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Outcomes Reported in Prospective Long-Term Observational Studies and Registries of Patients With Rheumatoid Arthritis Worldwide: An Outcome Measures in Rheumatology Systematic Review

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Objective. Prospective long-term observational studies (LOS) in rheumatoid arthritis (RA) lack a core set of universally collected outcome measures, particularly patient-centered outcomes, precluding accurate comparisons across studies. Our aim was to identify long-term outcome measures collected and reported in these studies.

Methods. We conducted a systematic review of registries and LOS of patients with RA, searching in ClinicalTrials.gov, the Agency for Healthcare Research and Quality Registry of Patient Registries, and Google Scholar. The names and acronyms of registries and LOS were further searched in the Medline and Embase databases to retrieve published articles. Two independent reviewers undertook data collection, quality appraisal, and data extraction.

Results. We identified 88 registries/LOS that met our eligibility criteria. These were divided into 2 groups: disease-based (52 [59%]) and therapy-based (36 [41%]). Methodologic and reporting standards varied across the eligible studies. For clinical outcomes, disease activity was recorded in 88 (100%) of all LOS/registries. The most commonly reported measure (86 [98%]) was the composite outcome Disease Activity Score using 28 joints. Of the patient-centered outcomes collected, physical functioning was most frequently reported (75 [85%]) with the Health Assessment Questionnaire (75 [85%]) as the most commonly used instrument within this domain. Other domains of patient-centered outcomes were comparatively infrequently recorded: mental (29 [33%]), social (20 [23%]), and health-related quality of life (37 [42%]).

Conclusion. Most registries/LOS collect measures of disease activity and physical function. However, there is substantial heterogeneity in the collection of relevant patient-centered outcomes that measure symptom burden and mental and social ramifications of RA.

INTRODUCTION

Over the past few decades, there has been growing interest and need for prospective long-term observational studies (LOS) and registries pertaining to rheumatoid arthritis (RA). Randomized controlled trials (RCTs) are generally held in the highest esteem because they are likely to provide the best evidence for causality. However, they most often focus on addressing one specific question, and unless they are designed as community-based pragmatic trials, they may not provide real-world data. The strict inclusion and exclusion criteria of RCTs ensure internal validity but can lead to uncertainty about generalizability. In addition, RCTs provide information on the efficacy of therapies for RA in the shorter term but may not be ideal to address longer-term effectiveness. Prospective LOS and patient registries can address questions about long-term effectiveness and collect multiple outcomes as well as rare adverse events associated with therapy, which is typically not feasible in RCTs. Numerous RA cohorts and registries around the world are collecting longitudinal data to complement evidence obtained from RCTs. A few studies examining the features of

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SIGNIFICANCE & INNOVATIONS

- We identified 88 prospective long-term observational studies and registries across the world reporting outcomes in patients with rheumatoid arthritis.
- Globally, there is significant heterogeneity of collected and reported outcomes across observational studies and registries, varying according to the type of registry (i.e., disease-based versus therapy-based).
- Patient-centered outcomes measuring symptom burden and mental and social aspects of disease are not consistently collected and/or reported.

selected registries/LOS in RA have found significant heterogeneity in the outcomes collected, creating challenges in the comparability of findings across studies (1–3). Although there have been efforts to reduce the variability in data collection and analysis, a well-defined and universally accepted core set of outcomes to be measured in LOS that includes important patient-centered domains with specific relevance to long-term outcomes has yet to be agreed upon (4–6). The European Alliance of Associations for Rheumatology proposed a core set that primarily included pathophysiologic measures. Although they recommended measuring quality of life and function, specific subdomains were not proposed (5). Barber et al in Canada also proposed a core set of measures to be collected in clinical practice to improve quality of care, rather than for longitudinal outcome studies (6).

Using the Strengthening the Reporting of Observational Studies in Epidemiology statement, a previous study reviewed registries and cohorts of RA patients receiving biologic therapy in the US and Europe to compare differences in study design and methods that may explain heterogeneous results (1). The review compared methodologic domains such as recruitment methods and inclusion data among selected therapy-based registries. However, only selected clinical outcomes could be evaluated due to the heterogeneity of outcomes collected, and no data on outcomes potentially important to patients (e.g., fatigue, sleep, productivity) were assessed except for physical function and health-related quality of life (HRQoL).

In 2017, a European Alliance of Associations for Rheumatology task force agreed upon a set of 21 core set domains and instruments for observational studies in RA (5). Many domains important to patients, such as productivity, social engagement, and survival, were not included as core measures, but merely as desirable or complementary. Furthermore, how RA patients view the importance and relevance of outcomes reported in studies is not clear (7,8). The Outcome Measures in Rheumatology (OMERACT) initiative has designed and implemented strategies to develop and validate outcomes to be reported in rheumatic diseases such as RA, and continues to be a significant driving force behind this effort (9). OMERACT relies on the inclusion of the patient's voice in discussions regarding the relevance and appropriateness of outcome measures, recognizing and including the patient perspective (10). Although designed for use in RCTs and LOS, most of the RA outcome measures agreed upon in OMERACT have been adopted in the setting of an RCT or short-term studies. A wide consensus on what outcomes, especially patient-centered outcomes, should be collected in RA registries has yet to be reached.

