Stakeholder Endorsement Advancing the Implementation of a Patient-Reported Domain for Harms in Rheumatology Clinical Trials: Outcome of the OMERACT Safety Working Group

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SUMMARY

Objectives: To develop an understanding of the concept of safety/harms experienced by patients involved in clinical trials for their rheumatic and musculoskeletal diseases (RMDs) and to seek input from the OMERACT community before moving forward to developing or selecting an outcome measurement instrument.

Methods: OMERACT 2023 presented and discussed interview results from 34 patients indicating that up to 171 items might be important for patients' harm-reporting.

Results: Domain was defined in detail and supported by qualitative work. Participants in the Special-Interest-Group endorsed (96%) that enough qualitative data are available to start Delphi survey(s).

Conclusion: We present a definition of safety/harms that represents the patient voice (i.e., patients' perception of safety) evaluating the symptomatic treatment-related adverse events for people with RMDs enrolled in clinical trials.

INTRODUCTION

Sponsors collect extensive information on safety throughout the course of medicinal product development. This includes clinical and laboratory data plus, usually, imaging, genetic and biomarker data, and, of course, adverse events (harms). A robust database of potential harms is the basis for the characterization of the safety profile of a drug (1). Harm reporting for drugs is poor (2–4), despite existing guidelines (5), and patient-reported outcome measures are lacking (6). However, the U.S. Food and Drug Administration (FDA) now also encourages patient-focused drug development and evaluation of treatment benefits, risks, and burdens, aiming to better incorporate the patient's voice (7), and for these patient-reported measures are of course essential. Therefore, the Outcome Measures in Rheumatology (OMERACT) Safety Working Group (SWG) brought patient, researcher, clinician, regulator, and pharma representatives together to develop one or more patient-reported measures for people receiving a treatment for their rheumatologic or musculoskeletal disease (RMD) to directly report the harms they experience from their medical treatment in a clinical trial instead of indirectly through the investigator's interpretation of their report to them.

Many definitions are used to address negative consequences of a medical treatment, and patients might prefer "side effects" as some side effects might be beneficial - however "effects" suggest causality (8). Some health care professionals might prefer "adverse events", but these are considered physiological or pathological changes - often detected by laboratory tests - that can lead to a symptomatic adverse reaction (9). In this paper we focus on negative symptoms of drug treatment. Therefore, we use the term "harms" as these are the direct opposite of benefits, against which they must be compared (5,8).

As an initial step to better understand the safety issues experience by patients in arthritis trials we identified patients' concerns regarding DMARD use (10), and discussed the development of domains and measures of patient-valued harm-related outcomes at OMERACT 2018 (11). We then searched for appropriate patient-reported harm domains in the literature (12), but no relevant data were found. Therefore, we conducted a systematic literature review identifying a list of specific harms that could be reported by patients (13). We then examined patients' perspectives on themes (such as

‘brain and nerves’) and specific harms (such as ‘dizziness’) in our list and what patients consider important to measure about harms in clinical trials.

We presented preliminary results from our qualitative study at the Safety Special-Interest-Group (SIG) at OMERACT 2023 in Colorado Springs, USA. The objective of our SIG was to develop an understanding of the concept of safety (harms) experienced by patients involved in clinical trials for their RMDs and to seek input from the OMERACT community before moving forward to developing or selecting an outcome measurement instrument.

METHODS

Generating a preliminary list of harm-related themes

To generate a preliminary list of harm-related themes, we merged results of our previous systematic review identifying 117 specific harms appropriate for patient reporting from clinical trials (13) with results of a Canadian survey study examining the cancer harm tool Common Terminology Criteria For Adverse Events (PRO-CTCAE) in people with rheumatoid arthritis (RA) (14) and with results from the OMERACT Glucocorticoids Impact Working Group identifying individual physical and psychological harm symptoms important to patients using systemic glucocorticoids (15). Thus, in this initial list of specific harms, we included 135 symptomatic harms, categorized into 12 modified body system themes in the PRO-CTCAE item library version 1.0 (16) and added lay-language terms suggested by de Vries et al. (17), which were further adjusted by the patient research partners (PRPs) in the SWG (18).

We then invited patients with confirmed inflammatory arthritis (RA, psoriatic arthritis [PsA] or axial spondylarthritis [AxSpA]) to participate in online focus groups. Further, we invited a purposive sample of 10 focus-group participants to individual interviews based on various demographics (age, sex, diagnosis, ethnicity, and employment status). We used a pre-defined topic guide in all discussions (18). In the focus groups, we asked patients to discuss what they thought was important to know about potential harms in clinical trials. During the individual interviews, we presented our initial list of themes and specific harms to patients, who gave their perspectives on relevance, comprehension and adjustments to the list. All discussions were recorded, transcribed, anonymized, and analyzed (using thematic analysis for focus groups and content analysis

for individual interviews). The input from patients allowed us to develop a preliminary list of harm-related themes to present at the SIG. The list reflected all themes, sub-themes, and specific harms discussed and identified with patients.

