Scope of Outcomes in Trials and Observational Studies of Interventions Targeting Medication Adherence in Rheumatic Conditions: A Systematic Review

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ABSTRACT. Objective. Nonadherence to medications is common in rheumatic conditions and associated with increased morbidity. Heterogeneous outcome reporting by researchers compromises the synthesis of evidence of interventions targeting adherence. We aimed to assess the scope of outcomes in interventional studies of medication adherence.

Methods. We searched electronic databases to February 2019 for published randomized controlled trials and observational studies of interventions with the primary outcome of medication adherence including adults with any rheumatic condition, written in English. We extracted and analyzed all outcome domains and adherence measures with prespecified extraction and analysis protocols.

Results. Overall, 53 studies reported 71 outcome domains classified into adherence (1 domain), health outcomes (38 domains), and adherence-related factors (e.g., medication knowledge; 32 domains). We subdivided adherence into 3 phases: initiation (n = 13 studies, 25%), implementation (n = 32, 60%), persistence (n = 27, 51%), and phase unclear (n = 20, 38%). Thirty-seven different instruments reported adherence in 115 unique ways (this includes different adherence definitions and calculations, metric, and method of aggregation). Forty-one studies (77%) reported health outcomes. The most frequently reported were medication adverse events (n = 24, 45%), disease activity (n = 11, 21%), bone turnover markers/physical function/ quality of life (each n = 10, 19%). Thirty-three studies (62%) reported adherence-related factors. The most frequently reported were medication beliefs (n = 8, 15%), illness perception/medication satisfaction/satisfaction with medication information (each n = 5, 9%), condition knowledge/medication knowledge/trust in doctor (each n = 3, 6%).

Conclusion. The outcome domains and adherence measures in interventional studies targeting adherence are heterogeneous. Consensus on relevant outcomes will improve the comparison of different strategies to support medication adherence in rheumatology.

Key Indexing Terms: clinical trials, medication adherence, outcome assessment (health care), patient compliance, rheumatic diseases, systematic review

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Many rheumatic conditions require the long-term use of medications, yet adherence may be suboptimal. Adherence may be defined as "the extent to which a person's behavior - taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider"¹. In rheumatoid arthritis (RA), medication adherence ranges from 14% to 80% and nonadherence can lead to poorer health outcomes such as increased disease activity, poorer quality of life, and radiological progression^{2,3}. In osteoporosis, fewer than 70% of patients start prescribed treatment and about 50% discontinue therapy within 1 year, statistics associated with an increased risk of fracture⁴. Researchers are increasing efforts to develop and test strategies to improve medication adherence in rheumatology. However, differences in the design of these interventional studies, including outcome selection and reporting, hamper the comparison of these strategies.

Adherence studies to date have used heterogeneous adherence outcome measures, definitions, and thresholds, and often have not assessed clinically meaningful health outcomes⁵. If researchers omit important outcome domains, or use different measures, end users of the research are unable to judge the relative effectiveness of interventions or understand the clinical relevance of research findings. Core domain sets, which are defined as the minimum set of outcome domains that should be measured and reported in specific clinical trials, reduce inconsistent reporting and reporting bias, and can help ensure the measurement of outcomes that are important to patients and decision makers⁶. The Outcome Measures in Rheumatology (OMERACT) initiative has developed core domain sets for many rheumatic conditions⁶.

The aims of our study were to describe the scope and consistency of outcome domains and adherence measures in studies (including both randomized controlled trials and observational studies) of interventions to improve medication adherence in adults with rheumatic conditions.

MATERIALS AND METHODS

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to report this systematic review

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(Supplementary Table 1, available from the authors on request). We have published the original protocol and protocol amendments^{7,8}.

Search and selection criteria. The inclusion criteria are described with the PICOS framework (Participant/Intervention/Comparator/Outcome/ Study design): (1) participants are adults aged 18 or older with any rheumatic condition; (2) intervention is any strategy to improve adherence; (3) comparator is management as usual (if a comparator arm was included in the study); (4) outcomes are all outcome domains, including only studies with medication adherence as the primary outcome; (5) study design is randomized controlled trials (RCT) and observational studies (non-randomized comparison studies, including pilot studies, that incorporated an intervention targeting adherence). We included both RCT and observational studies because we anticipated a limited number of informative RCT of adherence interventions in rheumatic conditions.

We searched MEDLINE, PsycINFO, EMBASE, CINAHL, and CENTRAL from inception to February 25, 2019, to identify all studies of interventions designed to improve medication adherence in any rheumatic condition. The search strategy included MESH terms ("Rheumatoid arthritis," "Spondyloarthritis," "Osteoporosis," "Systemic lupus erythematosus," "Systemic scleroderma," "Vasculitis," "Connective tissue diseases," "Medication adherence," "Treatment adherence and compliance," and "Treatment refusal"; Supplementary Table 2 contains the full search strategy and is available from the authors on request). We also hand-searched the reference list of selected systematic reviews of adherence studies^{9,10,11} and Google Scholar. We excluded conference reports, protocols, and abstracts given the limited information provided; however, we searched for the full publications of these and contacted authors if needed. We included only English language articles. Two reviewers (AK and LCS) independently screened abstracts and full texts of all identified studies. A third reviewer (KT) resolved any disagreements on included studies.