To build upon the interests of research groups, a first step is to identify outcome domains and measures, including patient-centered outcomes, currently collected in long-term studies of RA patients. We therefore conducted a systematic review of registries/LOS of patients with RA, primarily evaluating data collection and reporting patient-centered outcomes.

MATERIALS AND METHODS

Eligibility criteria. We included both registries and prospective LOS. Although the distinction is not always clear, registries are generally considered to be databases with ongoing longitudinal data collection of individual patients, with data not necessarily collected to answer specific research questions; they are often population-based (11). In contrast, LOS usually include patients in specific settings and often aim to answer defined research questions.

To be included in our review, registries/LOS had to include patients with RA, assess outcomes or prognosis, include clinical outcomes or patient-centered outcomes in their data collection (we used the definitions and concepts provided by the Patient-Centered Outcomes Research Institute) (12), and have appeared in at least 1 publication written in English since 2013. Registries/LOS were excluded if they were an open label extension of a clinical trial, the purpose of the registry was to answer a particular question unrelated to clinical, patient-centered, or safety outcomes (e.g., biomarkers, lifestyle habits), or entry into the registry was limited to those with a specific articular or extraarticular manifestation of RA (e.g., anemia) or a certain study subpopulation (e.g., those with interstitial lung disease).

Registry identification and selection. Our search strategy started with a Google Scholar search using the names of the 193 United Nations member states as listed on the organization's website (13). Then, for each member state, the name was combined with the keywords "rheumatoid" and "registry," and the first 15 results were selected for review. To help reduce false hits in the search results, we searched multiple-word names as a phrase (e.g., "Marshall Islands"), and a few single-word names were searched within quotation marks (e.g., "Niger" to avoid retrieving "Nigeria"). Some member states were searched using both the formal and common names (e.g., "Côte D'Ivoire" and "Ivory Coast"), and others were searched using only a simplified name (e.g., "Bolivia" rather than "The Plurinational State of Bolivia"). We also searched

2 databases of registries: the Agency for Healthcare Research and Quality (AHRQ) Registry of Patient Registries (RoPR) and ClinicalTrials.gov, using terms related to RA and registries. Additional handsearching was performed for identified registries/LOS when URLs were not readily available through the previous searches. This search strategy resulted in 2,996 URLs, of which 2,766 were excluded as per Figure 1, leaving 230 URLs corresponding to 88 unique registries/LOS. The decision to include an LOS/registry in the review was made by 2 independent pairs of reviewers (either RJZ and JdB or NVZ and DR). Consensus was reached by discussion or third-party adjudication (MES-A).

Data collection process. Data sources to retrieve information from the selected registries/LOS included websites and publications in the medical literature. For each registry included in the review, we identified public websites and the corresponding URLs. Initial sources of data, when available, included information from the websites or in the databases of registries (RoPR and ClinicalTrials.gov). For the next step, an expert health sciences librarian (GP) conducted searches in the Medline and Embase databases (via the Ovid platform) using the names and acronyms of the identified registries/LOS for all publications until August 2018. When retrieval was sparse, proximity operators were used in the search strings for names of registries. When available, ClinicalTrials.gov identifiers were also included. For example, literature involving the Consortium of Early Arthritis Cohorts USA was searched in all fields of database records using (Consortium adj3 "Early Arthritis" adj3 Cohort* or "CATCH US" or CATCH-US or NCT02386527.af.) To further identify relevant citations, those retrieved were cross-referenced with subject heading (National Library of Medicine [MeSH] or Embase [Emtree]) terms related to RA and registry or cohort keywords. Preference was given to literature describing the registries/cohorts themselves and to citations published from January 2013 to August 2018.

Publications related to each registry were compiled in EndNote (Clarivate Analytics), and all citations were grouped by registry. Only English language publications were reviewed. To extract variables of interest, 2 reviewers (RJZ and JdB) independently examined the websites, databases of registries/LOS, and full-text publications related to each registry. For scientific publications, we

