Identifying Possible Outcome Domains from Existing Outcome Measures to Inform an OMERACT Core Domain Set for Safety in Rheumatology Trials

Louise Klokker, Dorthe B. Berthelsen [ID], Thasia Woodworth, Kathleen M. Andersen [ID], Daniel E. Furst, Dan Devoe, Paula R. Williamson, Maria E. Suarez-Almazor, Vibeke Strand [ID], Amye L. Leong, Niti Goel [ID], Maarten Boers, Peter M. Brooks, Lyn March, Victor S. Sloan, Peter Tugwell, Lee S. Simon, and Robin Christensen [ID]

ABSTRACT. Objective. The Outcome Measures in Rheumatology (OMERACT) Safety Working Group objective was to identify harm domains from existing outcome measurements in rheumatology.
Methods. Systematically searching the MEDLINE database on January 24, 2017, we identified full-text articles that could be used for harm outcomes in rheumatology. Domains/items from the identified instruments were described and the content synthesized to provide a preliminary framework for harm outcomes.
Results. From 435 possible references, 24 were read in full text and 9 were included: 7 measurement instruments were identified. Investigation of domains/items revealed considerable heterogeneity in the grouping and approach.
Conclusion. The ideal way to assess harm aspects from the patients' perspective has not yet been ascertained. (First Release May 15 2019; J Rheumatol 2019;46:1173–8; doi:10.3899/jrheum.190196)

Key Indexing Terms:
ADVERSE EVENTS   SAFETY   HARM   CORE OUTCOME SET   OMERACT   ARTHRITIS

From the Clinical Epidemiology, Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen; Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark; David Geffen School of Medicine, Division of Rheumatology, University of California at Los Angeles (UCLA), Los Angeles; Division of Immunology and Rheumatology, Stanford University, Stanford; Healthy Motivation, and Global Alliance for Musculoskeletal Health, Bone and Joint Decade, Santa Barbara, California; Section of Rheumatology and Clinical Immunology, University of Texas MD Anderson Cancer Center, Houston, Texas; Division of Rheumatology, Duke University School of Medicine, Durham; UCB Bio Sciences Inc., Raleigh, North Carolina; Rutgers-Robert Wood Johnson Medical School, New Brunswick, New Jersey; SDG LLC, Cambridge, Massachusetts, USA; Department of Family Medicine, McGill University, Montreal, Quebec; Health Services Research, Department of Medicine, University of Calgary, Cumming School of Medicine, Calgary, Alberta; Division of Rheumatology, Department of Medicine, and School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa; Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada; Institute of Translational Medicine, University of Liverpool, Liverpool, UK; Department of Epidemiology and Biostatistics, Amsterdam Rheumatology and Immunology Center, VU University Medical Center, Amsterdam, the Netherlands; Centre for Health Policy Melbourne School of Population and Global Health, University of Melbourne, Melbourne; University of Sydney, Sydney, Australia.

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L. Klokker, PT, MSc, PhD, Clinical Epidemiology, Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital; D.B. Berthelsen, PT, MSc, Clinical Epidemiology, Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital; T. Woodworth, MD, David Geffen School of Medicine, Division of Rheumatology, UCLA; K. Andersen, MSc, PhD Fellow, Department of Family Medicine, McGill University; D.E. Furst, MD, David Geffen School of Medicine, Division of Rheumatology, UCLA;