Data extraction. For each study, 2 reviewers (AK, KT) independently extracted the following study characteristics: first author, year of publication, participating countries, study design, type of intervention, sample size, study duration, and participants' mean age, sex, medication, rheumatic condition, and disease duration. In addition, the reviewers independently extracted all outcome domains, measures and the instrument, metric, method of aggregation, and timepoints of all adherence measures.

Data synthesis and analysis. Two reviewers (AK and LCS) grouped all outcome domains into 3 overarching groups: adherence, health outcomes, and adherence-related factors. We calculated the number of studies reporting each outcome domain. The 2 reviewers discussed any discrepancies between the extracted outcomes and outcome domain grouping until agreement was reached and consulted a third reviewer (KT) when necessary.

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We subdivided adherence into phases: (1) initiation, defined as when the patient takes the first dose of prescribed medication; (2) implementation, defined as the extent to which a patient's actual dosing corresponds to the prescribed dosing; or (3) persistence, defined as the length of time between initiation and the last dose immediately preceding discontinuation¹².

We categorized each adherence measure into subjective and objective measures. Subjective measures included all self-report questionnaire/ diary/interview and clinician judgment (i.e., clinician estimate of adherence). Objective measures included direct observation, drug concentration in body fluid, electronic monitoring [e.g., medication event monitoring systems (MEMS)], pharmacy refill record, and pill count. We also recorded the name of each instrument used to measure adherence, e.g., different self-report measures and drug levels were recorded separately. Finally, to demonstrate the heterogeneity in adherence measure reporting, we recorded a unique adherence measure that included the instrument, details on the adherence measures as change from baseline, end value or time to event), and method of aggregation (categorical, or use of means or medians when reported as a continuous measure). We recorded the timepoints for all adherence measures.

Health outcomes included any condition-specific outcome domain that informed the effect of the intervention on any clinical aspect of the condition including pathophysiological manifestations (e.g., fracture, pain), life effect (e.g., quality of life), death, or resource use (e.g., costs to use) as defined in the OMERACT Handbook⁶. To evaluate whether studies reported important health outcome domains, we assessed whether existing studies of adherence interventions reported on medication adverse events. We also compared the health outcome domains in the included studies with existing condition-specific core domain sets through OMERACT (omeract.org) and Core Outcome Measures in Effectiveness Trials Websites (www.comet-initiative.org), noting whether these core domain sets were available at least 5 years before publication of the adherence trial for feasible inclusion within the trial.

Adherence-related factors included any factors that could influence adherence behavior using the COM-B ("capability," "opportunity," "motivation," and "behavior") framework described by Michie, *et al*¹³, reported as an outcome (e.g., medication knowledge). Supplementary Table 3 (available from the authors on request) includes examples of adherence-related factors within the COM-B framework.

RESULTS

Study characteristics. We included 53 studies (41 RCT, 77%) with a total of 26,361 participants (Figure 1). Interventional studies in adherence in rheumatology have exponentially increased over the last 2 decades (Supplementary Figure 1, available from the authors on request). Table 1 provides the characteristics of included studies. Supplementary Table 4 includes a descriptive summary of all studies. The review included studies conducted in 33 countries (4 studies in multiple countries) with participants with 9 rheumatic conditions (osteoporosis, RA, gout, systemic lupus erythematosus, psoriatic arthritis, "systemic rheumatic diseases," "early inflammatory arthritis," "inflammatory polyarthritis," and "degenerative joint disease"). Studies had a mean follow-up duration of 13 months (range 4 weeks to 2 yrs for RCT, 10 days to 5 years for observational studies) and mean sample size of 497 participants (range 18-2382 for RCT, 18–5413 for observational studies).

Adherence as an outcome domain and its measurement. The phases of adherence measured included initiation (n = 13 studies, n = 13 studies)

25%), implementation (n = 32, 60%), and persistence (n = 27, 51%). The phase of adherence was unclear in 20 studies (38%). Self-report questionnaires that assessed more than 1 phase of adherence were used in most of the studies with an unclear phase of adherence.

We categorized all adherence measures into subjective and objective measures. Studies used objective measures more often overall (n = 28, 53%). This included pharmacy refill records, pill count, MEMS, and drug concentration in body fluid. Subjective measures included all self-report questionnaires/interviews/ diaries (n = 25 studies, 47%). Five studies combined subjective and objective measures to report a single value for adherence (e.g., combining pharmacy refill record and self-report, n = 5, 9%). RCT used more objective measures (n = 20, 49% of RCT) compared with observational studies (n = 5, 42% of observational studies). Osteoporosis studies used more objective measures (n = 20, 61% of osteoporosis studies) compared with RA studies (n = 4, 33% of RA studies).

In total, studies used 37 different instruments to measure adherence (mean 1.5 instruments per study, range 1–5). The 5 most frequently reported instruments were pharmacy refill record (n = 20 studies, 38%), pill count (n = 7, 13%), 4-item Morisky scale (n = 6, 11%), Compliance Questionnaire in Rheumatology (n = 4, 8%), and MEMS (n = 4, 8%). Six studies (11%) did not specify the instrument used to measure adherence. Twenty-nine instruments appeared in 1 study only. These were predominantly self-report questionnaires or interviews created specifically for the study. Figure 2 depicts the range of all adherence instruments and their timepoints.