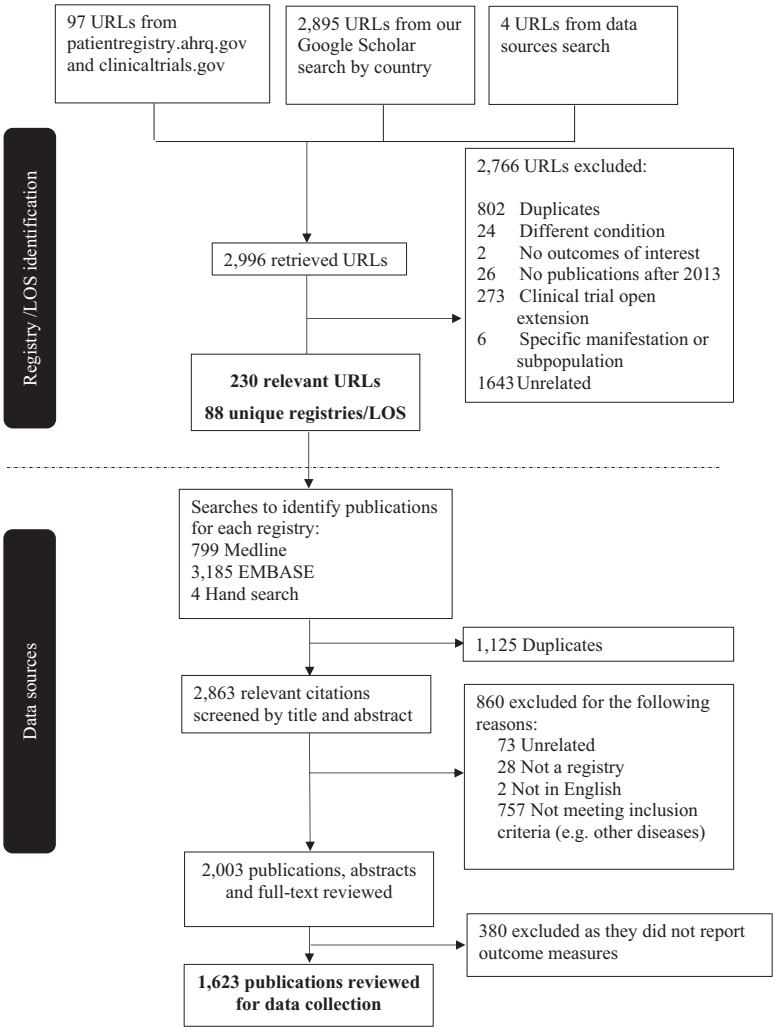

Figure 1. Flow diagram of the identification and selection process. LOS = long-term observational studies.

extracted variables of interest from the Methods and Results sections. Disagreements regarding the data collected were resolved by consensus or third-party adjudication (MES-A).

We collected general registry information, including country, types of patients included, and the purpose of the registry/LOS when specified from all sources available, including websites and publications. Because we were primarily interested in patient-centered outcomes, we evaluated documentation of specific outcome domains and sociodemographic data broadly, covering commonly identified risk factors for RA outcomes, clinical outcomes, and patient-centered outcomes, primarily patient-reported outcomes. These included: socioeconomic status (e.g., education and income); comorbidities, including smoking; rheumatoid factor and/or anti–citrullinated protein antibody levels; clinical outcomes (e.g., radiographic evaluation and clinician-based disease activity indices); safety outcomes (e.g., serious adverse events [SAEs] and death); and patient-centered outcomes (e.g., measures of physical function or HRQoL, as well as assessments of symptom burden, such as pain, fatigue, stiffness, sleep, mental anguish [e.g., depression, anxiety], and social participation [e.g., working status]).

Quality appraisal. Two pairs of reviewers independently appraised the registries/LOS (either RJZ and JdB or NVZ and DR). Disagreements were resolved by consensus or third-party adjudication (MES-A). To appraise the quality of each registry, we used a guide developed by AHRQ (14) that includes the following items: 1) planning (written registry protocol with goals, a defined target population, specific methods for collecting information, and appropriate personnel and storage of data); 2) design (appropriate review of the literature, description of the target population, defined inclusion and exclusion criteria of patients, and estimated follow-up time); 3) data elements and resources (including appropriate and validated scales for assessing outcomes); and 4) ethics (including protection of human subjects such as privacy and informed consent, and review and approval by oversight committees).

Synthesis of results. Characteristics and reported variables were summarized overall and by type of registry/LOS (disease-based or therapy-based). Descriptive statistics were used to synthesize the data collected; unweighted frequencies and percentages were used for categorical variables.

RESULTS

We identified 97 URLs for registries/LOS from RoPR and ClinicalTrials.gov. The Google Scholar search identified 2,895 URLs, and an additional 4 were identified through handsearching. After cross-referencing and selection, we included 230 relevant URLs corresponding to 88 registries/LOS (Figure 1 and Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24163/abstract). One of these was a collaboration among registries (not a registry on its own), which we decided to include because it provided data from registries with no individual data from different countries (15).

Table 1. Characteristics of the registries and prospective long-term observational studies included in our analysis*

Characteristic	Disease-based (n = 52)	Therapy-based (n = 36)	Total (n = 88)
Location			
Asia	9 (17)	5 (14)	14 (16)
Europe	29 (56)	24 (67)	53 (60)
North America	9 (17)	3 (8)	12 (14)
South America	3 (6)	3 (8)	6 (7)
Oceania	1 (2)	–	1 (1)
International	1 (2)	1 (3)	2 (2)
Data source			
Publications	52 (100)	36 (100)	88 (100)
Website	22 (42)	9 (25)	31 (35)
ClinicalTrials.gov	9 (17)	7 (19)	16 (18)
Patients with only RA	39 (75)	14 (39)	53 (60)

* Values are the number (%). RA = rheumatoid arthritis.

To ascertain outcome measures, in addition to reviewing websites, we conducted a publication search that yielded 2,863 publications after deduplication (Figure 1). Titles and abstracts of 2,863 publications were reviewed; 860 of these articles were excluded for reasons detailed in Figure 1. The full text of the remaining 2,003 publications was reviewed, and an additional 380 were excluded because they did not report outcome measures, leaving 1,623 publications eligible for review.

Characteristics of registries/LOS. Table 1 shows the characteristics of the included registries/LOS. Of the 88, 52 (59%) were disease-based, and 36 (41%) were therapy-based. The origin of the registries/LOS included 36 different countries across South America, North America, Asia, Oceania, and Europe, with most originating from the US. Registries/LOS primarily included patients with RA; however, 34 (13 disease-based and 21 therapy-based) also included patients with diseases other than RA, including myositis, systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis, osteoporosis, osteoarthritis, gout, fibromyalgia, juvenile idiopathic arthritis, Crohn's disease, and ulcerative colitis.