Stakeholder meeting

To allow for informed discussion, we provided potential SIG participants with a lay language summary and a video to familiarize them to the topic prior to the stakeholder meeting. At OMERACT 2023, we conducted our SIG session to facilitate stakeholder engagement and encourage discussion of the qualitative results from our focus groups and interviews.

During the session, the existing reporting frameworks and current standard of adverse event collection for clinical trials were presented such that study participants' answers are typically collected and interpreted through the lens of the investigator. Next, PRPs presented their frustration at the currently missing voice of patients in drug safety reporting on aspects of harms, especially those that could impact health related quality of life (HRQOL). PRPs expressed an urgent need for outcome measures representing aspects important to patients that could be collected without interpretation by the trial investigators. We then presented synthesized results from the focus groups and interviews for discussion, and finished with the following two polls: "Do you agree that there are enough qualitative data to move forward to the Delphi state?" (yes/no/don't know) and "If you feel we are missing anything important, please elaborate".

RESULTS

Generating a preliminary list of harm-related themes

34 patients participated in the discussions across focus groups and among them, 10 joined the individual interviews. In all, there were 9 from Australia, 14 from Europe, and 11 from North America. The mean age was 58 (±SD 14) years, 65% were female (*n*=22), 97% white (*n*=33), and nearly 60% (*n*=20) had RA while approximately 20% had PsA (*n*=7) and AxSpA (*n*=7) respectively. The most commonly used medical therapy was biologic DMARDs (*n*=24, 71%) followed by conventional DMARDs (*n*=17, 50%).

Patients considered some themes, sub-themes, and specific harms 'unclear or unspecific' (e.g., 'feeling badly'), and others 'not relevant' (e.g., 'skin burns from radiation').

However, several were ‘clear and relevant’ (e.g., ‘headache’) to patients. Patients had suggestions for new items and for adjustment of several existing themes, sub-themes, and specific harms. Various perspectives indicated ‘overlaps’ between and within some themes, sub-themes, and specific harms. **Appendix A** illustrates 12 themes, 28 sub-themes, and 171 specific harms that were discussed with patients during the interviews. Important aspects of potential harms of interventions from the patients’ perspective are presented in **Appendix B**. Further results from the focus groups are reported elsewhere (19).

Stakeholder meeting

Of the 30 participants who attended the 90-minute SIG session, 29 were in person, and one was virtual (**Table 1**). At this meeting the definition of patient’s perception of safety was discussed and further refined at follow up calls of members within the group. It was agreed that a domain for patients’ perception of safety can be defined as an outcome that represents the patient voice evaluating the symptomatic treatment-related adverse events for people with RMDs enrolled in clinical trials.This would include severity, frequency, and interference of symptoms (i.e., distinct from ‘signs’) from different body systems (see **Appendix C** for the full definition also with exemplars and rationale for the definition).

The burden of any future harms-related instrument was also discussed at the session as some participants questioned whether patients would be willing to use such a instrument. The PRPs present at the SIG argued that harms are important and relevant to them, and that patients would definitely use a harms-related instrument. Nevertheless, it was stated that clear information needed to be provided to patients on the aim of any harm reporting instrument to motivate them to use it. Further, a patient-reported harm instrument could make use of computer interfaces to allow for the skipping of unnecessary questions, or options like computer adaptive testing to decrease the burden of completing a questionnaire on this topic.

In the discussion it was noted that multiple interventions such as having blood tests taken, visiting clinics, transportation, and taking pills or shots can be a huge burden to patients especially in the beginning of a disease. Regulators pointed that evaluating the balance between benefit and harms when assessing treatment effects of drug therapies is a common struggle for them (20,21). Thus, a discussion point was whether a single item

could be introduced to assess the global burden of harms or the global burden of treatment. Some argued that the global burden of treatment would cover far more than the burden posed by potential harms and would therefore go beyond the scope of our work. It was also mentioned there may be other tools that address this issue, e.g., the Treatment Satisfaction Questionnaire for Medication (TSQM). Some also argued that it was too early to settle for a single measure as the team was focused on getting a better understanding of the breadth of the concept of harm in arthritis trials, but it was clarified that a single item would not replace the more granular assessment.

The process provided an indepth view of the specific harms that could possibly by experienced in intervention trials. However, future work will focus on binning and winnowing these into clusters that might reduce overlap or reduncancy to make the list of candidate items and any future instrument more understandable and less overwhelming. This would aim for a more representative set of items by capturing the meaning and construct from the items and eliminating unnecessary redundancy in them (22).

