

1 **Identifying possible outcome domains from existing outcome measures to inform**
2 **an OMERACT core domain set for safety in rheumatology trials**

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16 None
17

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25

26 **Running head**

27 Safety domains in rheumatology

28

1 **ABSTRACT**

2 **Objective:**

3 The OMERACT Safety Working Group objective was to identify harm domains from existing outcome
4 measurements in rheumatology.

5 **Methods:**

6 Systematically searching the MEDLINE database January 24, 2017, we identified full-text articles that could
7 be used for harm outcomes in rheumatology. Domains/items from the identified instruments were described
8 and the content synthesized to provide a preliminary framework for harm outcomes.

9 **Results:**

10 From 435 possible references, 24 were read in full text, and 9 were included: Seven measurement
11 instruments were identified. Exploration of domains/items revealed considerable heterogeneity in the
12 grouping and approach.

13 **Conclusion:**

14 The ideal way to assess harm aspects from the patients' perspective has not yet been ascertained.

15

1 INTRODUCTION

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

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

22 METHODS

23 The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO,
24 registration number CRD42017055861). A scoping review aims to map the existing literature in a field of

1 interest in terms of the volume, nature, and characteristics of the primary research, which is feasible when
2 the topic has not yet been extensively reviewed or is of a complex or heterogeneous nature (11). The purpose
3 of a scoping review is to sum up the best available research on a specific question (12).

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

18 Verbatim names for the harm aspects as termed by the instrument developers were extracted
19 and all Patient-Reported Outcome Measures (PROMs; scales, subscales and single items) were collated in a
20 list. Using a standardized form, one reviewer (LK) extracted data from each included study. Another
21 reviewer (RC) verified the data. Extracted data, if available, included: first author, study publication year,
22 aim of the study, name and abbreviation of outcome measurement instrument, reported harm aspects (i.e.
23 scales/domains and items), definition of harm aspects, target population. All PROM items assessing adverse
24 effects were systematically categorized into conceptual health domains according to the issue they addressed.
25 As suggested by Macefield (9) and applied by McNair (10): (i) we summarize PROMs and (ii) categorize
26 their PRO content to inform the development of a minimum ‘safety core’ outcome set to be measured in all

1 rheumatology trials. Individual items from all questionnaires were extracted and formed into a long-list
2 before categorization into health domains by two researchers (LK and RC).

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

8

9 **RESULTS**

10 As illustrated in **Figure 1**, of 435 unique references identified, 24 were read in full text, and of these, 9 were
11 included (14–22). One reference was excluded due to ‘other language than English’. An overview of the 9
12 included studies is presented in **Table 1**. From these, eight unique instruments were identified. Two
13 instruments (STI and RCTC) were the subject of two studies each, the newest study describing a revision or
14 update of the original instrument. There were seven individual measurement instruments, and one
15 methodological proposal referred as the OMERACT 3x3 (19): (i) Stanford Toxicity Index (STI) (14); (ii)
16 Revised Stanford Toxicity Index (rSTI) (15); (iii) Rheumatology Common Toxicity Criteria 2.0 (RCTC 2.0)
17 (18); (iv) The Patient Self-Report Adverse Event Instrument and the Investigator Report Adverse Event
18 instrument (17); (v) The BioSecure questionnaire (20); (vi) Safety of Estrogens in Lupus Erythematosus
19 National Assessment (SELENA)-SLEDAI flare index (cSFI) (21); (vii) Glucocorticoid Toxicity Index (GTI)
20 (22).

21 Five of the seven individual instruments aimed to assess ‘toxicity’, one of these instruments
22 specifically in relation to treatment with corticosteroids. The content, indicated by subscales of the
23 instruments, varied despite the common construct of ‘toxicity’. The other instruments aimed to assess
24 different harm aspects: ‘Event importance’, ‘Benefit and harm’, ‘Self-care safety skills’, and ‘Flare’.

1 The structure of the instruments varied; one was a PROM (20), the others were
2 investigator/clinician reported. Altogether there were 205 unique items, or 223 when taking into account the
3 response options (e.g. the item ‘What was (were) the side effects?’, was accompanied by 37 response
4 options). Different types of information were retrieved by the items, as shown in **Table 2**. Most (125) items
5 or response options each represented a symptom, sign or diagnosis which could be an adverse effect (further
6 details are available from the corresponding author).