Quality assessment. Data elements and resources was the most frequent quality domain in compliance with guidelines in both types of registries/LOS: 39 (75%) for disease-based, and 29 (81%) for therapy-based (Table 2). Planning and design were the

Table 2. Compliance with AHRQ quality domains (ref. 14)*

Registry type	Planning	Design	Data elements and resources	Ethics
Disease-based (n = 52)	7 (13)	10 (19)	39 (75)	32 (62)
Therapy-based (n = 36)	8 (22)	8 (22)	29 (81)	14 (39)
Total (n = 88)	15 (17)	18 (20)	68 (77)	46 (52)

* Values are the number (%). AHRQ = Agency for Healthcare Research and Quality; ref. = reference.

least frequently reported domains: 7 (13%) in disease-based and 8 (22%) in therapy-based for planning, and 10 (19%) in disease-based and 8 (22%) in therapy-based for design.

Data collected. A summary of the data collected in the registries/LOS is shown in Tables 3 and 4. We evaluated a total of 43 outcomes, including clinical outcomes (disease activity, imaging, safety), and patient-centered outcomes comprising 3 domains: physical, mental, and social wellbeing, as well as HRQoL. The mean ± SD of outcomes collected by disease-based registries/LOS was 12.1 ± 5.0 and by therapy-based registries was 10.1 ± 4.0. The mean ± SD of patient-centered outcomes collected by disease-based registries was 4.8 ± 3.0 and by therapy-based registries was 2.4 ± 2.2.

Sociodemographic data and risk factors. All registries/LOS reported data collection of sociodemographic data and risk factors. The collection of serologic markers, including rheumatoid factor and anti–cyclic citrullinated peptide (73 [83%]), was the most frequently reported variable, with comorbidities (72 [82%]) being the second most frequently reported variable. Alcohol consumption was reported in 10 (11%) of registries/LOS, whereas smoking was reported in 63 (73%).

Clinical outcomes. All registries/LOS reported the collection of at least 1 disease activity measure or composite index. The most commonly reported disease activity outcome was the Disease Activity Score using 28 joints (DAS28) or 1 of its versions (86 [98%]) (16). Other indices reported included the American College of Rheumatology 20% improvement criteria (10 [11%]) (17,18), the Simplified Disease Activity Index (35 [40%]) (19), the Clinical Disease Activity Index (38 [43%]) (20), and the physician global assessment (37 [42%]). Other markers of disease activity included erythrocyte sedimentation rate, C-reactive protein level, and tender and/or swollen joint counts. Patient global assessments of disease activity scores were reported in 40 (77%) and 26 (2%) of condition- and therapy-based registries/LOS, respectively. More disease-based than therapy-based registries reported imaging data: 37 (71%) versus 18 (50%). The most common instrument score reported was the Sharp/van der Heijde score (21,22).

Table 3. Variables and outcomes reported in the registries and prospective long-term observational studies in our analysis*

	Disease-based (n = 52)	Therapy-based (n = 36)	Total (n = 88)
Sociodemographic data			
Education status	21 (40)	7 (19)	28 (32)
Income	16 (31)	–	16 (18)
Financial measures (nonspecified)	17 (33)	6 (17)	23 (26)
Lifestyle factors			
Alcohol	9 (17)	1 (3)	10 (11)
Smoking	40 (77)	24 (67)	64 (73)
Clinical characteristics			
RF/ACPA	46 (88)	27 (75)	73 (83)
Comorbidities	41 (79)	31 (86)	72 (82)
Disease activity	52 (100)	36 (100)	88 (100)
DAS28/DAS28-CRP/ESR	50 (96)	36 (100)	86 (98)
DAS28-CRP	17 (33)	10 (28)	27 (31)
DAS28-ESR	11 (21)	11 (31)	22 (25)
ACR20	6 (12)	4 (11)	10 (11)
SDAI	23 (44)	12 (33)	35 (40)
CDAI	21 (40)	17 (47)	38 (43)
Patient global assessment	40 (77)	26 (72)	66 (75)
Physician global assessment	26 (50)	11 (31)	37 (42)
RADAI	9 (17)	1 (3)	10 (11)
RAID	1 (2)	4 (11)	5 (6)
RAPID	12 (23)	4 (11)	16 (18)
Drug safety			
Serious adverse events	17 (33)	36 (100)	53 (60)
Deaths	16 (31)	17 (47)	33 (38)
Imaging	37 (71)	18 (50)	55 (63)

* Values are the number (%). ACPA = anti–citrullinated protein antibody; ACR20 = American College of Rheumatology 20% improvement criteria (refs. 17,18); CDAI = Clinical Disease Activity Index (ref. 20); DAS28 = Disease Activity Score using 28 joints (ref. 16); DAS28-CRP = DAS28 using the C-reactive protein level (ref. 31); DAS28-ESR = DAS28 using the erythrocyte sedimentation rate (ref. 32); RADAI = Rheumatoid Arthritis Disease Activity Index; RAID = Rheumatoid Arthritis Impact of Disease (ref. 33); RAPID = Routine Assessment of Patient Index Data (ref. 34); RF = rheumatoid factor; SDAI = Simplified Disease Activity Index (ref. 19).

