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Improving benefit-harm assessment of therapies from the patient perspectives: OMERACT pre-meeting towards consensus on core sets for randomized controlled trials

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Abstract

BACKGROUND: OMERACT convened a pre-meeting to bring together patients, regulators, researchers, clinicians and consumers in order to build upon previous OMERACT drug safety work, with patients fully engaged throughout all phases.

METHODS: Day 1 included a brief introduction to the history of OMERACT and methodology, and an overview of current efforts within and outside OMERACT to identify patient-reported medication safety concerns. On day 2, two working groups presented results; after each, breakout groups were assembled to discuss findings.

RESULTS: Five themes pertaining to drug safety measurement emerged.

CONCLUSION: Current approaches have failed to include data from the patient's perspective. A better understanding of how individuals with rheumatic diseases view potential benefits and harms of therapies is essential.

Keywords

OMERACT
Patient satisfaction
Clinical trials
Disease modifying antirheumatic drugs
Risk assessment

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BACKGROUND

Outcome Measures in Rheumatology (OMERACT) is an international initiative aimed at improving outcome measurement across rheumatologic conditions. Immediately prior to OMERACT 2018 biannual event, a special pre-meeting was convened entitled *Improving Risk-Benefit Assessment of Drugs, with an Emphasis on Patients and their Perspectives* on May 13-14, 2018 in Terrigal, New South Wales, Australia. The meeting was designed to bring together stakeholders reflecting multiple perspectives to discuss current policies and approaches in patient-focused drug development, and review ongoing work by OMERACT and other initiatives in this area (1-4). Notably, as this meeting included representatives from multiple regulatory and pharmaceutical industries from around the world, it offered a unique opportunity to hear perspectives from around the world of the growing importance of patient engagement in regulatory affairs.

While OMERACT has a legacy of work in this area, notable research over the past two years represented a fresh look at drug safety. Consistent with OMERACT principles, in this work patients were fully engaged as patient research partners (PRPs) throughout all phases of the work from conceptualization through interpretation of results.

The specific aims of the meeting were to invite our PRPs to: 1) convene with multiple stakeholders to review ongoing global efforts in patient-focused drug development; 2) identify opportunities for co-learning and development of patient-centered methods to assess potential harms in rheumatology, oncology, and nephrology clinical trials; and 3) develop this white paper outlining key considerations for the development of core outcome sets and measures of patient-valued safety outcomes for use in RCTs.

METHODS

Participants included 42 stakeholders (9 PRPs, 2 rheumatology fellows, 26 clinician/researchers, 5 regulators, payers or industry scientists; some individuals contributed to multiple categories) and included new and returning OMERACT members. A professional scribe created visual representations of the discussions on a white board throughout the meeting.

During the first day, a brief introduction to history of OMERACT, and current methodologies in terms of previous drug safety work was presented by OMERACT executive members along with an brief overview of the new OMERACT Filter 2.1(5, 6) approaches to core set development (Figure 1). Current patient-centered efforts to assess benefits and harms were presented from PRPs and regulatory representatives from the United States (US) Food and Drug Administration, Canadian Agency for Drugs and Technologies in Health, European Medicines Agency, Ministry of Health New Zealand and Pharmaceutical Benefits Advisory Committee of Australia. Colleagues from nephrology (7) and oncology (8) presented new patient-reported outcomes (PROs) querying side effects and adverse events in their fields.

On the second day, two OMERACT working groups presented new results exploring patient attitudes and experiences with rheumatology therapies. The OMERACT Safety Group presented results from six focus groups with inflammatory arthritis patients in Canada, the US, and Australia regarding their experiences and considerations with DMARDs. The OMERACT Glucocorticoid Impact Group summarized work completed over the past two years including two literature reviews, a survey, and patient interviews used to inform an ongoing Delphi to prioritize patient-valued outcomes regarding steroid use in rheumatology. Following each presentation, breakout groups of 8-10 different stakeholders were assembled to discuss key

findings, implications, opportunities and identify additional work needed. The full group was reconvened, and a representative from each group summarized the discussion and key messages for all attendees.

RESULTS

The initial presentations introduced attendees to OMERACT's long-standing commitment to fully engaging PRPs as co-producers in the development and validation of outcome measures in rheumatology. Patient attendees then discussed the challenges many of them had faced understanding the relative benefits and harms of therapeutics, how discussions (or lack thereof) with providers influenced their perceptions of safety and effectiveness, and individual considerations regarding safety that reflected personal priorities and values. Consensus quickly emerged that the outcomes that clinicians and trialists who monitor safety in drug development often differ from those that patients value most. For example, patients taking methotrexate to control their disease often reported considerable impact of what are often terms "nuisance side effects" (mental fog, nausea and gastrointestinal upset) on quality of life. In contrast, clinicians are primarily concerned with pathophysiologic manifestations such as hepatotoxicity when monitoring the effects of treatment.

Next, examples of patient-centered safety monitoring strategies in nephrology and oncology were presented. A representative from the Standardised Outcomes in Nephrology (SONG) Initiative briefly summarized ongoing work to identify patient-valued core domain sets and measures for use in nephrology trials across a range of diseases. Similar to rheumatology, the nephrology community views current reporting of harms in RCTs as poorly defined, inadequate, unreliable and failing to capture the range of patient experiences. Adapted from

the OMERACT onion(5), SONG has a conceptual schema of a kidney that represents disease-specific mandatory and discretionary outcomes they recommend be measured in trials(9).

