)	1 (20.0)
Psoriatic arthritis	8 (21.1)	1 (11.1)	6 (60.0)	-	-	-	1 (20.0)
Rheumatoid arthritis	23 (60.5)	7 (77.8)	6 (60.0)	5 (71.4)	2 (50.0)	-	3 (60.0)
Disease duration (years), 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 (%)*							
Adalimumab	9 (23.7)	3 (33.3)	4 (40.0)	1 (14.3)	1 (25.0)		
Certolizumab	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)

*Participants could report multiple answers and therefore the sum exceeds 100 percent.

Table 2: Five types of outcome domains of a medication adherence trial 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 behaviour 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 Healthcare professional support Family support Community support General emotional support Memory/forgetfulness Medication effectiveness Medication side effects Self-efficacy
Pathophysiology	<u>Physical</u> 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 <u>Psychological</u> Well-being Fatigue Anger/Irritability Depression Helplessness Satisfaction Morale Confidence <u>Medication side effects</u> 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 utilisation Productivity loss

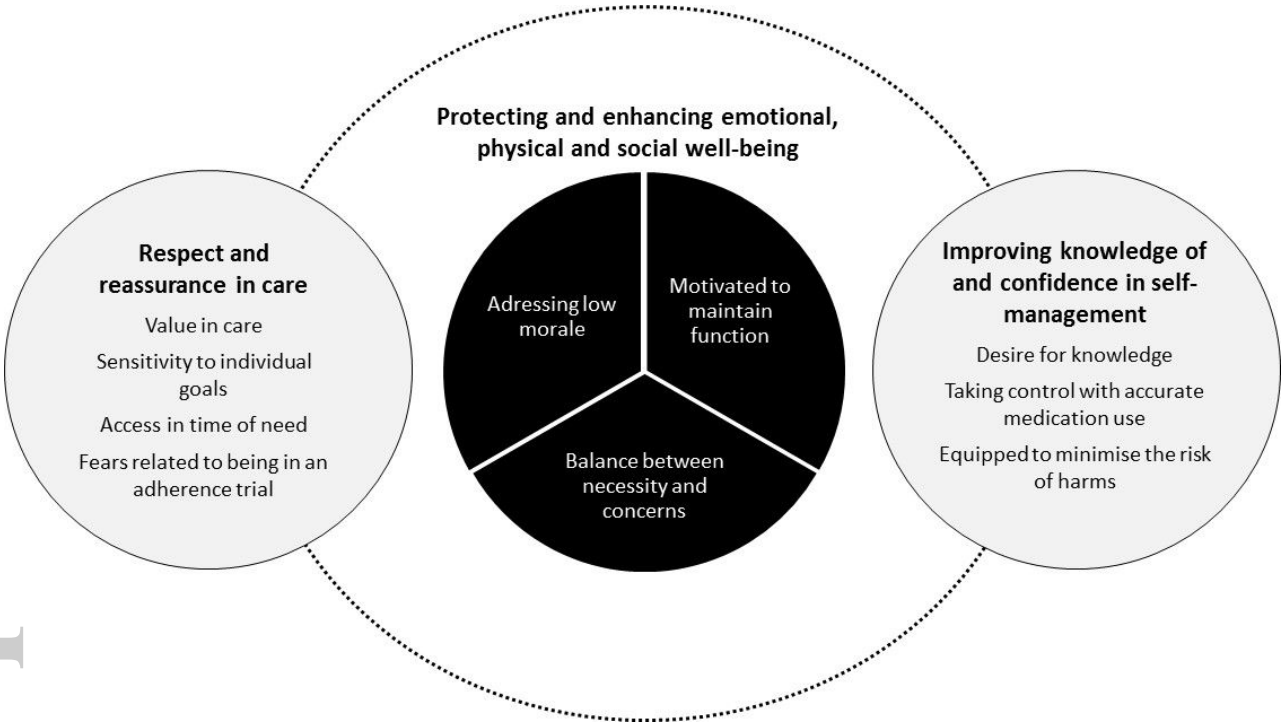

Figure 1: Schematic presentation of overarching themes reflecting reasons why outcome domains of medication adherence trials matters to patients. In the setting of an adherence trial, patients were most concerned with outcome domains related to their overall well-being. In addition, patients valued improved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