Table 4. The frequencies of patient-centered outcomes*

	Disease-based (n = 52)	Therapy-based (n = 36)	Total (n = 88)
Health-related quality of life	27 (52)	10 (28)	37 (42)
EQ-5D	19 (37)	7 (19)	26 (30)
SF-6D	3 (6)	2 (6)	5 (6)
SF-36	16 (31)	8 (22)	24 (27)
SF-12	–	2 (4)	2 (2)
AIMS2	–	1 (2)	1 (1)
RAQoL	2 (4)	–	2 (2)
EQ-VAS	3 (6)	–	3 (3)
PROMIS-29	1 (2)	2 (6)	3 (3)
Physical domain	48 (92)	28 (78)	76 (86)
Function	48 (92)	27 (75)	75 (85)
HAQ†	48 (92)	27 (75)	75 (85)
HAQ DI	45 (87)	25 (69)	70 (80)
MDHAQ	9 (17)	4 (11)	13 (15)
HAQ-II	5 (10)	1 (3)	6 (7)
PAS-II	1 (2)	–	1 (1)
FFbH	–	1 (3)	1 (1)
VAS function	8 (15)	–	8 (9)
Symptom burden	46 (88)	19 (53)	65 (74)
Pain	43 (83)	18 (50)	61 (69)
Sleep	12 (23)	–	12 (14)
Fatigue	22 (42)	9 (25)	31 (35)
Stiffness	23 (44)	6 (17)	29 (33)
Mental domain	23 (44)	6 (17)	29 (33)
Depression	19 (37)	6 (17)	25 (28)
Anxiety	8 (15)	1 (3)	9 (10)
Fear	2 (4)	–	2 (2)
Coping	2 (4)	1 (3)	3 (3)
Helplessness	1 (2)	–	1 (1)
Social domain	12 (23)	8 (22)	20 (23)
Working status	9 (17)	6 (17)	15 (17)
WPAI	3 (6)	3 (8)	6 (7)

* Values are the number (%). AIMS2 = Arthritis Impact Measurement Scale 2 (ref. 40); EQ-5D = EuroQol 5-domain questionnaire (ref. 24); EQ-VAS = EuroQol visual analog scale (ref. 42); FFbH = Funktionsfragebogen Hannover; HAQ = Health Assessment Questionnaire; HAQ DI = HAQ disability index (ref. 23); MDHAQ = multidimensional HAQ (ref. 35); PAS-II = Patient Activity Scale II (ref. 37); PROMIS-29 = Patient-Reported Outcomes Measurement Information System 29; RAQoL = Rheumatoid Arthritis Quality of Life questionnaire (ref. 41); SF-6D = Short Form 6 dimensions (ref. 38); SF-12 = SF 12-item questionnaire (ref. 39); SF-36 = SF 36-item questionnaire (ref. 25); VAS = visual analog scale; WPAI = Work Productivity and Activity Impairment questionnaire (ref. 43).
† Three forms of HAQ collected included HAQ DI, MDHAQ, and HAQ II (ref. 36).

Safety. We assessed the reporting of SAEs and deaths. Only one-third of disease-based registries reported the collection of SAEs, compared with all therapy-based registries. Death was also less frequently reported as being recorded in the disease-based than in the therapy-based registries: 16 (31%) compared with 17 (47%).

Patient-centered outcomes. We examined patient-centered outcomes because they pertain to HRQoL and its 3 major domains: physical (comprising function and symptom burden), mental, and social. Among different Health Assessment Questionnaire (HAQ) scales used, the HAQ disability index (HAQ DI) (23) was reported in 45 (87%) of the disease-based and 25 (69%) of the therapy-based registries. Among the 8 different scales used to assess HRQoL, the EuroQol 5-domain questionnaire (24) was most commonly reported in disease-based registries (19 [37%]). In therapy-based registries, the Medical Outcomes Study Short Form 36-item questionnaire (25) was reported most frequently, used by 8 (22%) of these registries.

Registries/LOS reported collection of patient-centered outcomes pertaining to the physical domain (76 [86%]) more frequently than either the mental (29 [33%]) or social (20 [23%]) domains. Within the physical domain, outcomes related to function (disease-based 48 [92%], therapy-based 27 [75%]) were collected more frequently than symptom burden (disease-based 46 [88%], therapy-based 19 [53%]). The mental domain was reported least frequently in the therapy-based registries/LOS (6 [17%]) when compared to all other patient-centered outcomes. The reporting of outcomes in the social domain was similar for disease-based and therapy-based registries/LOS, 12 (23%) versus 8 (22%), respectively (Table 4). The most frequently reported outcome within the subgroup of function was HAQ DI, where 45 (87%) of disease-based and 25 (69%) of therapy-based registries/LOS reported collection. The most frequently reported outcome within the subgroup of symptom burden was pain, which was collected in 43 (83%) of disease-based and 18 (50%) of therapy-based registries/LOS. The most frequently reported outcome within the mental domain was depression, with 19 (37%) of disease-based and 6 (17%) of therapy-based registries/LOS reporting collection. Patient-centered outcomes identified in our search relating to the social domain were working status (disease-based 9 [17%], therapy-based 6 [17%]) and the Work Productivity and Activity Impairment questionnaire (disease-based 3 [6%], therapy-based 3 [8%]) (Table 4). Considerable heterogeneity across registries within close geographic proximity was observed with respect to the types of instruments used to measure disease activity, HRQoL, and patient-centered outcomes (data not shown).

