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

Ayano Kelly, Luke Crimston-Smith, Allison Tong, Susan J. Bartlett, Charlotte L. Bekker, Robin Christensen, Mary A. De Vera, Maarten de Wit, Vicki Evans, Michael Gill, Lyn March, Karine Manera, Robby Nieuwlaat, Shahrzad Salmasi, Marieke Scholte-Voshaar, Jasvinder A. Singh, Daniel Sumpton, Karine Toupin-April, Peter Tugwell, Bart van den Bemt, Suzanne Verstappen, and Kathleen Tymms

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. (J Rheumatol First Release August 15 2020; doi:10.3899/jrheum.190726)

Key Indexing Terms:
SYSTEMATIC REVIEW MEDICATION ADHERENCE RHEUMATIC DISEASES
PATIENT COMPLIANCE CLINICAL TRIALS OUTCOME ASSESSMENT (HEALTH CARE)

From the College of Health and Medicine, Australian National University, Canberra, ACT; Canberra Rheumatology, Canberra, ACT; Centre for Kidney Research, The Children's Hospital at Westmead, Sydney, NSW; Sydney School of Public Health, The University of Sydney, Sydney, NSW, Australia; Department of Medicine, McGill University and Research Institute, McGill University Health Centres, Montreal, Quebec, Canada; Division of Rheumatology, Johns Hopkins School of Medicine, Baltimore, Maryland, USA; Department of Pharmacy, Radboud University Medical Centre, Nijmegen, the Netherlands; Musculoskeletal Statistics Unit, the Parker Institute, Copenhagen University Hospital, Copenhagen, Denmark; Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Odense, Denmark; Collaboration for Outcomes Research and Evaluation, Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver; Arthritis Research Canada, Richmond, British Columbia, Canada; OMERACT Patient Research Partner, the Netherlands; Clear Vision Consulting, and OMERACT Patient Research Partner, Canberra, ACT; Discipline of Optometry, University of Canberra, Canberra, ACT; Dragon Claw Website, and OMERACT Patient Research Partner, Sydney, NSW; Institute of Bone and Joint Research, Kolling Institute of Medical Research, Sydney, NSW; Department of Rheumatology, Royal North Shore Hospital, Sydney, NSW; Northern Clinical School, The University of Sydney, Sydney, NSW, Australia; Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada; Department of Psychology, Health and Technology, University of Twente, Enschede, the Netherlands, and OMERACT Patient Research Partner; Medicine Service, VA Medical Center, Birmingham, Alabama; Department of Medicine, School of Medicine, and Division of Epidemiology, School of Public Health, University of Alabama, Birmingham, Alabama, USA; University of Alabama, Birmingham, Alabama, USA; Department of Rheumatology, Concord Hospital, Sydney, NSW, Australia; The Children's Hospital of Eastern Ontario Research Institute, Ottawa; Department of Pediatrics and School of Rehabilitation Sciences, and Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada; Department

of Pharmacy, Sint Maartenskliniek, Ubbergen, the Netherlands; Centre for Epidemiology Versus Arthritis, Centre for Musculoskeletal Research, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester; UK National Institute for Health Research (NIHR) Manchester Biomedical Research Centre, Manchester University Hospitals National Health Service (NHS) Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK; Department of Rheumatology, Canberra Hospital, Canberra, ACT, Australia.

The work reported in this manuscript was supported by the 2018 Arthritis Australia Project Grant. AK is supported by the Australian Government Research Training Scholarship. SV is supported by Versus Arthritis (grant number 20385) and NIHR Manchester Biomedical Research Centre. RC (The Parker Institute, Copenhagen University Hospital) is supported by a core grant from the Oak Foundation (OCAY-13-309). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