When combining the instrument, definition/calculation for adherence, metric, and method of aggregation, studies reported adherence in 115 unique ways (Figure 3). The most frequent were pharmacy refill record, adherence defined as filling an initial prescription, reported as an end value, categorical method of aggregation (n = 8 studies, 15%); pharmacy refill record, adherence defined as no discontinuation of therapy, reported as an end value, categorical method of aggregation (n = 5 studies, 9%); pill count, adherence calculated as the percentage of tablets taken, reported as an end value, continuous method of aggregation (mean; n = 4, 8%). Ninety-four (82%) appeared in 1 study only. Supplementary Table 4 (available from the authors on request) includes the unique adherence measurement approaches for each study.

Health outcomes. Forty-one studies (77%) reported 38 health outcomes. Twenty-four studies (45%) reported on medication adverse events. We reviewed the compatibility of the reported health outcomes in the included adherence studies against the existing condition-specific core domain sets. We excluded 5 studies from this analysis because they included conditions for which no core domain set currently exists or existed at least 5 years prior to the date of the publication of the respective study. Of the remaining 48 studies, only 1 study reported all outcome domains in the existing condition-specific core domain set, 32 studies (67%) reported at least 1 domain, and 16 studies (33%)



Figure 1. Search results.

did not use any outcome domains from the existing condition-specific core domain set (Table $2^{14.66}$).

Thirty-three studies (including 28 RCT) with participants with osteoporosis-related conditions assessed the effect of the adherence intervention on a total of 10 health outcomes. The 5 most frequently reported health outcomes were adverse events (n = 17 studies, 52%), bone turnover markers (n = 10, 30%), bone mineral density (n = 5, 15%), fractures (n = 5, 15%), and quality of life (n = 4, 12%). None of the studies reported on pain or height, which are outcome domains in the existing core domain set for osteoporosis⁶⁷.

Studies including participants with RA (12 studies in total, including 8 RCT) reported 26 health outcomes. The 5 most commonly reported health outcomes were disease activity (n = 7 studies, 58%), physical function (n = 7, 58%), pain (n = 5, 42%), quality of life (n = 4, 35%), adverse events (n = 3, 25%), and erythrocyte sedimentation rate or C-reactive protein (n = 3, 25%). In RA, only 1 study reported on all outcome domains from the existing RA core domain set⁴⁷.

Adherence-related factors. Thirty-three studies (62%) reported 32 adherence-related factors. Table 3 outlines the proportion of studies reporting each factor. The most frequently reported factor was reasons for adherence/nonadherence (n =12 studies, 23%), where studies would list a variety of reasons elicited from participants. The next 4 most commonly reported factors were medication beliefs (including necessity, concerns, harms, overuse; n = 8, 15%), illness perception, medication satisfaction, and satisfaction with medication information (each n = 5, 9%).

DISCUSSION

This systematic review of 53 studies shows that researchers are conducting an increasing number of studies, especially RCT, to evaluate strategies to improve adherence in rheumatic conditions. There is considerable heterogeneity in the outcome domains and adherence measures that assess the effect of these interventions. A third of studies had an unclear phase of adherence and the review identified 37 different instruments that measured and reported adherence in 115 unique ways. Although adherence was linked to health outcomes in 77% of studies, the 38 reported health outcome domains were varied. Studies rarely used the existing disease-specific core domain sets and only half of studies reported medication adverse events. Studies evaluated multiple adherence-related factors. However, the review did not find any specific factor in more than 15% of studies.

Studies included in this systematic review assessed medication initiation least frequently compared to other phases of medication adherence. This may be due to difficulty in patient recruitment, because patients who are not intending to start treatment are unlikely to agree to participate in an adherence trial. In previously published studies, medication adherence dramatically drops in the first year after initiation⁶⁸. The step

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Table 1. Characteristics of included studies
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Study Characteristic	No. Studies	(%)
Type of study		
Randomized controlled trial	41	(77)
Observational studies	12	(23)
Year of publication		
1981-2000	2	(4)
2001-2010	17	(32)
2011-2019	34	(64)
Country		
United States	16	(30)
United Kingdom	6	(11)
Other*	27	(51)
Multinational studies	4	(8)
Sample size		
1-100	14	(26)
101-300	19	(36)
> 300	20	(38)
Duration of study, months		
≤ 6	14	(26)
> 6-12	29	(55)
> 12	10	(19)
Condition		
Osteoporosis/osteopenia/fracture/	'at risk	
of osteoporosis	33	(62)
Rheumatoid arthritis	12	(23)
Gout	2	(4)
Systemic lupus erythematosus	1	(2)
Systemic rheumatic diseases	1	(2)
Early inflammatory arthritis	1	(2)
Multiple [†]	3	(6)

* 1–3 studies: Australia, Canada, Denmark, Egypt, France, India, Italy, Japan, Korea, Malaysia, the Netherlands, New Zealand, Spain, Thailand, Turkey. [†]RA and degenerative joint disease; RA and PsA; RA, PsA, and inflammatory polyarthritis. RA: rheumatoid arthritis; PsA: psoriatic arthritis.

prior to this — the actual rate of initiation of prescribed medications — is still poorly characterized in rheumatology studies.

Adherence measures varied at many levels: instrument, definitions for the calculation of adherence, metric, and method of aggregation. There are many adherence measures available, with no gold standard of adherence measurement. Measures may differ for different phases of adherence and require differing amounts of time, expertise, and costs associated with their use. Variability in medication dosing, route, and polypharmacy further complicates how adherence is measured and reported in rheumatic conditions.