D. Devoe, BA, MSc, PhD Student, Research Associate, Health Services Research, Department of Medicine, University of Calgary, Cumming School of Medicine; P. Williamson, MSc, PhD, Professor of Medical Statistics, Institute of Translational Medicine, University of Liverpool; M.E. Suarez-Almazor, MD, PhD, Barnts Family Distinguished Professor, Section of Rheumatology and Clinical Immunology, University of Texas MD Anderson Cancer Center; V. Strand, MD, Biopharmaceutical Consultant; A.L. Leong, MBA, President and CEO, Healthy Motivation, and Director of Strategic Relations, Global Alliance for Musculoskeletal Health, Bone and Joint Decade; N. Goel, MD, Vice President, Strategic Drug Development, Advisory Services, Quintiles and Adjunct Assistant Professor, Division of Rheumatology, Duke University School of Medicine; M. Boers, MSc, MD, PhD, Professor of Clinical Epidemiology, Department of Epidemiology and Biostatistics, Amsterdam Rheumatology and Immunology Center, VU University Medical Center; P.M. Brooks, MD, FRACP, Honorary Professor Fellow, Centre for Health Policy Melbourne School of Population and Global Health, University of Melbourne; L. March, PhD, University of Sydney; V.S. Sloan, MD, UCB Bio Sciences Inc., and Clinical Associate Professor of Medicine, Rutgers-Robert Wood Johnson Medical School; P. Tugwell, OC, LRCP, MRCS, MD, MSc, FRCPS, FRCP(UK), FCAHS, Division of Rheumatology, Department of Medicine, and School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, and Clinical Epidemiology Program, Ottawa Hospital Research Institute; L.S. Simon, MD, SDG LLC; R. Christensen, BSc, MSc, PhD, Head of Unit, Professor of Biostatistics and Clinical Epidemiology, Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital, and Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital. L. Klokker and D.B. Berthelsen are first co-authors.

Address correspondence to R. Christensen, Professor of Biostatistics and Clinical Epidemiology and Head of Musculoskeletal Statistics Unit (MSU), The Parker Institute, Bispebjerg og Frederiksberg Hospital, Nordre Fasanvej 57; DK-2000 Copenhagen F, Denmark. E-mail: Robin.Christensen@regionh.dk

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Harms provide important context for healthcare practitioners about the benefit-risk ratio of interventions[1]. To improve transparency and credibility in the published results from randomized trials, the reporting of harms associated with an intervention needs to be explicit regarding what is patient-important, which may be different from that reported by clinicians submitting adverse event reports[2]. The Consolidated Standards of Reporting Trials (CONSORT) group has provided recommendations on the appropriate reporting of harms in randomized controlled trials (RCT)[3]. However, systematic reviews conclude that adherence to these CONSORT harm recommendations is suboptimal in RCT for (non)pharmacological treatment of rheumatoid arthritis and hip or knee osteoarthritis[4,5] as reported in leading medical journals. According to Hadi, et al[5], more than half (56%) of the RCT reported ≤ 50% of the recommended CONSORT harm items. While some CONSORT harm items might be more important to consider reporting than others, there is a need to improve harms reporting in RCT to allow transparent and balanced assessment of the benefit-risk ratio in clinical decision making[5].

Following the concerns about inadequate reporting of harm outcomes in randomized trials[3] and systematic reviews[1,6], the Outcome Measures in Rheumatology (OMERACT) Safety Working Group is advancing the work to identify additional harm aspects for assessment in rheumatology trials[7,8]. To inform this work, we performed a scoping review of harm aspects, assessed in existing measurement instruments, using an approach suggested by Macefield, et al[9] and McNair, et al[10]. The objective was to identify harm domains from the patient perspective by examining currently available outcome measurement instruments.

MATERIALS AND METHODS

The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42017055861). A scoping review aims to map the existing literature in a field of interest in terms of the volume, design, and characteristics of the primary research, which is feasible when the topic has not yet been extensively reviewed or is of a complex or heterogeneous design[11]. The purpose of a scoping review is to sum up the best available research on a specific question[12].

