Review Article on Pain Therapy

Pain assessment in clinical trials: a narrative review

Livia Puljak[1]^, Krste Boric[2], Svjetlana Dosenovic[3]

[1]Center for Evidence-Based Medicine and Health Care, Catholic University of Croatia, Zagreb, Croatia; [2]Department of Surgery, University Hospital Center Split, Split, Croatia; [3]Department of Anesthesiology and Intensive Care, University Hospital Center Split, Split, Croatia

Contributions: (I) Conception and design: L Puljak; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Prof. Livia Puljak, MD, PhD. Center for Evidence-Based Medicine and Health Care, Catholic University of Croatia, Ilica 242, 10000 Zagreb, Croatia. Email: livia.puljak@unicath.hr.

Abstract: Pain is a symptom measured in many clinical trials. For pain as an outcome domain, trialists need to choose adequate outcome measure(s), as there are myriad outcome measures for pain to choose from. To ensure consistency and uniformity in clinical trials and systematic reviews, core outcome sets (COS) have been defined; COS includes a predefined minimal list of core outcomes that should be measured within a trial, to ensure their consistency and comparability. COS is defined via consensus procedure, which includes relevant stakeholders such as experts from a specific field and patients. Along with outcomes, outcome measures for each outcome need to be defined to make sure that the outcomes will be measured consistently and uniformly. Hereby we reviewed studies that have examined use of recommended core outcome domains and outcome measures in clinical trials that would be expected to measure pain. Despite the existence of COS and defined core outcome measures (COMs), multiple studies have shown that these are not necessarily used in clinical trials, or in the relevant systematic reviews, which further increases heterogeneity of existing evidence, hinders evidence synthesis and trial comparability, and assessment of comparative effectiveness of interventions. Trialists are encouraged to use COS and COMs when designing clinical trials. Research community is encouraged to design interventions that will help with identifying barriers for using COS and COMs and interventions to foster their uptake. Use of consistent pain outcomes and pain outcome measures is in the interest of patients, research community, healthcare workers and decision-makers. For clinical conditions for which there are no COS and COMs, efforts to design them would be beneficial.

Keywords: Pain; outcomes; clinical trials; research methodology

Submitted Apr 21, 2020. Accepted for publication Jun 16, 2020.
doi: 10.21037/atm-20-3451
View this article at: http://dx.doi.org/10.21037/atm-20-3451

Introduction

Pain is one of the most common symptoms that brings patients to a physician, and it is a symptom seen in many diseases. Thus, it is expected that pain as an outcome would be measured in many clinical trials. However, it is also necessary to use standardized measures, so that the results from different trials are comparable. When considering an outcome, there is a consideration of an outcome domain, such as pain, and an outcome measure, such as visual analog scale (VAS). Standardization of outcome domains and outcome measures helps to ensure consistency and homogeneity of research findings.

Core outcome set (COS) is an agreed, consensus collection of outcomes that are recommended for measuring

^ ORCID: 0000-0002-8467-6061.

and reporting in a specific health research area. According to the COMET (Core Outcome Measures in Effectiveness Trials) Initiative, COS is a minimum of outcomes that are recommended to be measured and reported in all clinical trials addressing a specific condition (1). Using a COS will also ensure larger amount of usable data in evidence syntheses (2). Besides COS, researchers have also designed core outcome measures (COMs) that should be used for the COS defined in a specific area.

Various initiatives were established to define COS in various fields of health research. In the field of rheumatology, outcome standardization started very early; as the Outcome Measures in Rheumatology (OMERACT) initiative recommended a COS for osteoarthritis in 1997 (3).

For example, in 2003, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) defined COS in the field of chronic pain (4); pain was the first among the list of six core outcomes in the IMMPACT recommendations. Two years later, specific outcome measures for assessing those outcome domains of that COS were published (5).

It was recognized that measuring pain in children has specific challenges, particularly with different needs for different ages of children. Thus, in 2008, Pediatric Initiative for Methods, Measurement, and Pain Assessment in Clinical Trials (PedIMMPACT) has recommended COS for children aged 3 years and above (6) to ensure standardization of COS and COMs for pain in children. PedIMMPACT included two core outcome domain sets, one was defined for acute pain and the other one was defined for chronic and recurrent pain in both children and adolescents (6).