Health outcomes are dependent on both the efficacy of the medication and adherence. Patients and health professionals may perceive health outcomes to be important outcome domains of medication adherence studies. Despite this, 23% of studies in this review did not report on any health outcomes. Further, the condition-specific core domain set includes outcome domains that are mandatory in all clinical trials⁶ and represent the minimum set of outcome domains of highest importance to multiple observers. However, only 1 adherence study

in this review used the entire condition-specific core domain set to assess health outcomes. There may be some explanations for this, including considerations of study power and duration of follow-up, or the added participant burden and study costs when researchers incorporate health outcomes into their studies. Qualitative studies indicate that concerns about medication adverse effects and experience of side effects influence adherence behavior⁶⁹. Conversely, adherence can also affect the occurrence of side effects. However, only half of the studies reported on this.

Our review identified many adherence-related factors. Members of the OMERACT-Adherence group found it difficult to delineate which factors should be considered candidate domains for a core domain set to be used for interventional studies targeting adherence. These factors may be better classified as intervention targets or explanatory variables for adherence (i.e., in the causal pathway to adherence) and not true outcome domains⁸. Some of the same factors could be considered potential contextual factors (a covariate that could be measured at baseline that could serve as an effect modifier of the outcome, e.g., trust in the doctor). No specific adherence-related factor was reported frequently, perhaps because factors influencing adherence are complex and numerous and some factors are tied directly to theories of adherence used to design the intervention (e.g., medication beliefs). Therefore, any single factor may not have relevance across all potential adherence interventions in different rheumatic conditions and is unlikely to be in the core domain set for adherence interventions.

Many systematic reviews in rheumatic conditions and a broader range of chronic conditions have noted the difficulty of combining adherence results because of the inconsistency in adherence measurement^{5,9}. This review adds an in-depth analysis of different points at which heterogeneity exists at the level of instrument, definition/calculation of adherence, metric, and method of aggregation. A previous systematic review and metaanalysis of medication adherence interventions across multiple health conditions showed a positive effect of adherence interventions on some patient-centered outcome domains including quality of life, physical function, and symptoms⁷⁰. However, it remains unclear which outcome domains are of most importance to patients in trials targeting adherence in rheumatic conditions, which is needed to inform the design of patient-centered adherence interventions.

This review provides a detailed analysis of the scope and consistency of outcome domains, including adherence measures across a large number of adherence interventions in rheumatic conditions from 33 countries. However, there are some limitations. We included studies published in English and did not include studies published in other languages. The majority of studies in this systematic review focused on osteoporosis. The findings are likely to differ in other rheumatic conditions and may therefore not be generalizable.

This review provides a broad understanding of the outcomes reported in interventional studies across multiple rheumatic conditions. The evidence from this review informs the next phases



Figure 2. Frequency and timepoints of instruments measuring adherence. NS: not specified; CQR: Compliance Questionnaire in Rheumatology; MEMS: Medication Event Monitoring System; MARS: Medication Adherence Report Scale; MASRI: Medication Adherence Self-Report Inventory; MTB-Thai: Medication Taking Behaviour measure for Thai patients; ULT: urate-lowering therapy.

in the OMERACT-Adherence 5-phase project, which includes qualitative research with patients and researchers, a Delphi survey, and consensus voting⁷. The OMERACT-Adherence group aims to develop a core domain set that includes outcome domains that are important to patients and health professionals and also feasible for researchers. A core domain set for adherence interventions can enhance the quality of adherence research conducted in rheumatology and ensure studies lead to improvements for patients in outcomes that are important and relevant to them.

This systematic review also demonstrates the need for clear guidance of the method for measuring and reporting adherence in interventional studies targeting adherence in rheumatic conditions. A consensus-based recommendation for adherence measures in adherence trials should be specific for the phase of adherence and applicable to the different frequencies, modes of administration, and combinations of medications used in rheumatology, and should consider the time, resources, and expertise needed for their use.

Studies of adherence interventions in adults with rheumatic conditions measure and report a broad range of adherence outcomes, health outcomes, and adherence-related factors. Adherence measures are highly heterogeneous and there is no consistency in which health outcomes are reported. A significant portion of outcome domains were not true outcomes and are better classified as determinants of adherence whose improvement may lead to better adherence (i.e., a time-dependent contextual factor). A core domain set will enhance the

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115 unique ways of measuring and reporting adherence														
Top 6				Studies	(%)									
Pharmacy refill record	Filled initial prescription	End value	Categorical	6	(11)									
Pharmacy refill record	Persistent if no discontinuation of therapy	End value	Categorical	5	(9)									
Pill count	Percentage of tablets taken	End value	Continuous (Mean)	4	(8)									
Pharmacy refill record	Medication Possession Ratio >80%	End value	Categorical	3	(6)									
Pharmacy refill record	Medication Possession Ratio	End value	Continuous (Mean)	3	(6)									
Pharmacy refill record	Medication Possession Ratio	End value	Continuous (Median)	3	(6)									
Instrument	Adherence definition and calculation	Metric M	ethod of aggregation	1										

Figure 3. Unique ways of measuring and reporting adherence.

Table 2. Reporting of health outcomes, core domain set, and medication-related adverse events.