DISCUSSION

This study was the first step from an OMERACT initiative to identify outcome domains and measures, including patient-centered outcomes, currently collected in long-term studies of RA patients. We therefore conducted one of the largest systematic reviews scrutinizing the data collection of RA registries/LOS worldwide. We found substantial heterogeneity in the collected outcome measures and variability in the instruments used to define these outcomes. We inferred the perceived importance of these variables by how frequently they were reported. For the purpose of our study, we divided registries into 2 groups: disease-based and therapy-based.

We observed differences in the quality domains between the types of registries. Planning and design were more commonly reported in the therapy-based than in the disease-based

registries. This finding is likely because data collection surrounding drug administration is more stringently regulated. Regarding the data collected, disease-based registries collected more variables than therapy-based registries. This practice may be because therapy-based registries often focus on pharmacovigilance and adverse events related to therapy, limiting their scope of collection. A therapy-based registry focus on adverse-events related to therapy explains why safety data annotating serious adverse reactions were recorded in 17 (33%) of the disease-based registries versus 36 (100%) of the therapy-based registries. Imaging data were recorded in 55 (63%) of all registries, with a higher proportion of disease-based than therapy-based registries collecting this information. These data may have been omitted from the therapy-based registries because the efficacy of the drug had already been proven in an RCT. Given the additional expense of imaging, the administrators of the therapy-based registries may have considered it unnecessary. Conceivably, given the fact that imaging is a surrogate marker for long-term outcomes, if a registry was collecting alternative long-term outcomes, the collection of imaging data might also have been considered redundant.

More than half of the registries were from European countries. This fact was not surprising because many European countries are under a national health system, allowing for data collection across their populations, and some registries were introduced as a requirement for the pharmacovigilance of biologic agents. However, the type of disease activity, HRQoL, and patient-centered outcomes instruments varied within close geographic regions. Variation in the outcomes instruments used within close geographic regions could be due to an individual registry's conceptualization and provenance occurring independently in a similar time frame, without collaboration at early design and implementation stages.

One or more patient-centered outcomes were collected by the majority of registries. However, the degree of heterogeneity for patient-centered outcomes was considerably greater than that of outcomes related to disease activity. When patient-centered outcomes were divided into domains, we noted significant differences, with those relating to physical function and symptom burden being most frequently reported compared to the mental and social domains. Interestingly, within the social domain we only identified 2 specific reported outcomes outside generic instruments, and both focused on productivity. All other aspects of social participation that are not already captured by HRQoL outcomes were not reported. Other aspects of social participation were not reported, which illuminates the limited emphasis placed on collecting outcomes focused on assessing both the mental and social domains, despite the fact that, over the past decade, there has been increasing pressure from government agencies and the research community to provide a more holistic view of disease (26). There has also been a change in the doctor-patient relationship, moving away from medical paternalism towards shared decision-making, autonomy, and inclusion. This shift does not appear to be well reflected yet in registry design and data collection. Evidence suggests that the use of outcomes that are relevant to patients increases patient satisfaction and improves patient–provider communication, as well as overall patient HRQoL (27). In the clinical setting, patient-centered outcomes may help patients in making informed decisions about their care (by providing results across time and assessing their perspective to these results and treatment) and aid clinicians in monitoring the progress of care.

Our findings are consistent with previous analyses of RA registries. Radner et al (3) evaluated the variables contained in 27 registries across 16 European countries and determined that the most frequently recorded variables were those that described disease activity; DAS28 was reported as being recorded in 100% of the registries. The researchers' work also demonstrated a substantial amount of heterogeneity in collected outcome measures across the European continent (3). Curtis et al (1) performed an analysis of European and American registries, comparing patient characteristics, drug therapy, and adverse events recorded in the various registries. This analysis also reported heterogeneity in the outcomes collected. The authors of that article used a similar strategy to ours of identifying which outcomes were collected by the registries of interest (1).

Registries are created to collect specific, pertinent data. An important purpose of the data collected is to improve patient experience, outcome, and quality of life. However, if data are recorded but never scrutinized, then the purpose of these data may be questioned. Thus, even if data were not captured by our search, the absence of these data from publication lends credence to our salient point that homogeneity in data collection and research is required. In the current review, we did not identify how often data were recorded by each registry. Although the first step in ensuring homogeneity of data collection is to define a core set of outcome measures, ideally the frequency of recording such data will also be standardized.

As the importance of registry data continues to increase, an effort has been made to help define what should be universally recorded by registries (28,29). In 2017, the European Alliance of Associations for Rheumatology outlined 21 variables as the minimum number of data points that should be collected by any registry. This list provides an excellent framework for researchers to determine which outcome measures are important not only to clinicians but also to their patients. However, within this recommendation, there is a relative paucity of guidance on patient-centered outcomes. Of the 21 recommended variables, only 3 are included: HAQ, EuroQol 5-domain questionnaire, and pain (5). We found that 2 of these measures were the most frequently reported (HAQ: 75 [85%], and pain: 61 [64%]). The HAQ might be most frequently reported because functional status is an outcome of relevance for both patients and providers and has been available for decades. Evidence suggests that the HAQ is also a useful monitoring tool that is easily completed by patients in the clinical setting (30).