Adherence to COS and COMs in clinical trials

Despite the fact that core outcome domains and COMs have been defined for various fields, including trials where measuring pain is important, it has been reported that the trialists and systematic review authors do not adhere to those recommendations, which contributes to high heterogeneity and non-comparability of available evidence.

In a study of 337 trials, which analyzed outcome domains and pain outcome measures in randomized controlled trials (RCTs) of interventions for treatment of postoperative pain in children and adolescents and compared them with recommendations of the PedIMMPACT, it was found that the median number of outcomes reported in RCTs was 2 for PedIMMPACT outcomes (range, 0 to 6) (7). Two most commonly utilized outcome domains in the analyzed trials were pain intensity in 93% of analyzed RCTs, and symptoms and adverse events, which was analyzed in 83% of analyzed RCTs (7). This result indicates that in RCTs specifically aimed towards treatment of pediatric postoperative pain, not all trials have analyzed pain intensity, which is very puzzling. All the other PedIMMPACT outcome domains were used in less than a third of analyzed RCTs. Another unexpected result was that among 213 RCTs that have reported using pain intensity as an outcome domain, not all of the trials have specified which pain outcome measure they used (97% trials reported it). The most commonly used outcome measures for pain in children included in those trials were VAS (used in 24% of the trials) and Children's Hospital of Eastern Ontario Pain Scale (used in 18% of the trials). In the 303 RCTs that have reported using pain intensity outcome measure, the authors have used 33 different assessment tools (7).

Other studies have pointed out to similar inconsistencies in trials on different topics, where pain was measured. Pushpanathan *et al.* analyzed postoperative pain outcome measurements that were used in RCTs exploring regional anesthesia that were published between 2005 and 2017. Their study included 31 RCTs, in which 15 different outcomes measures were used for assessing postoperative pain (8).

Froud *et al.* have explored outcome measures used in clinical trials on low back pain (LBP) published between 1980 and 2012. They included 401 trials, and reported difficulties with finding explicit descriptions of a primary outcome measure, as 50% RCTs had an explicit mention of what was a primary outcome measure, while in another 20% of trials this could be concluded from sample size estimation. They also reported heterogeneity in usage of pain outcome measures (9). Froud *et al.* concluded that recommendations for standardizing outcome domains and measures have had a limited effect on practice in clinical trials, and that perhaps those that create COS and COMs need to do it in a way that would improve their uptake in the practice (9).

Mulla *et al.* assessed reporting of core outcome domains recommended by IMMPACT in trials about opioids for chronic non-cancer pain; they included 156 trials in their analysis, and found that the reported use of IMMPACT-recommended outcome domains was extremely variable, as it ranged from 99% for pain to 7% for interpersonal functioning. More recent trials were better regarding adherence to IMMPACT recommendations, and it was

encouraging that the authors reported that the adherence to IMMPACT recommendations was improving over time (10).

Krsticevic *et al.* analyzed 334 RCTs of non-surgical interventions for osteoarthritis, and found that the adherence to OMERACT COS was inadequate, as it was fully used in only 14% of the analyzed trials. Those trials used 50 different outcome measures for pain (11).

For some diseases, there are no COS and COMs. Some studies explored outcomes used in pain trials to explore which outcome domains and outcome measures should be recommended for future trials. In 2015, Page *et al.* reported such study of trials about the effects of physical therapy on shoulder pain. They analyzed 171 trials, of which 87% measured pain; 35 different instruments for measuring pain were used in the analyzed trials (12).

Grieve *et al.* analyzed 104 clinical trials about complex regional pain syndrome (CRPS), to inform creation of the COMs set. They searched literature published from 2000 to 2014, and found that the analyzed trials used 68 questionnaire outcome measures, of which only 5 were validated for CRPS (13).

Systematic reviews also do not use recommended core outcome domains and measures

It has been reported that authors of systematic reviews also do not use recommended core outcome domains and measures. Boric *et al.* reported analysis of 50 systematic reviews about postoperative pain in children, they found that the median number of outcomes used was 4, and the median number of the PedIMMPACT core outcome domains used was 3, out of 6. Pain intensity was not the most commonly used core outcome domain in the analyzed reviews; it was used by 75% of the analyzed reviews (14). Furthermore, slightly more than 50% of analyzed reviews that have analyzed pain intensity have specified the pain assessment tool that was eligible in their methods (14).