An electronic search was performed on January 24, 2017, using Medline through PubMed to identify studies describing or evaluating measurement instruments including harm outcomes that could be used in rheumatology trials. The search strategy included terms for harms, rheumatic disease, and outcome measures. No filters were activated (e.g., no article type, availability, publication date, language restrictions). Additional references were identified through reference lists of included studies and by consulting experts within rheumatology (i.e., snowballing). One review author (LK) screened the titles and abstracts of the identified publications. A second reviewer (RC) screened a random sample of abstracts to check accuracy of inclusion. Publications were eligible if they described or evaluated instruments including harm outcomes (either domains or measurements) that could be used in rheumatology trials. Full text was obtained for all titles that appeared to be eligible or where there was any uncertainty. Two reviewers (LK and RC) screened the full texts and excluded publications not in English, and publications reporting results from trials, i.e., studies with the purpose of evaluating the effects of a treatment. Reasons for exclusion of publications were documented. Every step of the selection process was documented by a flowchart. Reference manager 12 (Thomson Reuters) was used to manage references.

Verbatim names for the harm aspects as termed by the instrument developers were extracted and all patient-reported outcome measures (PROM; scales, subscales, and single items) were collated in a list. Using a standardized form, 1 reviewer (LK) extracted data from each included study. Another reviewer (RC) verified the data. Extracted data, if available, included first author, study publication year, aim of the study, name and abbreviation of outcome measurement instrument, reported harm aspects (i.e., scales/domains and items), definition of harm aspects, and target population. All PROM items assessing adverse effects were systematically categorized into conceptual health domains according to the issue they addressed. As suggested by Macefield, et al[9] and applied by McNair, et al[10], we summarize PROM and categorize their PRO content to inform the development of a minimum "safety core" outcome set to be measured in all rheumatology trials. Individual items from all questionnaires were extracted and formed into a longlist before categorization into health domains by 2 researchers (LK and RC).

Following this, 8 of the authors (LK, MB, DD, VSS, NG, LM, PT, RC) were encouraged to categorize all items "in any way they found meaningful," and subsequently to name the categories as they rationalized based on experience (further details are available from the corresponding author upon request). Using concept mapping software, the average categorization was estimated through multidimensional scaling analysis, as an expression of consensus of the distribution of items[13].

RESULTS

As illustrated in Figure 1, of 435 unique references identified, 24 were read in full text, and of these, 9 were included[14,15,16,17,18,19,20,21,22]. One reference was excluded because of "other language than English." An overview of the 9 included studies is presented in Table 1. From these, 8 unique instruments were identified. Two instruments [the Stanford Toxicity Index (STI) and the Rheumatology Common Toxicity Criteria (RCTC)] were the subject of 2 studies each, the newest study describing a revision or update of the original instrument. There were 7 individual measurement instruments and 1 methodological proposal referred as the OMERACT 3 × 3[19]: (1) STI[14], (2) revised rSTI[15], (3) RCTC 2.0[18], (4) The Patient Self-Report Adverse Event Instrument and the Investigator Report Adverse Event instrument[17], (5) The BioSecure questionnaire[20], (6) Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity flare index[21], (7) Glucocorticoid Toxicity Index[22].

Five of the 7 individual instruments aimed to assess "toxicity," 1 of these instruments specifically in relation to treatment with corticosteroids. The content, indicated by subscales of the instruments, varied despite the common construct of "toxicity." The other instruments aimed to assess different harm aspects: event importance, benefit and harm, self-care safety skills, and flare.