Some limitations to our study merit further discussion. Unfortunately, there was no single data collection form or method used by all of the registries to assemble the collected variables. For this reason, we relied on information gleaned from published articles, Google Scholar searches, registry websites, ClinicalTrials.gov, and RoPR to determine which variables were recorded by the individual registries. Another limitation of the study is also true for our quality assessment, which was done only using the data reported in articles meeting our eligibility criteria. Studies published before the year 2013 could have reported registry data that were not captured in subsequent publications. Also, given the scope of our study, we were unable to directly contact the administrators of individual registries. Therefore, we cannot ensure that our search was able to fully capture all variables recorded by the individual registries. However, the frequencies we obtained are similar to those noted in previous studies in which registry administrators were contacted (3). In addition, our search strategy included only English publications, and this limitation may have resulted in relevant publications being omitted.

Registries provide pertinent information about the long-term trajectory of disease and disease burden. The current study demonstrates the heterogeneity of collected variables among international registries and indicates that a strategy is needed to reduce the variability of data collection. Further, the study highlights the need for greater emphasis to be placed on the collection of patient-centered outcomes other than physical function and symptom burden. Although we found that patient-centered outcomes that assess physical function (76 [86%]) and symptom burden (65 [74%]) are collected with some regularity, those outcomes that assess other aspects of disease burden were collected inconsistently. Patient-centered outcomes measures provide vital information regarding the patient experience; hopefully, their collection can be routinely incorporated into registry design in the future. Additional studies will be needed to further assess the acceptability and comfort that patients may have answering questions related to psychosocial domains, and whether social desirability factors may impact the completeness and validity of data collection and analysis.

Due to the long-term outlook of registries, outcome measures that are essential in RCTs may not be as important to registries and may not provide the information most relevant to patients. A core set of clearly defined outcomes that are relevant to patients would allow for collaborative research and comparisons across registries and would facilitate analyses that could potentially identify geographic, racial, and cultural differences in disease outcomes.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Suarez-Almazor had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1. Curtis JR, Jain A, Askling J, Bridges SL Jr, Carmona L, Dixon W, et al. A comparison of patient characteristics and outcomes in selected European and U.S. rheumatoid arthritis registries. Semin Arthritis Rheum 2010;40:2–14.
2. Kearsley-Fleet L, Zavada J, Hetland ML, Nordstrom DC, Aaltonen KJ, Listing J, et al. The EULAR Study Group for Registers and Observational Drug Studies: comparability of the patient case mix in the European biologic disease modifying anti-rheumatic drug registers. Rheumatology (Oxford) 2015;54:1074–9.
3. Radner H, Dixon W, Hyrich K, Askling J. Consistency and utility of data items across European rheumatoid arthritis clinical cohorts and registers. Arthritis Care Res (Hoboken) 2015;67:1219–29.
4. Baillet A, Gossec L, Carmona L, Wit M, van Eijk-Hustings Y, Bertheussen H, et al. Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. Ann Rheum Dis 2016;75:965–73.
5. Radner H, Chatzidionysiou K, Nikiphorou E, Gossec L, Hyrich KL, Zabalan C, et al. 2017 EULAR recommendations for a core data set to support observational research and clinical care in rheumatoid arthritis. Ann Rheum Dis 2018;77:476–9.
6. Barber CE, Mosher DP, Ahluwalia V, Zummer M, Marshall DA, Choquette D, et al. Development of a Canadian core clinical dataset to support high-quality care for Canadian patients with rheumatoid arthritis. J Rheumatol 2017;44:1813–22.
7. Dougados M, Nataf H, Steinberg G, Rouanet S, Falissard B. Relative importance of doctor-reported outcomes vs patient-reported outcomes in DMARD intensification for rheumatoid arthritis: the DUO study. Rheumatology (Oxford) 2013;52:391–9.
8. Primdahl J, Jensen DV, Meincke RH, Jensen KV, Ziegler C, Nielsen SW, et al. Patients' views on routine collection of patient-reported outcomes in rheumatology outpatient care: a multicenter focus group study. Arthritis Care Res (Hoboken) 2020;72:1331–8.
9. Boers M, Tugwell P, Felson DT, van Riel PL, Kirwan JR, Edmonds JP, et al. World Health Organization and International League of Associations for Rheumatology core endpoints for symptom modifying antirheumatic drugs in rheumatoid arthritis clinical trials. J Rheumatol Suppl 1994;41:86–9.
10. Hsiao B, Fraenkel L. Incorporating the patient's perspective in outcomes research. Curr Opin Rheumatol 2017;29:144–9.
11. Curbelo RJ, Loza E, de Yebenes MJ, Carmona L. Databases and registers: useful tools for research, no studies. Rheumatol Int 2014;34:447–52.
12. Patient-Centered Outcomes Research Institute. Establishing the definition of patient-centered outcomes research. 2012. URL: https://www.pcori.org/research-results/about-our-research/patient-centered-outcomes-research/establishing-definition.