					Osto	eoporosi	s/osteop	oenia/fra	cture/at r	isk for c	osteopoi	rosis					
Study (ref.)	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Health outcome	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
No. CDS items	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1
Adverse events	1	1	1	1	1	1	X	1	1	1	1	1	1	1	1	X	X
					Osto	eoporosi	s/osteoj	penia/fra	cture/at r	isk for c	osteopoi	cosis					
Study (ref.)	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	
Health outcome	1	1	1	1	1	×	x	×	×	x	x	×	×	x	×	x	
No. CDS items	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Adverse events	X	1	1	\checkmark	X	X	X	×	×	X	X	×	×	X	×	X	
							RI	neumatoi	d Arthrit	is							
Study (ref.)	47	48	49	50	51	52	53	54	55	56	57	58					
Health outcome	1	1	1	1	1	1	1	1	1	1	1	1					
No. CDS items	7	6	6	5	5	4	4	3	1	1	1	0					
Adverse events	X	1	1	×	X	1	×	×	×	×	X	1					
	G	out	SLE	0	ther or l	Multiple	Condit	tions									
Study (ref.)	59	60	61	62	63	64	65	66									
Health outcome	1	1	1	1	1	1	1	1									
No. CDS items	5	2	2	NA	NA	NA	NA	NA									
Adverse events	1	1	×	1	1	×	X	×									

✓ Reported. ✗ Not reported. CDS: core domain set (no. items in the core domain set that was reported in each study; ✓: full core domain set reported; ✗: full core domain set not reported); NA: not applicable (no core domain set existing or did not exist at least 5 yrs prior to date of publication).

ability to compare results across adherence studies on outcomes of significance to patients and others.

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Table 3. Studies reporting each adherence-related factor.

Adherence-related Factor	No. Studies	(%)
Reasons for adherence/nonadherence	12	(23)
Medication beliefs (necessity/concerns/		
overuse/harms)	8	(15)
Illness perception	5	(9)
Medication satisfaction	5	(9)
Satisfaction with medication information	5	(9)
Condition knowledge	3	(6)
Medication and condition knowledge	3	(6)
Trust in doctor	3	(6)
Decisional conflict	2	(4)
Illness risk	2	(4)
Intervention satisfaction	2	(4)
Intervention's influence on adherence	2	(4)
Involvement in decision making	2	(4)
Medication initiation decision	2	(4)
Medication knowledge	2	(4)
Satisfaction with medical care	2	(4)
Anxiety	1	(2)
Drug interactions	1	(2)
Duplication of prescriptions	1	(2)
Duplication of therapeutic class	1	(2)
Health and medication information source	1	(2)
Helpfulness of pharmacist's recommendatio	n 1	(2)
Intention to adhere	1	(2)
Medication bother	1	(2)
Medication cost	1	(2)
Medication preference	1	(2)
Medication problems	1	(2)
Patient activation (engagement with therapy	v) 1	(2)
Prescription documentation	1	(2)
Safety of pharmacist's recommendations	1	(2)
Self-efficacy	1	(2)
Unmet treatment needs	1	(2)

REFERENCES

- Sabaté E. Adherence to long-term therapies: evidence for action. World Health Organization; 2003. [Internet. Accessed June 4, 2020.] Available from: www.who.int/chp/knowledge/publications/ adherence_report/en
- van den Bemt BJ, Zwikker HE, van den Ende CH. Medication adherence in patients with rheumatoid arthritis: a critical appraisal of the existing literature. Expert Rev Cli n Immunol 2012;8:337-51.
- Waimann CA, Marengo MF, de Achaval S, Cox VL, Garcia-Gonzalez A, Reveille JD, et al. Electronic monitoring of oral therapies in ethnically diverse and economically disadvantaged patients with rheumatoid arthritis: consequences of low adherence. Arthritis Rheum 2013;65:1421-9.
- Kothawala P, Badamgarav E, Ryu S, Miller RM, Halbert R. Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis. Mayo Clin Proc 2007;82:1493-501.
- Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, et al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev 2014;11: CD000011.
- Boers M, Tugwell P, Beaton D, Bingham CO III, Conaghan PG, D'Agostino M, et al. The OMERACT Handbook. [Internet. Accessed June 4, 2020.] Available from: omeracthandbook.org/ handbook.
- 7. Kelly A, Tong A, Tymms K, March L, Craig JC, De Vera M, et al. Outcome Measures in Rheumatology - interventions for medication

adherence (OMERACT-Adherence) core domain set for trials of interventions for medication adherence in rheumatology: 5 phase study protocol. Trials 2018;19:204.