The structure of the instruments varied: 1 was a PROM[20] and the others were investigator/clinician-reported. Altogether there were 205 unique items, or 223 when taking into account the response options [e.g., the item "What was (were) the side effects?" was accompanied by 37 response
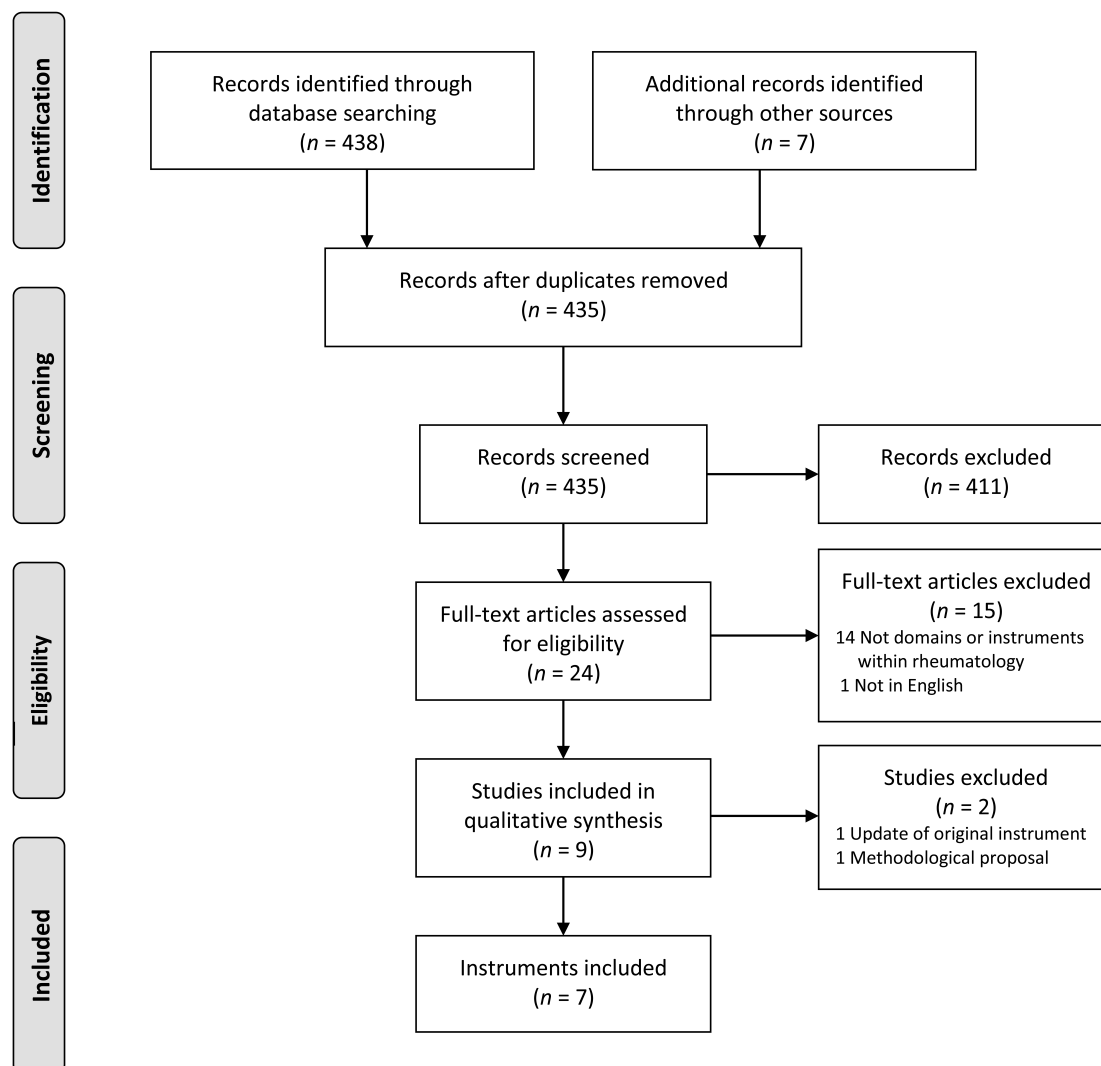
Figure 1. PRISMA flow diagram of studies considered for the scoping review. PRISMA: Preferred Reporting Items for Systematic Reviews.

options]. Different types of information were retrieved by the items, as shown in Table 2[14,15,16,18,19,20,21]. Most (125) items or response options each represented a symptom, sign, or diagnosis which could be an adverse effect (further details are available from the corresponding author).