13. The United Nations. List of member states. URL: http://www.un.org/en/member-states/.
14. Gliklich RE, Dreyer NA, eds. Registries for evaluating patient outcomes: a user's guide. Rockville (MD): Agency for Healthcare Research and Quality; 2014.
15. Chatzidionysiou K, Lie E, Lukina G, Hetland ML, Hauge EM, Pavelka K, et al. Rituximab retreatment in rheumatoid arthritis in a real-life cohort: data from the CERERRA collaboration. J Rheumatol 2017; 44:162–9.
16. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.
17. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. Arthritis Rheum 1993;36:729–40.
18. American College of Rheumatology Committee to Reevaluate Improvement Criteria. A proposed revision to the ACR20: the hybrid measure of American College of Rheumatology response. Arthritis Rheum 2007;57:193–202.
19. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford) 2003;42:244–57.
20. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 2005;7:R796–806.
21. Van der Heijde DM, van Riel PL, Nuver-Zwart IH, Gribnau FW, van de Putte LB. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989;1:1036–8.
22. Van der Heijde DM, van Leeuwen MA, van Riel PL, Koster AM, van 't Hof MA, van Rijswijk MH, et al. Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. Arthritis Rheum 1992;35:26–34.
23. Cole JC, Khanna D, Clements PJ, Seibold JR, Tashkin DP, Paulus HE, et al. Single-factor scoring validation for the Health Assessment Questionnaire-Disability Index (HAQ-DI) in patients with systemic sclerosis and comparison with early rheumatoid arthritis patients. Qual Life Res 2006;15:1383–94.
24. Hurst NP, Kind P, Ruta D, Hunter M, Stubbings A. Measuring health-related quality of life in rheumatoid arthritis: validity, responsiveness and reliability of EuroQol (EQ-5D). Br J Rheumatol 1997;36:551–9.
25. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I: conceptual framework and item selection. Med Care 1992;30:473–83.
26. Weldring T, Smith SM. Patient-reported outcomes (PROs) and patient-reported outcome measures (PROMs). Health Serv Insights 2013;6:61–8.
27. Locklear T, DeBar LL, Willig J, Rundell S, Blackhall L, Zatzick D, et al. Case studies from the clinic: initiating and implementing patient-reported outcome measures. EGEMS (Wash DC) 2017; 5:7.
28. Zavada J, Dixon WG, Askling J. Launch of a checklist for reporting longitudinal observational drug studies in rheumatology: a EULAR extension of STROBE guidelines based on experience from biologics registries. Ann Rheum Dis 2014;73:628.
29. Dixon WG, Carmona L, Finckh A, Hetland ML, Kvien TK, Landewe R, et al. EULAR points to consider when establishing, analysing and reporting safety data of biologics registers in rheumatology. Ann Rheum Dis 2010;69:1596–602.
30. Greenwood MC, Doyle DV, Ensor M. Does the Stanford Health Assessment Questionnaire have potential as a monitoring tool for subjects with rheumatoid arthritis? Ann Rheum Dis 2001;60:344–8.
31. Wells G, Becker JC, Teng J, Dougados M, Schiff M, Smolen J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis 2009;68:954–60.
32. Van Gestel AM, Haagsma CJ, van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum 1998;41:1845–50.
33. Gossec L, Paternotte S, Aanerud GJ, Balanescu A, Boumpas DT, Carmona L, et al. Finalisation and validation of the rheumatoid arthritis impact of disease score, a patient-derived composite measure of impact of rheumatoid arthritis: a EULAR initiative. Ann Rheum Dis 2011;70:935–42.
34. Pincus T, Swearingen CJ, Bergman M, Yazici Y. RAPID3 (Routine Assessment of Patient Index Data 3), a rheumatoid arthritis index without formal joint counts for routine care: proposed severity categories compared to disease activity score and clinical disease activity index categories. J Rheumatol 2008;35:2136–47.
35. Pincus T, Swearingen C, Wolfe F. Toward a multidimensional Health Assessment Questionnaire (MDHAQ): assessment of advanced activities of daily living and psychological status in the patient-friendly health assessment questionnaire format. Arthritis Rheum 1999;42:2220–30.
36. Wolfe F, Michaud K, Pincus T. Development and validation of the Health Assessment Questionnaire II: a revised version of the Health Assessment Questionnaire. Arthritis Rheum 2004;50:3296–305.
37. Wolfe F, Michaud K, Pincus T. A composite disease activity scale for clinical practice, observational studies, and clinical trials: the patient activity scale (PAS/PAS-II). J Rheumatol 2005;32:2410–5.
38. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ 2002; 21:271–92.
39. Ware J Jr, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220–33.
40. Meenan RF, Mason JH, Anderson JJ, Guccione AA, Kazis LE. AIMS2. AIMS2: the content and properties of a revised and expanded Arthritis Impact Measurement Scales Health Status Questionnaire. Arthritis Rheum 1992;35:1–10.
41. Tijhuis GJ, de Jong Z, Zwinderman AH, Zuijderduin WM, Jansen LM, Hazes JM, et al. The validity of the Rheumatoid Arthritis Quality of Life (RAQoL) questionnaire. Rheumatology (Oxford) 2001;40:1112–9.
42. Brooks R. EuroQol: the current state of play. Health Policy 1996; 37:53–72.
43. Zhang W, Bansback N, Boonen A, Young A, Singh A, Anis AH. Validity of the work productivity and activity impairment questionnaire: general health version in patients with rheumatoid arthritis. Arthritis Res Ther 2010;12:R177.