7

8 **DISCUSSION**

9 Based on a scoping review, we identified instruments to assess harm aspects in rheumatology trials. ‘Harm
10 aspects’ is a very broad and complex construct, and this review illustrates that there are many potential
11 approaches to address it. Harm aspects reported with existing instruments included: ‘Toxicity’, ‘Event
12 importance’, ‘Benefit and harm’, ‘Self-care safety skills’, and ‘Flare’. These could be categorized as patient
13 reports, clinician/researcher reports, laboratory results, qualitative descriptions of patients’ experiences and
14 data from medical records, and only 4 instruments provided a patient perspective. Feasibility around this
15 review made us perform the systematic search including only one electronic bibliographic database
16 (Medline), as well as the manual search in reference lists and contact with key opinion leaders in
17 rheumatology. Thus, a potential limitation to the present manuscript is that we did not include additional
18 electronic databases.

19 The current “clinical trial practice” for reporting adverse events is based on the implicit
20 assumption that an accurate portrait of patients’ subjective experiences can be provided by clinicians’
21 documentation alone. Our findings derived from the existing instruments developed for rheumatology (14–
22 18,20–22) at least seem to support the grouping which was previously suggested by US National Cancer
23 Institute’s Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events
24 (PRO-CTCAE) initiative (23). Our work support the idea that there are three broad categories of “harms”
25 available from the current Medical Dictionary for Regulatory Activities (MedDRA) framework: (*i*)

1 laboratory-based events, (ii) observable/measurable events, and (iii) symptomatic adverse events. Yet, how
2 the clinician/trialist reports of symptomatic AEs as recorded on case report forms (CRFs) lacks reliability.
3 There is a risk that clinicians underreport the incidence and severity of symptoms compared to patients’
4 direct reports, especially for subjective symptoms, in part because the clinician cannot observe these
5 symptoms. If a patient-reported outcome measure was available, it could enable direct patients reporting of
6 their own symptomatic AEs, providing important evidence of patients’ adverse experiences with an
7 intervention to contribute to shared decision-making.

8 From this scoping review, we hope to raise awareness about the need for a novel explicit harm
9 reporting paradigm in rheumatology research, with a focus on patient self-report with the potential to enable
10 reporting of safety rather than harms. One important issue is how best to collect data on harm and/or safety
11 outcomes, and whether available measurement instruments are suitable for the purpose. Harm aspects can be
12 defined and targeted in many ways, reflecting the complexity of the construct. It is clear from this review
13 that the ideal way to assess harm aspects has not yet been achieved, as well as the language used to cover the
14 various “domains” is difficult to comprehend for laymen (incl. patients). The OMERACT safety working
15 group will continue to explore harm aspects, with a specific focus on patients’ perspectives on safety.

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17 **REFERENCES**

- 18 1. Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, et al. PRISMA harms
19 checklist: improving harms reporting in systematic reviews. *BMJ (Clinical research ed)* 2016;352:i157.
- 20 2. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the
21 question and deciding on important outcomes. *Journal of clinical epidemiology* 2011;64:395-400.
- 22 3. Ioannidis JP, Evans SJ, Gotzsche PC, O’Neill RT, Altman DG, Schulz K, et al. Better reporting of
23 harms in randomized trials: an extension of the CONSORT statement. *Annals of internal medicine*
24 2004;141:781-8.
- 25 4. Ethgen M, Boutron I, Baron G, Giraudeau B, Sibilia J, Ravaud P. Reporting of harm in randomized,
26 controlled trials of nonpharmacologic treatment for rheumatic disease. *Annals of internal medicine*
27 2005;143:20-5.