- Kelly A, Bartlett SJ, de Wit MP, Beaton DE, Dawson T, Evans V, et al. Addressing challenges in developing a core domain set in adherence interventions in rheumatology: a report from the OMERACT-Adherence Group. J Rheumatol 2019;46:1202-6.
- 9. Galo JS, Mehat P, Rai SK, Avina-Zubieta A, De Vera MA. What are the effects of medication adherence interventions in rheumatic diseases: a systematic review. Ann Rheum Dis 2016;75:667-73.
- Hiligsmann M, Salas M, Hughes DA, Manias E, Gwadry-Sridhar FH, Linck P, et al. Interventions to improve osteoporosis medication adherence and persistence: a systematic review and literature appraisal by the ISPOR Medication Adherence & Persistence Special Interest Group. Osteoporos Int 2013;24:2907-18.
- Hartman L, Lems WF, Boers M. Outcome measures for adherence data from a medication event monitoring system: a literature review. J Clin Pharm Ther 2019;44:1-5.
- Vrijens B, De Geest S, Hughes DA, Przemysław K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Bri J Clin Pharmacol 2012;73:691-705.
- 13. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci 2011;6:42.
- Clowes J, Peel N, Eastell R. The impact of monitoring on adherence and persistence with antiresorptive treatment for postmenopausal osteoporosis: a randomized controlled trial. J Clin Endocrinol Metab 2004;89:1117-23.
- Delmas P, Vrijens B, Eastell R, Roux C, Pols H, Ringe J, et al. Effect of monitoring bone turnover markers on persistence with risedronate treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab 2007;92:1296-304.
- Gorai I, Tanaka Y, Hattori S, Iwaoki Y. Assessment of adherence to treatment of postmenopausal osteoporosis with raloxifene and/ or alfacalcidol in postmenopausal Japanese women. J Bone Miner Metab 2010;28:176-84.
- Kendler D, McClung M, Freemantle N, Lillestol M, Moffett A, Borenstein J, et al. Adherence, preference, and satisfaction of postmenopausal women taking denosumab or alendronate. Osteoporos Int 2011;22:1725-35.
- McAlister FA, Ye C, Beaupre LA, Rowe BH, Johnson JA, Bellerose D, et al. Adherence to osteoporosis therapy after an upper extremity fracture: a pre-specified substudy of the C-STOP randomized controlled trial. Osteoporos Int 2019;30:127-34.
- Tüzün Ş, Akyüz G, Eskiyurt N, Memi A, Kuran B, İçağasıoğlu A, et al. Impact of the training on the compliance and persistence of weekly bisphosphonate treatment in postmenopausal osteoporosis: a randomized controlled study. Int J Med Sci 2013;10:1880-7.
- Ganda K, Schaffer A, Pearson S, Seibel M. Compliance and persistence to oral bisphosphonate therapy following initiation within a secondary fracture prevention program: a randomised controlled trial of specialist vs. non-specialist management. Osteoporos Int 2014;25:1345-55.
- Gonnelli S, Caffarelli C, Rossi S, Munno O, Malavolta N, Isaia G, et al. How the knowledge of fracture risk might influence adherence to oral therapy of osteoporosis in Italy: the ADEOST study. Aging Clin Exp Res 2016;28:459-68.
- Guilera M, Fuentes M, Grifols M, Ferrer J, Badia X. Does an educational leaflet improve self-reported adherence to therapy in osteoporosis? The OPTIMA study. Osteoporos Int 2006;17:664-71.
- 23. Kung A, Rachman I, Adam J, Roeshadi D, Torralba T, Navarra S, et al. Impact of bone marker feedback on adherence to once monthly

ibandronate for osteoporosis among Asian postmenopausal women. Int J Rheum Dis 2009;12:216-24.

- 24. Lai P, Chua S, Chew Y, Chan S. Effects of pharmaceutical care on adherence and persistence to bisphosphonates in postmenopausal osteoporotic women. J Clin Pharm Ther 2011;36:557-67.
- 25. Muratore M, Quarta E, Quarta L. Intramuscular neridronate in patients with rheumatoid arthritis using corticosteroids: evaluation of treatment adherence in a randomized, open-label comparison with other bisphosphonates. Acta Biomed 2013;84:23-9.
- 26. Oral A, Lorenc R. Compliance, persistence, and preference outcomes of postmenopausal osteoporotic women receiving a flexible or fixed regimen of daily risedronate: a multicenter, prospective, parallel group study. Acta Orthop Traumatol Turc 2015;49:67-74.
- 27. Roh YH, Noh JH, Gong HS, Baek GH. Comparative adherence to weekly oral and quarterly intravenous bisphosphonates among patients with limited health literacy who sustained distal radius fractures. J Bone Miner Metab 2018;36:589-95.
- Roux C, Giraudeau B, Rouanet S, Dubourg G, Perrodeau E, Ravaud P. Monitoring of bone turnover markers does not improve persistence with ibandronate treatment. Joint Bone Spine 2012;79:389-92.
- LeBlanc A, Wang A, Wyatt K, Branda M, Shah N, Houten H, et al. Encounter decision aid vs. clinical decision support or usual care to support patient-centered treatment decisions in osteoporosis: the Osteoporosis Choice randomized trial II. PLoS One 2015;10: e0128063.
- Silverman S, Nasser K, Nattrass S, Drinkwater B. Impact of bone turnover markers and/or educational information on persistence to oral bisphosphonate therapy: a community setting-based trial. Osteoporos Int 2012;23:1069-74.
- Solomon DH, Iversen MD, Avorn J, Gleeson T, Brookhart MA, Patrick AR, et al. Osteoporosis telephonic intervention to improve medication regimen adherence: a large, pragmatic, randomized controlled trial. Arch Int Med 2012;172:477-83.
- 32. Akarirmak U, Kocyigit H, Eskiyurt N, Esmaeilzadeh S, Kuru O, Yalcinkaya E, et al. Influence of patient training on persistence, compliance, and tolerability of different dosing frequency regimens of bisphosphonate therapy: an observational study in Turkish patients with postmenopausal osteoporosis. Acta Orthop Traumatol Turc 2016;50:415-23.
- 33. Briot K, Ravaud P, Dargent-Molina P, Zylberman M, Liu-Leage S, Roux C. Persistence with teriparatide in postmenopausal osteoporosis; impact of a patient education and follow-up program: the French experience. Osteoporos Int 2009;20:625-30.
- 34. Nielsen D, Ryg J, Nielsen W, Knold B, Nissen N, Brixen K. Patient education in groups increases knowledge of osteoporosis and adherence to treatment: a two-year randomized controlled trial. Patient Educ Counsel 2010;81:155-60.
- 35. Majumdar SR, Johnson JA, Lier DA, Russell AS, Hanley DA, Blitz S, et al. Persistence, reproducibility, and cost-effectiveness of an intervention to improve the quality of osteoporosis care after a fracture of the wrist: results of a controlled trial. Osteoporos Int 2007;18:261-70.
- Bianchi M, Duca P, Vai S, Guglielmi G, Viti R, Battista C, et al. Improving adherence to and persistence with oral therapy of osteoporosis. Osteoporos Int 2015;26:1629-38.
- Cizmic A, Heilmann R, Milchak J, Riggs C, Billups S. Impact of interactive voice response technology on primary adherence to bisphosphonate therapy: a randomized controlled trial. Osteoporos Int 2015;26:2131-6.
- Ducoulombier V, Luraschi H, Forzy G, Vandecandelaere M, Houvenagel E. Contribution of phone follow-up to improved