Table 1 Participants present at the SIG session

	Patients (*n*=9)	**HCP/others (*n*=21)***
Type of attendance		
In-person	8 (89%)	21 (100%)
Online	1 (11%)	0 (0%)
Continent		
Australia	1 (11%)	2 (10%)
Europe	3 (33%)	10 (48%)
North America	5 (56%)	9 (43%)
Had attended an in-person OMERACT conference before	6 (67%)	11 (52%)

Data are expressed as number (%).
Abbreviations: HCP, health care providers.
*Described as: 10 "Principal investigators (Researchers and their funders)"; 7 "Providers Individuals (e.g. nurses, physicians, mental health counselors, pharmacists, and other providers of care and support services) and organizations that provide care to patients and populations"; 3 "Product makers (Drug and device manufacturers)"; and 1 "Policy makers (FDA, EMA, CADTH, PBAC, Departments of Health and Human Services, Congress, states, professional associations, intermediaries, and other policy-making entities)".

Result of polls during the SIG-session

A total of 25 participants (7 PRPs) voted on question 1, and 14 participants provided elaborated feedback to question 2. The result of poll question 1 is shown in **Table 2**. Participants reached consensus (96% endorsement) that there are enough qualitative data

to feel the group could move forward into the instrument development phase (i.e., Delphi survey). Most comments (8 out of 14) in question 2 were on the overall burden discussed in the session, while four stated they had nothing further to add, one asked for the specific list of domains that should go into the Delphi, and one questioned whether the items would be relevant to other rheumatic diseases or to minority ethnic groups given the demographics of participants in our qualitative work.

Table 2 Polling results from the SIG

Question 1 poll options	**Total (*N*=25)**	**Patients (*n*=7)**	**HCP/others (*n*=18)***
Yes, I agree (that there are enough qualitative data to move forward to the Delphi state),	24 (96)	6 (86)	18 (100)
No, I don't agree (that there are enough qualitative data to move forward to the Delphi state)	0 (0)	0 (0)	0 (0)
Don't know	1 (4)	1 (14)	0 (0)

Data are expressed as number (%).
Abbreviations: HCP, health care providers.
*Described as: 8 "Principal investigators (Researchers and their funders)"; 6 "Providers Individuals (e.g. nurses, physicians, mental health counselors, pharmacists, and other providers of care and support services) and organizations that provide care to patients and populations"; 3 "Product makers (Drug and device manufacturers)"; and 1 "Policy makers (FDA, EMA, CADTH, PBAC, Departments of Health and Human Services, Congress, states, professional associations, intermediaries, and other policy-making entities)".

CONCLUSION

In conclusion, progress has been made in understanding the components of safety from a patient's perspective. A clear definition was finalized, and stakeholders agreed that there are sufficient qualitative data from patients to support this definition and to move forward to developing or selecting an outcome measurement instrument for patients' perception of safety. From the specific harms listed - based on substantial input from patients and other stakeholders – these will now undergo further refinement through cognitive interviews with patients to establish content validity. Such domain will represent the patient voice evaluating the symptomatic treatment-related adverse events for people with RMDs enrolled in clinical trials.This would include severity, frequency, and interference of symptoms (i.e., distinct from 'signs') from different body systems.

CRediT author statement

Dorthe B. Berthelsen: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration

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Robin Christensen: Conceptualization, Methodology, Validation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration

Declaration of Competing Interests

Dorthe B. Berthelsen: None; fellow of the OMERACT Safety Working Group.

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Vibeke Strand: Reports being a founding member of the executive committee of Outcome Measures in Rheumatology (OMERACT) [1992 – present], an international consensus organization that develops and validates outcome measures in rheumatology randomized controlled trials and longitudinal observational studies and has received arms-length funding from as many as 36 sponsors.
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Ethics approval

Our qualitative study generating harm-related themes was carried out in accordance with the Helsinki Declaration. Permission was obtained on 14 March 2022 (confirmation

number P-2022-94) from the Data Protection Agency of the capital region in Denmark, and data was handled according to agreements. Patients were asked to provide written informed consent to participate in this qualitative study.

References

1. IHC. E19 A selective approach to safety data collection in specific late-stage pre-approval or post-approval clinical trials; 2022; [cited 2023 May 30]; Available from: https://ich.org/page/efficacy-guidelines

2. Golder S, Loke YK, Wright K, Norman G. Reporting of adverse events in published and unpublished studies of health care interventions: A Systematic Review. PLoS Med. 2016 Sep;13(9):e1002127.

3. Phillips R, Hazell L, Sauzet O, Cornelius V. Analysis and reporting of adverse events in randomised controlled trials: a review. BMJ Open. 2019 Feb;9(2):e024537.

