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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.

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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].

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.

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

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)".

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)".

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.

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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.

CRediT authorship contribution statement

Dorthe B. Berthelsen: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration. **Lee S. Simon:** Conceptualization, Methodology, Writing – review & editing, Visualization, Supervision. **John P.A. Ioannidis:** Writing – review & editing. **Marieke Voshaar:** Methodology, Writing – review & editing, Visualization, Supervision. **Pam Richards:** Methodology, Writing – review & editing, Visualization, Supervision. **Niti Goel:** Methodology, Writing – review & editing, Visualization. **Vibeke Strand:** Writing – review & editing, Visualization. **Sabrina M. Nielsen:** Methodology, Writing – review & editing, Supervision. **Beverly J. Shea:** Methodology, Validation, Writing – review & editing, Supervision. **Peter Tugwell:** Methodology, Validation, Writing – review & editing. **Susan J. Bartlett:** Methodology, Writing – review & editing. **Glen S. Hazlewood:** Methodology, Writing – review & editing. **Lyn March:** Writing – review & editing. **Jasvinder A. Singh:** Writing – review & editing. **Maria E. Suarez-Almazor:** Writing – review & editing. **Maarten Boers:** Writing – review & editing. **Randall M. Stevens:** Writing – review & editing. **Daniel E. Furst:** Writing – review & editing. **Thasia Woodworth:** Writing – review & editing. **Amye Leong:** Writing – review & editing. **Peter M. Brooks:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Caroline Flurey:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – review & editing, Visualization, Supervision. **Robin Christensen:** Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration.

Declaration of Competing Interest

Dorthe B. Berthelsen: None; fellow of the OMERACT Safety Working Group. Lee S. Simon: None; co-chair of the OMERACT Safety Working Group. John P. A. Ioannidis: Part of the CONSORT Harms Group. Marieke Voshaar: None. Pam Richards: None. Niti Goel: No relevant disclosures. 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. Sabrina M. Nielsen: None. Beverly J. Shea: None. Peter Tugwell: None. Susan J. Bartlett: None. Glen S. Hazlewood: None. Lyn March: Has received institutional support from Janssen Australia and the Australian Government. Jasvinder A. Singh: JAS has received consultant fees from Schipher, Crealta/Horizon, Medisys, Fidia, PK Med, Two labs Inc., Adept Field Solutions, Clinical Care options, Clearview healthcare partners, Putnam associates, Focus forward, Navigant consulting, Spherix, MedIQ, Jupiter Life Science, UBM LLC, Trio Health, Medscape, WebMD, and Practice Point communications; the National Institutes of Health; and the American College of Rheumatology. JAS has received institutional research support from Biomet Holdings. JAS received food and beverage payments from Intuitive Surgical Inc./Philips Electronics North America. JAS owns stock options in Atai life sciences, Kintara therapeutics, Intelligent Biosolutions, Acumen pharmaceutical, TPT Global Tech, Vaxart pharmaceuticals, Atyu biopharma, Adaptimmune Therapeutics, GeoVax Labs, Pieris Pharmaceuticals, Enzolytics Inc., Seres Therapeutics, Tonix Pharmaceuticals Holding Corp., and Charlotte's Web Holdings, Inc. JAS previously owned stock options in Amarin, Viking and Moderna pharmaceuticals. JAS is on the speaker's bureau of Simply Speaking. JAS was a member of the executive of Outcomes Measures in Rheumatology (OMERACT), an organization that develops outcome measures in rheumatology and receives arms-length funding from 8 companies. Maria E. Suarez-Almazor: Has received consultant fees from Eli Lilly, Pfizer, Celgene and Syneos Health Maarten Boers: None. Randall M Stevens: None. Daniel E. Furst: None. Thasia Woodworth: None. Amye Leong: None. Peter M Brooks: None; co-chair of the OMERACT Safety Working Group. Caroline Flurey: None; co-chair of the OMERACT Safety Working Group. Robin Christensen: None; co-chair of the OMERACT Safety Working Group.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2023.152288.

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