adherence to oral osteoporosis treatment. Am J Pharm Benefits 2015;7:e81-e9.

- Montori V, Shah N, Pencille L, Branda M, Houten H, Swiglo B, et al. Use of a decision aid to improve treatment decisions in osteoporosis: the osteoporosis choice randomized trial. Am J Med 2011;124:549-56.
- Naranjo A, Ojeda-Bruno S, Bilbao-Cantarero A, Quevedo-Abeledo J, Diaz-González B, Rodríguez-Lozano C. Two-year adherence to treatment and associated factors in a fracture liaison service in Spain. Osteoporos Int 2015;26:2579-85.
- Robbins B, Rausch KJ, Garcia RI, Prestwood KM. Multicultural medication adherence: a comparative study. J Gerontol Nurs 2004;30:25-32.
- 42. Schousboe J, DeBold R, Kuno L, Weiss T, Chen YT, Abbott IT. Education and phone follow-up in postmenopausal women at risk for osteoporosis: effects on calcium intake, exercise frequency, and medication use. Dis Manag Health Outcomes 2005;13:395-404.
- 43. Shu AD, Stedman MR, Polinski JM, Jan SA, Patel M, Truppo C, et al. Adherence to osteoporosis medications after patient and physician brief education: post hoc analysis of a randomized controlled trial. Am J Manag Care 2009;15:417-24.
- 44. Stephens MH, Grey A, Fernandez J, Kalluru R, Faasse K, Horne A, et al. 3-D bone models to improve treatment initiation among patients with osteoporosis: a randomised controlled pilot trial. Psychol Health 2016;31:487-97.
- 45. Stuurman-Bieze A, Hiddink E, Boven J, Vegter S. Proactive pharmaceutical care interventions decrease patients' nonadherence to osteoporosis medication. Osteoporos Int 2014;25:1807-12.
- 46. Waalen J, Bruning A, Peters M, Blau E. A telephone-based intervention for increasing the use of osteoporosis medication: a randomized controlled trial. Am J Manag Care 2009;15:e60-70.
- Taibanguay N, Chaiamnuay S, Asavatanabodee P, Narongroeknawin P. Effect of patient education on medication adherence in patient with rheumatoid arthritis: a randomized controlled trial. Patient Pref Adherence 2019;13:119-29.
- Alhefny A, El-Rahman M, El-Moteleb S, Shedid N, Sakr H, Hassan R. Evaluation of adherence to drug treatment in patients with rheumatoid arthritis. Egypt J Rheumatol Clin Immunol 2016; 4:81-92.
- Miedany Y, Gaafary M, Arousy N, Ahmed I, Youssef S, Palmer D. Arthritis education: the integration of patient-reported outcome measures and patient self-management. Clin Exp Rheumatol 2012;30:899-904.
- 50. Brus H, Laar M, Taal E, Rasker J, Wiegman O. Effects of patient education on compliance with basic treatment regimens and health in recent onset active rheumatoid arthritis. Ann Rheum Dis 1998;57:146-51.
- Ferguson A, Ibrahim F, Thomas V, Weinman J, Simpson C, Cope A, et al. Improving medication adherence in rheumatoid arthritis (RA): A pilot study. Psychol Health Med 2015;20:781-9.
- 52. Hill J, Bird H, Johnson S. Effect of patient education on adherence to drug treatment for rheumatoid arthritis: a randomised controlled trial. Ann Rheum Dis 2001;60:869-75.
- Ravindran V, Jadhav R. The effect of rheumatoid arthritis disease education on adherence to medications and followup in Kerala, India. J Rheumatol 2013;40:1460-1.
- 54. Joplin SK, van der Zwan R, Bagga H, Joshua F, Wong PK. Pilot study assessing the novel use of musculoskeletal ultrasound in patients with rheumatoid arthritis to improve patient attitudes and adherence to medication. Int J Rheum Dis 2016;19:658-64.
- 55. Stockl KM, Shin JS, Lew HC, Zakharyan A, Harada AS, Solow BK, et al. Outcomes of a rheumatoid arthritis disease therapy

management program focusing on medication adherence. J Manag Care Pharm 2010;16:593-604.