A. Kelly, MBBS, FRACP, College of Health and Medicine, Australian National University, and Canberra Rheumatology, and Centre for Kidney Research, The Children's Hospital at Westmead; L. Crimston-Smith, BN, College of Health and Medicine, Australian National University, and Canberra Rheumatology; A. Tong, PhD, Professor, Centre for Kidney Research, The Children's Hospital at Westmead, and Sydney School of Public Health, The University of Sydney; S.J. Bartlett, PhD, Professor, Department of Medicine, McGill University and Research Institute, McGill University Health Centres, and Division of Rheumatology, Johns Hopkins School of Medicine; C.L. Bekker, PhD, Department of Pharmacy, Radboud University Medical Centre; R. Christensen, Musculoskeletal Statistics Unit, the Parker Institute, Copenhagen University Hospital, and the Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital; M.A. De Vera, PhD, Assistant Professor, Collaboration for Outcomes Research and Evaluation, Faculty of Pharmaceutical Sciences, The University of British Columbia, and Arthritis Research Canada; M. de Wit, PhD, OMERACT Patient Research Partner; V. Evans, PhD, Clear Vision Consulting, and OMERACT Patient Research Partner, and Discipline of Optometry, University of Canberra; M. Gill, BA, Dragon Claw Website, and OMERACT Patient Research Partner; L. March, PhD, Professor, Institute of Bone and Joint Research, Kolling Institute of Medical Research, and the Department of Rheumatology, Royal North Shore Hospital, and the Northern Clinical School, The University of Sydney; K. Manera, MIPH, Centre for Kidney Research, The Children's Hospital at Westmead, and the Sydney School of Public Health, The University of Sydney; R. Nieuwlaat, PhD, Associate Professor, Department of Health Research Methods, Evidence, and Impact, McMaster University; S. Salmasi, MSc, Collaboration for Outcomes Research and Evaluation, Faculty of Pharmaceutical Sciences, University of British Columbia, and Arthritis Research Canada; M. Scholte-Voshaar, MSc, Department of Psychology, Health and Technology, University of Twente, and OMERACT Patient Research Partner; J.A. Singh, MD, Professor, Medicine Service, VA Medical Center, and Department of Medicine, School of Medicine, and Division of Epidemiology, School of Public Health, University of Alabama; D. Sumpton, MBBS, FRACP, Centre for Kidney Research, The Children's Hospital at Westmead, Sydney, and Sydney School of Public Health, The University of Sydney, and Department of Rheumatology, Concord Hospital; K. Toupin-April, PhD, Associate Scientist, The Children's Hospital of Eastern Ontario Research Institute, and Assistant Professor, the Department of Pediatrics and School of Rehabilitation Sciences, University of Ottawa; P. Tugwell, MD, Professor, Department of Medicine, University of Ottawa; B. van den Bemt, PhD, Assistant Professor, Department of Pharmacy, Radboud University Medical Centre, and Department of Pharmacy, Sint Maartenskliniek; S. Verstappen, PhD, Reader, Centre for Epidemiology Versus Arthritis, Centre for Musculoskeletal Research, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, and NIHR Manchester Biomedical Research Centre, Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre; K. Tymms, MBBS, FRACP, Associate Professor, College of Health and Medicine, Australian National University, and Canberra Rheumatology, and Department of Rheumatology, Canberra Hospital.

Address correspondence to A. Kelly, 40 Marcus Clarke St., Canberra City, ACT 2601, Australia. Email: ayano.kelly@anu.edu.au

Accepted for publication December 6, 2019.

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 fracture[4]. 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 outcomes[5]. 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 makers[6]. The Outcome Measures in Rheumatology (OMERACT) initiative has developed core domain sets for many rheumatic conditions[6].

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 (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 handsearched 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.

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 discontinuation[12].

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 calculation/cutoff determined for adherence, metric (e.g., reporting 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 Handbook[6]. 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, 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.