DISCUSSION

Based on a scoping review, we identified instruments to assess harm aspects in rheumatology trials. "Harm aspects" is a very broad and complex construct, and this review illustrates that there are many potential approaches to address it. Harm aspects reported with existing instruments included toxicity, event importance, benefit and harm, self-care safety skill, and flare. These could be categorized as patient reports, clinician/researcher reports, laboratory results, qualitative descriptions of patients' experiences, and data from medical records, and only 4 instruments provided a patient

perspective. Feasibility around this review made us perform the systematic search including only 1 electronic bibliographic database (Medline), as well as the manual search in reference lists and contact with key opinion leaders in rheumatology. Thus, a potential limitation to the present manuscript is that we did not include additional electronic databases.

The current "clinical trial practice" for reporting adverse events is based on the implicit assumption that an accurate portrait of patients' subjective experiences can be provided by clinicians' documentation alone. Our findings derived from the existing instruments developed for rheumatology[14,15,16,17,18,20,21,22] at least seem to support the grouping that was previously suggested by the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) initiative[23]. Our work supports the idea that

Table 1. Study characteristics, listed by year of publication.

Author (Framework)	Yr	Instrument	Population	Patient Input	Aim	Safety Aspect (Definition/content)
Fries, et al[14]	1990	STI	Rheumatic	Yes	This report describes the development of a morbidity toxicity index and a mortality toxicity index for comparing the overall toxicity of different drugs.	Toxicity (frequency, severity, laboratory features, importance to clinician)
Welch, et al[15]	2001	rSTI	Rheumatic	Not reported	(1) Propose revisions to the STI to satisfy attributes of OMERACT Drug Safety Working Party for patient-based safety assessment, and (2) propose methods for validation of rSTI as an outcome for clinical trials according to the OMERACT filter.	Toxicity (frequency, severity, importance to the clinician, importance to patient, effect on economic resources, integration of adverse effects with benefit; overall satisfaction)
Woodworth, et al[16]	2001	RCTC	Rheumatic (clinical trials)	No	To develop an adverse event assessment tool to enable the use of common terminology to improve the consistency of reporting severity of side effects.	Toxicity (allergic/immunologic, general, skin/integument, ophthalmologic, ENT, gastrointestinal, cardiac, pulmonary, musculoskeletal, neuropsychiatric, hematology, chemistry, urinalysis, autoimmune syndromes, if not part of basic disease)
Lassere, et al[17]	2005	Patient and investigator adverse event instruments	Rheumatic	Yes	To find the optimal tradeoff between comprehensiveness and ease of administration, enabling reports of adverse effects from the patient perspective, as well as that of the investigator.	Event importance (severity, frequency and duration, physical, psychological, dissatisfaction, general, head/eyes/ears/nose/mouth/throat, chest/lungs/heart, musculoskeletal, gastrointestinal tract, neurological and psychological, skin)
Woodworth, et al[18]	2007	RCTC 2.0	Rheumatic (clinical trials)	No	To revise and to stimulate the implementation of the RCTC.	Toxicity (allergic/immunologic, cardiac, general, dermatologic, ENT, eye/ophthalmologic, gastrointestinal, musculoskeletal, neuropsychiatric, pulmonary, hematology, chemistry, urinalysis)
Boers, et al[19]	2010	OMERACT 3 × 3	Rheumatic	No	To develop a simple system to assess benefit and harm of treatment on a single scale.	Benefit (any occurrence or change that results in a patient being in a better state than before treatment). Harm (any occurrence or change such that a patient is in a worse state than before treatment).
Gossec, et al[20]	2013	BioSecure questionnaire	Patients treated with biologic therapies	Yes	To elaborate a questionnaire to measure patient knowledge and skills regarding management of safety issues, for clinicians and patients during treatment with biologics.	Self-care safety skills (general knowledge; communication: who to contact; dealing with injuries, preventing infectious complications, vaccinations; planning child conception; dealing with infectious symptoms and fever; dealing with other infectious symptoms; planning surgery, information to share with the surgeon/anaesthesiologist; subcutaneous treatments: cold chain/cold storage, subcutaneous injection techniques; dental hygiene, preventing infectious complications, information to share with the dentist)
Thanou, et al[21]	2014	cSFI	Systemic lupus erythematosus	No	To examine the effect of modifications to the cSFI.	Flare (mild, moderate, or severe)
Miloslavsky, et al[22]	2016	GTI	Patients treated with GC	No	To develop a GTI useful across medical disciplines to assess the effect of GC-associated morbidity.	GC toxicity (composite GTI: toxicity likely to change during a clinical trial, and occurs commonly, varies with GC exposure). GC toxicity not included in the composite GTI (rare but important events)