While a PRO assessing potential harms is not yet available in rheumatology or nephrology, a measure has been developed and extensively validated in oncology(10). The US National Cancer Institute's *Patient-Reported Outcomes version* of the *Common Terminology Criteria for Adverse Events* (PRO-CTCAE) is comprised of a bank of 124 patient-reported items describing 78 symptomatic adverse events such as dysphagia, nausea, and sensory neuropathy in the context of cancer treatment(11, 12). Importantly, PRO-CTCAE moves beyond binary presence or absence of symptoms, and asks about frequency, severity, and interference with daily activities (where applicable) of each symptom. This represents a major advancement in more fully characterizing patient experiences. There was consensus among attendees during discussion following the presentation that it is important to fully capture relevant aspects of symptoms when designing a rheumatology safety PRO. The PRO-CTCAE item bank also allows investigators to tailor symptom queries based to a specific molecule or drug class, and separates treatment-related effects from overall disease burden. Importantly, the PRO-CTCAE is typically used for weekly reporting for treatment that is delivered during a defined period, which could be applicable to weekly reporting in rheumatology trials but may not be feasible in rheumatology clinical practice, where treatment is generally over a longer period of time.

As presentations results presented by the OMERACT Safety and Glucocorticoid Toxicity Groups are described in detail elsewhere (Andersen KM et al 2018, Cheah JT et al 2018), below we summarize the overarching themes resulting from the small and large group discussions, and proposed pathways forward (Figure 2). First, there was consensus that patients, their

families and caregivers often have differing priorities and expectations of benefits and harms from their clinicians and trialists. Discrepancies between patients and clinicians on what matters most were echoed by results from SONG, where patients once again reported higher concern about life impact (fatigue, negative emotions), while physicians reported greater concern about clinically-defined medical events (cardiac arrest, heart attack, stroke, heart failure)(13). Furthermore, in a cluster-randomized trial, oncologists who were provided with their patient's PRO-CTCAE scores were significantly more likely to themselves report important symptomatic adverse events that patients reported (pain, anxiety, fatigue, anorexia, dysphagia, depression) than oncologists who did not receive their patient's PRO-CTCAE scores(14). Thus, attendees agreed it is essential to consider multiple perspectives when identifying essential domains to include in core outcome sets.

Second, to capture the impact of safety events from the patient perspective, it is important to ask patients about the effect of medication-related symptoms on day-to-day life as the cumulative effects over time appear to be a key driver of patient priorities. It also may helpful for patients to ask their family and friends if they have noticed changes in their physical, emotional, and social function that are potentially treatment-related. Attendees acknowledged that clinicians are often reticent to discuss side effects when they perceive little can be done to attenuate these, especially when there are few or no therapeutic alternatives.

Third, some noted that capturing and quantifying the impact of side effects may be challenging. For instance, when a side effect is common, discussing the intensity and impact may be more meaningful to patients than simply describing the frequency or probability of occurrence. The PRO-CTCAE group noted that it was often important to adjust for baseline

symptoms to maximize differences in patient-reported adverse events. The possibility of also utilizing a single item to assess overall benefit-harm item was discussed where a patient would be asked to rate whether the perceived benefit outweighed the impact on day-to-day life (i.e., Was it worth it?).

Fourth, perceptions of benefit versus harm likely vary among subgroups and depending on individual circumstances. This theme is a current focus of the OMERACT Contextual Factors Working Group. For example, a person who is financially responsible for family members may be willing to tolerate more treatment-related symptoms if the medication allows them to continue working as compared with someone who does not have others relying on their ability to work. Inclusion of patients with diverse characteristics in race and ethnicity, age, sex, socio-economic status, and living situations is needed in future trials to better understand issues related to safety priorities and tolerability.

There also was general agreement that in drug trials, competing priorities may influence the willingness of patients to disclose safety events. Some patients may be willing to tolerate more risk or be less likely to report adverse events to remain enrolled in trials that offer the only access to treatment, or if they perceive the treatment is highly beneficial.

CONCLUSION

Robust systems for designing, conducting, and reporting safety events in rheumatology RCTs have been refined over many decades. However, to date, little attention has been given to understanding and measuring outcomes that matter most to patients. A better understanding is needed of how patients with rheumatic diseases view the relative benefits and potential harms of a treatment, in order to design and select more adequate outcome measures for

safety events monitoring. Such understanding can allow patients and clinicians to make informed choices about treatment and address longstanding challenges related to treatment initiation and long-term adherence. During the meeting, there was recognition that stakeholders view safety through multiple lenses. Indeed, the concept of safety seems inextricably linked to efficacy in that it is the relative balance of benefit and harm, rather than absolute frequency counts of symptoms, which may be most meaningful and informative to patients.

A research agenda to address this knowledge gap and develop patient-centered tools will require heightened appreciation for the full range of patient experiences, concerns, and preferences. The OMERACT Safety Group is currently conducting focus groups with international groups of patients to better elucidate patient perspectives and core domains needed to develop a new tool or adapt existing ones, such as the PRO-CTCAE. It will also be important to identify ways to capture the *cumulative* negative impact of what have traditionally been viewed as “nuisance side effects” such as nausea and address the added resources required to enhance collection, analysis and interpretation of safety PROs. As with all OMERACT initiatives, it is essential that patients are fully engaged in the co-development and co-production of this work.

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