- Unk JA, Brasington R. Efficacy study of multimedia rheumatoid arthritis patient education program. J Am Assoc Nurse Pract 2014;26:370-7.
- 57. van den Bemt BJ, den Broeder AA, van den Hoogen FH, Benraad B, Hekster YA, van Riel PL, et al. Making the rheumatologist aware of patients' non-adherence does not improve medication adherence in patients with rheumatoid arthritis. Scand J Rheumatol 2011;40:192-6.
- Clifford S, Barber N, Elliott R, Hartley E, Horne R. Patient-centred advice is effective in improving adherence to medicines. Pharm World Sci 2006;28:165-70.
- 59. Abhishek A, Jenkins W, La-Crette J, Fernandes G, Doherty M. Long-term persistence and adherence on urate-lowering treatment can be maintained in primary care--5-year follow-up of a proof-of-concept study. Rheumatology 2017;56:529-33.
- 60. Mikuls TR, Cheetham TC, Levy GD, Rashid N, Kerimian A, Low KJ, et al. Adherence and outcomes with urate-lowering therapy: a site-randomized trial. Am J Med 2019;132:354-61.
- Ting TV, Kudalkar D, Nelson S, Cortina S, Pendl J, Budhani S, et al. Usefulness of cellular text messaging for improving adherence among adolescents and young adults with systemic lupus erythematosus. J Rheumatol 2012;39:174-9.
- 62. Miedany Y, Gaafary M, Palmer D. Assessment of the utility of visual feedback in the treatment of early rheumatoid arthritis patients: a pilot study. Rheumatology Int 2012;32:3061-8.
- 63. Homer D, Nightingale P, Jobanputra P. Providing patients with information about disease-modifying anti-rheumatic drugs: individually or in groups? A pilot randomized controlled trial comparing adherence and satisfaction. Musculoskeletal Care 2009;7:78-92.

- 64. Feldman CH, Wohlfahrt A, Campos A, Gagne JJ, Iversen MD, Massarotti E, et al. Can patient navigators improve adherence to disease-modifying antirheumatic drugs? Quantitative findings from a six-month single-arm pilot intervention. Arthritis Care Res 2018;70:1400-5.
- Rudd R, Blanch D, Gall V, Chibnik L, Wright E, Reichmann W, et al. A randomized controlled trial of an intervention to reduce low literacy barriers in inflammatory arthritis management. Patient Educ Couns 2009;75:334-9.
- 66. Bond CA, Monson R. Sustained improvement in drug documentation, compliance, and disease control. A four-year analysis of an ambulatory care model. Arch Intern Med 1984;144:1159-62.
- 67. Cranney A, Welch V, Tugwell P, Wells G, Adachi JD, McGowan J, et al. Responsiveness of endpoints in osteoporosis clinical trials--an update. J Rheumatol 1999;26:222-8.
- 68. Pasma A, Schenk CV, Timman R, Busschbach JJV, van den Bemt BJF, Molenaar E, et al. Non-adherence to disease-modifying antirheumatic drugs is associated with higher disease activity in early arthritis patients in the first year of the disease. Arthritis Res Ther 2015;17:281.
- Kelly A, Tymms K, Tunnicliffe D, Sumpton D, Perera C, Fallon K, et al. Patients' attitudes and experiences of disease-modifying anti-rheumatic drugs in rheumatoid arthritis and spondyloarthritis; a qualitative synthesis. Arthritis Care Res 2018;70:525-32.
- Conn VS, Ruppar TM, Enriquez M, Cooper PS. Patient-centered outcomes of medication adherence interventions: systematic review and meta-analysis. Value Health 2016;19:277-85.



Correction

Scope of Outcomes in Trials and Observational Studies of Interventions Targeting Medication Adherence in Rheumatic Conditions: A Systematic Review

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In Table 2, the column heads indicating the studies used showed references 13–65. The correct studies should be references 14–66. A corrected Table 2 from the article follows below.

This correction only applies to the August 15 First Release. The correct table appears online and in the October print edition.

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Table 2. Reporting of health outcomes, core domain set, and medication-related adverse events.

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	• /	1.5	16	17	Oste	eoporosi	s/osteop	penia/frac	cture/at r	isk for c	steopoi	OS1S	26	07	20	20	20
Study (ref.)	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Health outcome	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
No. CDS items	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1
Adverse events	1	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	×	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	1	\checkmark	×	×
					Oste	eoporosi	s/osteop	oenia/frac	cture/at r	isk for c	osteopoi	osis					
Study (ref.)	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	
Health outcome	1	1	1	1	1	X	X	X	X	X	x	X	X	X	×	X	
No. CDS items	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Adverse events	X	1	1	\checkmark	X	X	×	X	×	X	X	X	×	×	X	×	
							Rŀ	neumatoi	d Arthrit	is							
Study (ref.)	47	48	49	50	51	52	53	54	55	56	57	58					
Health outcome	1	1	1	1	1	1	1	1	1	1	1	1					
No. CDS items	7	6	6	5	5	4	4	3	1	1	1	0					
Adverse events	X	1	1	X	X	1	×	X	×	X	X	1					
	G	out	SLE	С	ther or l	Multiple	Condit	ions									
Study (ref.)	59	60	61	62	63	64	65	66									
Health outcome	1	1	1	1	1	1	1	1									
No. CDS items	5	2	2	NA	NA	NA	NA	NA									
Adverse events	1	\checkmark	×	1	\checkmark	X	×	X									

✓ Reported. ✗ Not reported. CDS: core domain set (no. items in the core domain set that was reported in each study; ✓: full core domain set reported; ✗: full core domain set not reported); NA: not applicable (no core domain set existing or did not exist at least 5 yrs prior to date of publication).