RCTC: Rheumatology Common Toxicity Criteria; STI: Stanford Toxicity Index; rSTI: revised STI; OMERACT: Outcome Measures in Rheumatology; cSFI: classic Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index flare index; GC: glucocorticoid; GTI: Glucocorticoid Toxicity Index.

Table 2. Type of information retrieved by the instruments, with number of items for each type, an example of an item, and the instrument from which the example was taken.

Type	Items	Example	Instrument
Symptoms	125	Arthralgia, leg cramps, myalgia, flare, fatigue	RCTC 2.0[18]
Laboratory results	53	Creatinine (mg/dl), neutrophil count (cells/mm^3), hemoglobin (g/dl)	RCTC[16,18]
Drug-specific	34	5. Who do I need to tell about my biologic treatment?	BioSecure questionnaire[20]
Descriptive	3	4. Did you discontinue the drug as a result?	STI[14]
Severity	3	3. Were the side effects mild, moderate or severe?	STI[14], RCTC[18]
Importance	3	Considering the frequency, severity, and impact on activities, how important was this side effect to you?	rSTI[15]
Resource use	1	Data on endoscopy, outpatient procedures, hospitalization, emergency visits, and surgery. No data on extra physician visits due to drug-associated side effects.	rSTI[15]
Benefit	1	Benefit (any occurrence or change that results in a patient being in a better state than before treatment)	OMERACT 3 × 3[19]
Harm	1	Harm (any occurrence or change such that a patient is in a worse state than before treatment)	OMERACT 3 × 3[19]
Disease-specific	1	Hospitalization for SLE activity	cSFI[21]

RCTC: Rheumatology Common Toxicity Criteria; STI: Stanford Toxicity Index; rSTI: revised STI; OMERACT: Outcome Measures in Rheumatology; SLE: systemic lupus erythematosus; cSFI: classic Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index flare index.

there are 3 broad categories of "harms" available from the current Medical Dictionary for Regulatory Activities (MedDRA) framework: (1) laboratory-based events, (2) observable/measurable events, and (3) symptomatic adverse events. Yet, the clinician/trialist reports of symptomatic adverse events as recorded on case report forms lack reliability. There is a risk that clinicians underreport the incidence and severity of symptoms compared to patients' direct reports, especially for subjective symptoms, in part because the clinician cannot observe these symptoms. If a PROM was available, it could enable patients to directly report their own symptomatic adverse events, providing important evidence of patients' adverse experiences with an intervention to contribute to shared decision making.

From our scoping review, we hope to raise awareness about the need for a novel explicit harm reporting paradigm in rheumatology research, with a focus on patient self-report with the potential to enable reporting of safety rather than harms. One important issue is how best to collect data on harm and/or safety outcomes, and whether available measurement instruments are suitable for the purpose. Harm aspects can be defined and targeted in many ways, reflecting the complexity of the construct. It is clear from our review that the ideal way to assess harm aspects has not yet been achieved. In addition, the language used to cover the various "domains" is difficult to comprehend for a lay audience (including patients). The OMERACT Safety Working Group will continue to investigate harm aspects, with a specific focus on patients' perspectives on safety.

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