- 1 5. Hadi MA, McHugh GA, Conaghan PG. Quality of reporting of harms in randomised controlled trials of
2 pharmacological interventions for rheumatoid arthritis: a systematic review. *Evidence-based medicine*
3 2017;22:170-7.
- 4 6. Saini P, Loke YK, Gamble C, Altman DG, Williamson PR, Kirkham JJ. Selective reporting bias of
5 harm outcomes within studies: findings from a cohort of systematic reviews. *BMJ (Clinical research*
6 *ed)* 2014;349:g6501.
- 7 7. Klokke L, Tugwell P, Furst DE, Devoe D, Williamson P, Terwee CB, et al. Developing an
8 OMERACT Core Outcome Set for Assessing Safety Components in Rheumatology Trials: The
9 OMERACT Safety Working Group. *J Rheumatol* 2017;44:1916.
- 10 8. Boers M, Kirkham JR, Tugwell P, Beaton D, Bingham CO, Conaghan PG, et al. The OMERACT
11 Handbook [Internet]. Accessed February 18, 2019. Available from:
12 <https://omeracthandbook.org/handbook>
- 13 9. Macefield RC, Jacobs M, Korfage IJ, Nicklin J, Whistance RN, Brookes ST, et al. Developing core
14 outcomes sets: methods for identifying and including patient-reported outcomes (PROs). *Trials*
15 2014;15:49.
- 16 10. McNair AG, Whistance RN, Forsythe RO, Rees J, Jones JE, Pullyblank AM, et al. Synthesis and
17 summary of patient-reported outcome measures to inform the development of a core outcome set in
18 colorectal cancer surgery. *Colorectal disease : the official journal of the Association of Coloproctology*
19 *of Great Britain and Ireland* 2015;17:O217-29.
- 20 11. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *International Journal of*
21 *Social Research Methodology: Theory and Practice* 2005;8:19-32.
- 22 12. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA
23 statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare
24 interventions: explanation and elaboration. *BMJ (Clinical research ed)* 2009;339:b2700.
- 25 13. Kane M, Trochim W. *Concept mapping for planning and evaluation*. London: Sage Publications, Inc.;
26 2007.
- 27 14. Fries JF, Spitz PW, Williams CA, Bloch DA, Singh G, Hubert HB. A toxicity index for comparison of
28 side effects among different drugs. *Arthritis and rheumatism* 1990;33:121-30.
- 29 15. Welch V, Singh G, Strand V, Fries J, Boers M, Ramey D, et al. Patient based method of assessing
30 adverse events in clinical trials in rheumatology: the revised Stanford Toxicity Index. *The Journal of*
31 *rheumatology* 2001;28:1188-91.
- 32 16. Woodworth TG, Furst DE, Strand V, Kempeni J, Fenner H, Lau CS, et al. Standardizing assessment of
33 adverse effects in rheumatology clinical trials. Status of OMERACT Toxicity Working Group March
34 2000: towards a common understanding of comparative toxicity/safety profiles for antirheumatic
35 therapies. *The Journal of rheumatology* 2001;28:1163-9.
- 36 17. Lassere MN, Johnson KR, Van Santen S, Carlton K, Rappo J, Michael R, et al. Generic patient self-
37 report and investigator report instruments of therapeutic safety and tolerability. *The Journal of*
38 *rheumatology* 2005;32:2033-6.

- 1 18. Woodworth T, Furst DE, Alten R, Bingham CO 3rd, Yocum D, Sloan V, et al. Standardizing
2 assessment and reporting of adverse effects in rheumatology clinical trials II: the Rheumatology
3 Common Toxicity Criteria v.2.0. *The Journal of rheumatology* 2007;34:1401-14.
- 4 19. Boers M, Brooks P, Fries JF, Simon LS, Strand V, Tugwell P. A first step to assess harm and benefit in
5 clinical trials in one scale. *Journal of clinical epidemiology* 2010;63:627-32.
- 6 20. Gossec L, Fautrel B, Flipon E, Lecoq d'Andre F, Marguerie L, Nataf H, et al. Safety of biologics:
7 elaboration and validation of a questionnaire assessing patients' self-care safety skills: the BioSecure
8 questionnaire. An initiative of the French Rheumatology Society Therapeutic Education section. *Joint,
9 bone, spine : revue du rhumatisme* 2013;80:471-6.
- 10 21. Thanou A, Chakravarty E, James JA, Merrill JT. How should lupus flares be measured?
11 Deconstruction of the safety of estrogen in lupus erythematosus national assessment-systemic lupus
12 erythematosus disease activity index flare index. *Rheumatology (Oxford, England)* 2014;53:2175-81.
- 13 22. Miloslavsky EM, Naden RP, Bijlsma JW, Brogan PA, Brown ES, Brunetta P, et al. Development of a
14 Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. *Annals of the rheumatic
15 diseases* 2016;76:543-6.
- 16 23. Basch E, Reeve BB, Mitchell SA, Clauser SB, Minasian LM, Dueck AC, et al. Development of the
17 National Cancer Institute's patient-reported outcomes version of the common terminology criteria for
18 adverse events (PRO-CTCAE). *Journal of the National Cancer Institute* 2014;106.

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20 **FIGURE LEGENDS**

21 **Figure 1**

22 PRISMA = Preferred Reporting Items for Systematic Reviews