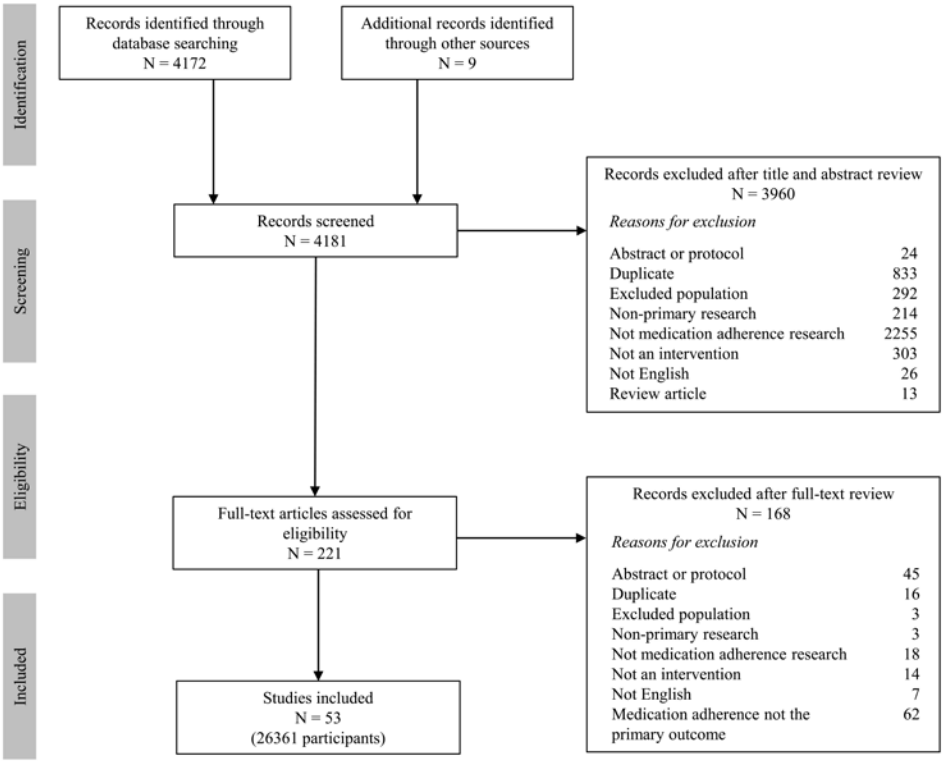

Figure 1. Search results.

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%) 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 osteoporosis[67].

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 set[47].

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

Table 1. Characteristics of included studies.

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.

(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 initiation[68]. The step 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 trials[6] 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 behavior[69]. 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 domains[8]. 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

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.

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 symptoms[70]. 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.

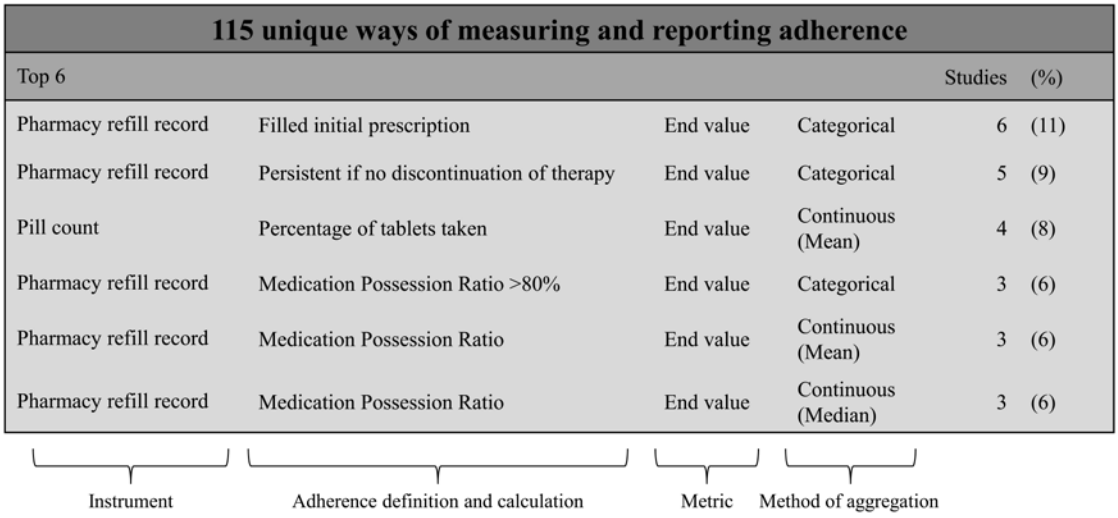

Figure 3. Unique ways of measuring and reporting adherence.