Dosenovic *et al.* analyzed 97 systematic reviews about neuropathic pain, published between 1995 and 2015. The study found that only 3 included reviews planned in methods to include all 6 IMMPACT domains recommended for chronic pain, while five reviews did not plan to include a single one IMMPACT domain. Among the core outcome domains reported in systematic review methods, pain was the most common, as it was reported in 86% of the reviews. In results of the analyzed reviews, the median number of IMMPACT-recommended core outcome domains was 4 (interquartile range, 2.75 to 5; range, 1 to 6) (15).

Why the authors of clinical trials and systematic reviews do not use core outcomes

The problem of insufficient utilization of core outcome domains and COMs was explored in surveys among authors. These surveys have shown that the authors do not use the existing COS and COMs mostly because they are not aware of it, or they do not find them adequate (16,17). Thus, multiple actions can be employed regarding the uptake of COS and COMs in clinical trials and evidence syntheses.

Those that develop COS and COMs for conditions that already do not have such recommendations should aim to engage wider audience when designing those recommendations, to ensure wider consensus and consequent uptake. Issues of generalizability and credibility may hinder uptake of COS and COMs. To ensure generalizability, development of COS needs to include large number of diverse stakeholders. To improve their credibility, COS and COMs need to capture adequately participants' views (18). Since COS and COMs are expected to be reached via consensus, this consensus will be credible only if all relevant stakeholders have a fair chance to participate, and each stakeholder should have the same chance to express their perspective and to participate in decision-making (18). It is not common to involve a large number of stakeholders from diverse countries and cultures in development of a COS (19). Furthermore, few COS developers include patients, and when they do, the majority includes patients from one country only (20). Relevant outcomes may be overlooked if only clinicians and trialists are involved in a development of COS and COMs (18). Also, patients need to be involved early in the process of selecting outcomes. Otherwise, they may be placed in a position where they need to choose from the "core outcomes" that somebody else has selected, and those "core outcomes" may not reflect patient priorities (18).

Methods for achieving consensus about COS and COMs need to include not only systematic literature review, but also Delphi method and face-to-face discussions. However, it has been shown that few published COS included Delphi method (20-23).

Enhancing the uptake and implementation of COS and COMs in trials and systematic reviews should be fostered. For this, interventions that can affect study design are needed. Research methodology curriculum of junior researchers should include education about the benefits of COS and COMs. Ethics committees need to be aware of the existence of COS and COMs, so that they

can require trialists to use them when submitting their trials for approval. Clinical trial registries could include mention of the applicable COS and COMs when authors are registering their clinical trials. Checklists for reporting RCT and SR protocols during their prospective registration should consider incorporating a statement of COS adherence. Involving regulatory authorities (24) is another opportunity for enhancing uptake and implementation of COS and COMs in trials, as trialists wishing to bring their products to the market need to develop trials that will conform to the requirements of bodies such as US Food and Drug Administration (FDA) and European Medicines Agency (EMA).

Finally, COS and COMs need to be regularly evaluated in terms of their use and acceptability, and updated/revised if needed.

Conclusions

Multiple studies have shown that trialists and authors conducting evidence syntheses in general do not sufficiently use recommended COS and COMs, that trials about pain often do not even measure pain intensity and that outcome measures used are highly heterogeneous. Stakeholders involved in generation of COS and COMs recommendations should include wider representation when making those recommendations. Studies assessing the COS uptake and acceptability should be regular part of COS and COMs assessment. If COS and COMs are found to be acceptable to the research community, interventions for increasing their uptake should be implemented.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Dr. Antonio Ruggiero) for the series "Pain Therapy" published in *Annals of Translational Medicine*. The article was sent for external peer review organized by the Guest Editor and the editorial office.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at: http://dx.doi.org/10.21037/atm-20-3451). The series "Pain Therapy" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. COMET. Core Outcome Measures in Effectiveness Trials. Available online: http://www.comet-initiative.org/
2. Kirkham JJ, Gargon E, Clarke M, et al. Can a core outcome set improve the quality of systematic reviews?--a survey of the Co-ordinating Editors of Cochrane Review Groups. Trials 2013;14:21.
3. Bellamy N, Kirwan J, Boers M, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. J Rheumatol 1997;24:799-802.
4. Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain 2003;106:337-45.
5. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113:9-19.
6. McGrath PJ, Walco GA, Turk DC, et al. Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. J Pain 2008;9:771-83.
7. Boric K, Jelicic Kadic A, Boric M, et al. Outcome domains and pain outcome measures in randomized controlled trials of interventions for postoperative pain in children and adolescents. Eur J Pain 2019;23:389-96.
8. Pushpanathan E, Setty T, Carvalho B, et al. A Systematic Review of Postoperative Pain Outcome Measurements Utilised in Regional Anesthesia Randomized Controlled