4. Hodkinson A, Kirkham JJ, Tudur-Smith C, Gamble C. Reporting of harms data in RCTs: a systematic review of empirical assessments against the CONSORT harms extension. BMJ Open. 2013 Sep 27;3(9):e003436.

5. Junqueira DR, Zorzela L, Golder S, Loke Y, Gagnier JJ, Julious SA, et al. CONSORT Harms 2022 statement, explanation, and elaboration: updated guideline for the reporting of harms in randomized trials. J Clin Epidemiol. 2023 Apr;S0895435623000902.

6. Basch E. The missing patient voice in drug-safety reporting. N Engl J Med. 2010 Mar 11;362(10):865–9.

7. Center for Drug Evaluation and Research. CDER Patient-Focused Drug Development. FDA [Internet]. 2022 Nov 15 [cited 2023 May 30]; Available from: https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development

8. Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med. 2004 Nov 16;141(10):781–8.

9. Aronson JK. Distinguishing hazards and harms, adverse drug effects and adverse drug reactions : implications for drug development, clinical trials, pharmacovigilance, biomarkers, and monitoring. Drug Saf. 2013 Mar;36(3):147–53.

10. Andersen KM, Kelly A, Lyddiatt A, Bingham CO, Bykerk VP, Batterman A, et al. Patient Perspectives on DMARD Safety Concerns in Rheumatology Trials: Results from Inflammatory Arthritis Patient Focus Groups and OMERACT Attendees Discussion. J Rheumatol. 2019 Sep;46(9):1168–72.

11. Andersen KM, Cheah JTL, March L, Bartlett SJ, Beaton D, Bingham CO, et al. Improving Benefit-harm Assessment of Therapies from the Patient Perspective:

OMERACT Premeeting Toward Consensus on Core Sets for Randomized Controlled Trials. J Rheumatol. 2019 Aug;46(8):1053–8.

12. Klokker L, Berthelsen DB, Woodworth T, Andersen KM, Furst DE, Devoe D, et al. Identifying possible outcome domains from existing outcome measures to inform an OMERACT core domain set for safety in rheumatology trials. J Rheumatol. 2019 May;46(9):1173–8.

13. Berthelsen DB, Woodworth TG, Goel N, Ioannidis JPA, Tugwell P, Devoe D, et al. Harms reported by patients in rheumatology drug trials: a systematic review of randomized trials in the cochrane library from an OMERACT working group. Semin Arthritis Rheum. 2021 Jun;51(3):607–17.

14. Hazlewood GS, Schieir O, Bykerk V, Mujaab K, Tugwell P, Wells G, et al. Frequency of Symptomatic Adverse Events in Rheumatoid Arthritis: An Exploratory Online Survey. J Rheumatol. 2022 Sep;49(9):998–1005.

15. Cheah JTL, Robson JC, Black RJ, Goodman SM, Lester S, Mackie SL, et al. The patient's perspective of the adverse effects of glucocorticoid use: A systematic review of quantitative and qualitative studies. From an OMERACT working group. Semin Arthritis Rheum. 2020 Oct 1;50(5):996–1005.

16. NCI - PRO-CTCAE™ Items - English; Item Library Version 1.0. Available from: https://healthcaredelivery.cancer.gov/pro-ctcae/instrument-pro.html. Accessed 2021.08.19.

17. de Vries ST, Mol PGM, de Zeeuw D, Haaijer-Ruskamp FM, Denig P. Development and Initial Validation of a Patient-Reported Adverse Drug Event Questionnaire. Drug Saf. 2013 Sep 1;36(9):765–77.

18. Berthelsen DB, Nielsen SM, Rasmussen MU, Ellingsen T, Bartlett SJ, Voshaar MS, et al. Symptoms, classifications, and themes related to harms in rheumatology: Qualitative semi-structured interviews with patients with inflammatory arthritis. Protocol available from: http://www.parkerinst.dk/sites/default/files/protocol_harms_in_rheumatology_-_qualitative_interview_study_v.2021.11.24_final.pdf. Accessed 2023.05.16.

19. Berthelsen D, et al. "I couldn't carry on taking a drug like that": A qualitative study of patient perspectives on harms from drug treatment in rheumatology from the OMERACT Safety Working Group. In preparation.

20. EMA. European Medicines Agency. 2018 [cited 2023 Oct 15]. Benefit-risk methodology. Available from: https://www.ema.europa.eu/en/about-us/what-we-do/regulatory-science-research/benefit-risk-methodology

21. U.S. Food and Drug Administration. FDA's Role in Managing Medication Risks. FDA [Internet]. 2018 Mar 11 [cited 2023 Oct 15]; Available from: https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/fdas-role-managing-medication-risks

22. DeWalt DA, Rothrock N, Yount S, Stone AA. Evaluation of Item Candidates: The PROMIS Qualitative Item Review. Med Care. 2007 May;45(5 Suppl 1):S12–21.