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

Osteoporosis/osteopenia/fracture/at risk for osteoporosis																	
Study (ref.)	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Health outcome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
No. CDS items	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1
Adverse events	✓	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗

Osteoporosis/osteopenia/fracture/at risk for osteoporosis																
Study (ref.)	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45
Health outcome	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
No. CDS items	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Adverse events	✗	✓	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗

Rheumatoid Arthritis												
Study (ref.)	46	47	48	49	50	51	52	53	54	55	56	57
Health outcome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
No. CDS items	7	6	6	5	5	4	4	3	1	1	1	0
Adverse events	✗	✓	✓	✗	✗	✓	✗	✗	✗	✗	✗	✓

	Gout		SLE	Other or Multiple Conditions				
Study (ref.)	58	59	60	61	62	63	64	65
Health outcome	✓	✓	✓	✓	✓	✓	✓	✓
No. CDS items	5	2	2	NA	NA	NA	NA	NA
Adverse events	✓	✓	✗	✓	✓	✗	✗	✗

✓ 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).

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 in the OMERACT-Adherence 5-phase project, which includes qualitative research with patients and researchers, a Delphi survey, and consensus voting[7]. 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

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 recommendation	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)	1	(2)
Prescription documentation	1	(2)
Safety of pharmacist's recommendations	1	(2)
Self-efficacy	1	(2)
Unmet treatment needs	1	(2)

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

ACKNOWLEDGMENT

We acknowledge the contributions of the other members of the OMERACT-Adherence working group, including discussion of the study results and involvement in other OMERACT-Adherence working group projects (Alexa Meara, Caroline Flurey, Catherine Hill, Christine Bailey, Dawn Richards, Dorcas Beaton, Ethan Craig, Francois Nantel, Geraldine Hassett, Helen Keen, Jose Negron, Lara Maxwell, Loreto Carmona, Lucy Henry, Luke Williamson, Maria Suarez-Almazor, Paul Bird, Peter Cheung, Peter Wong, Pongthorn Narongroeknawin, Premarani Sinnathurai, Rebecca Davey, Renske Hebing, Rieke Alten, Sabrina Mai Nielson, Sean O'Neill, Therese Dawson, Willemina Campbell, Yomei Shaw), and Gail Higgins for her review of the search strategy.

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The Journal of Rheumatology 2020;xxxxx
doi:10.3899/jrheum.190726.C1

The Journal of Rheumatology

Correction

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

Ayano Kelly, Luke Crimston-Smith, Allison Tong, Susan J. Bartlett, Charlotte L. Bekker, Robin Christensen, Mary A. De Vera, Maarten de Wit, Vicki Evans, Michael Gill, Lyn March, Karine Manera, Robby Nieuwlaat, Shahrzad Salmasi, Marieke Scholte-Voshaar, Jasvinder A. Singh, Daniel Sumpton, Karine Toupin-April, Peter Tugwell, Bart van den Bemt, Suzanne Verstappen, and Kathleen Tymms

J Rheumatol 2020; doi:10.3899/jrheum.190726

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.

doi:10.3899/jrheum.190726.C1

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

	Osteoporosis/osteopenia/fracture/at risk for osteoporosis																
Study (ref.)	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Health outcome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
No. CDS items	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1
Adverse events	✓	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗

	Osteoporosis/osteopenia/fracture/at risk for osteoporosis															
Study (ref.)	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46
Health outcome	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
No. CDS items	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Adverse events	✗	✓	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗

	Rheumatoid Arthritis											
Study (ref.)	47	48	49	50	51	52	53	54	55	56	57	58
Health outcome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
No. CDS items	7	6	6	5	5	4	4	3	1	1	1	0
Adverse events	✗	✓	✓	✗	✗	✓	✗	✗	✗	✗	✗	✓

	Gout		SLE	Other or Multiple Conditions				
Study (ref.)	59	60	61	62	63	64	65	66
Health outcome	✓	✓	✓	✓	✓	✓	✓	✓
No. CDS items	5	2	2	NA	NA	NA	NA	NA
Adverse events	✓	✓	✗	✓	✓	✗	✗	✗

✓ 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).