Trials. Anesthesiol Res Pract 2018;2018:9050239.
9. Froud R, Patel S, Rajendran D, et al. A Systematic Review of Outcome Measures Use, Analytical Approaches, Reporting Methods, and Publication Volume by Year in Low Back Pain Trials Published between 1980 and 2012: Respice, adspice, et prospice. PLoS One 2016;11:e0164573.
10. Mulla SM, Maqbool A, Sivananthan L, et al. Reporting of IMMPACT-recommended core outcome domains among trials assessing opioids for chronic non-cancer pain. Pain 2015;156:1615-9.
11. Krsticevic M, Dosenovic S, Dimcea DA, et al. Outcome Domains, Outcome Measures, and Characteristics of Randomized Controlled Trials Testing Nonsurgical Interventions for Osteoarthritis. J Rheumatol 2020;47:126-31.
12. Page MJ, McKenzie JE, Green SE, et al. Core domain and outcome measurement sets for shoulder pain trials are needed: systematic review of physical therapy trials. J Clin Epidemiol 2015;68:1270-81.
13. Grieve S, Jones L, Walsh N, et al. What outcome measures are commonly used for Complex Regional Pain Syndrome clinical trials? A systematic review of the literature. Eur J Pain 2016;20:331-40.
14. Boric K, Dosenovic S, Jelicic Kadic A, et al. Efficacy and Safety Outcomes in Systematic Reviews of Interventions for Postoperative Pain in Children: Comparison Against the Recommended Core Outcome Set. Pain Med 2018;19:2316-21.
15. Dosenovic S, Jelicic Kadic A, Jeric M, et al. Efficacy and Safety Outcome Domains and Outcome Measures in Systematic Reviews of Neuropathic Pain Conditions. Clin J Pain 2018;34:674-84.
16. Boric K, Boric M, Dosenovic S, et al. Authors' lack of awareness and use of core outcome set on postoperative pain in children is hindering comparative effectiveness research. J Comp Eff Res 2018;7:463-70.
17. Dosenovic S, Nikolic Z, Ivancev B, et al. Awareness and acceptability of Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials core outcome set for chronic pain among surveyed neuropathic pain authors. J Comp Eff Res 2019;8:671-83.
18. Chevance A, Tran VT, Ravaud P. Improving the generalizability and credibility of core outcome sets (COSs) by a large and international participation of diverse stakeholders. J Clin Epidemiol 2020. [Epub ahead of print].
19. Maxwell LJ, Beaton DE, Shea BJ, et al. Core Domain Set Selection According to OMERACT Filter 2.1: The OMERACT Methodology. J Rheumatol 2019;46:1014-20.
20. Davis K, Gorst SL, Harman N, et al. Choosing important health outcomes for comparative effectiveness research: An updated systematic review and involvement of low and middle income countries. PLoS One 2018;13:e0190695.
21. Gorst SL, Gargon E, Clarke M, et al. Choosing Important Health Outcomes for Comparative Effectiveness Research: An Updated Review and User Survey. PLoS One 2016;11:e0146444.
22. Gorst SL, Gargon E, Clarke M, et al. Choosing Important Health Outcomes for Comparative Effectiveness Research: An Updated Review and Identification of Gaps. PLoS One 2016;11:e0168403.
23. Gargon E, Gurung B, Medley N, et al. Choosing important health outcomes for comparative effectiveness research: a systematic review. PLoS One 2014;9:e99111.
24. Tunis SR, Maxwell LJ, Graham ID, et al. Engaging Stakeholders and Promoting Uptake of OMERACT Core Outcome Instrument Sets. J Rheumatol 2017;44:1551-9.

Cite this article as: Puljak L, Boric K, Dosenovic S. Pain assessment in clinical trials: a narrative review. Ann Transl Med 2021;9(2):188. doi: 10.21037/atm-20-3451

