Research Article

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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

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Aim: We assessed the knowledge and adoption of Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT)-recommended core outcome set (COS) and core outcome measures (COM) among authors of systematic reviews (SR) and randomized controlled trials (RCT) about interventions for neuropathic pain (NeuP). **Methods:** NeuP SR and RCT authors identified via a systematic literature search were surveyed. **Results:** The response rate was low. Although majority of respondents were familiar with the IMMPACT COS, only 61% of SR authors and 40% of RCT authors used the COS. The main perceived obstacle that prevented the adoption of the COS was the lack of awareness of the full IMMPACT COS. **Conclusion:** The adoption of IMMPACT-recommended COS and COM among NeuP authors was inadequate and their appropriateness needs to be further evaluated.

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Appropriate outcomes should be selected while designing clinical trials in order to allow the direct, meaningful comparison of the effects of interventions. Measuring and reporting relevant outcomes is one of the fundamental features of comparative effectiveness research [1]. Issues caused by heterogeneity in outcome measurement could be minimized with the use of a standardized set of outcomes. The Core Outcome Measures in Effectiveness Trials (COMET) initiative defines a core outcome set (COS) as an agreed minimum collection of outcomes, which should be measured and reported in all clinical trials conducted about a specific condition. A COS is usually developed by a group of key relevant stakeholders (including patients and the public, healthcare professionals and decision makers in healthcare) who need to make sure that the chosen outcomes are relevant and important in order to influence policy and practice [2].

In 2003, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) proposed a core set of outcome domains, which should be included in chronic pain trials [3], a COS that is relevant for neuropathic pain (NeuP). During development of this COS, a meeting of 27 people from healthcare disciplines which cover chronic pain and have research and clinical or administrative expertise relevant to chronic pain treatment outcomes (from academia, governmental agencies and the pharmaceutical industry) was held. The list of various domains generated by the participants was discussed during the 2-day meeting and consensus was reached based on the results of the discussion and a formal vote [3].

Future Medicine

Based on the IMMPACT consensus meeting, six domains were recommended as core outcome domains, which should be considered when designing chronic pain trials: pain; physical functioning; emotional functioning; participant ratings of improvement and satisfaction with treatment; symptoms and adverse events; and participant disposition [3]. A consensus was also reached for supplemental outcome domains (clinician or surrogate ratings of global improvement, role functioning, pharmacoeconomic measures, biological markers). Additionally, it has been recommended to supplement core domains by any additional outcomes deemed relevant to a specific treatment [3]. Once core outcome domains were identified, relevant outcome measures that meet appropriate psychometric standards were proposed for the assessment of each core domain at IMMPACT-II consensus meeting, called Core Outcome Measures (COMs) [4].

A previous overview of systematic reviews (SRs) summarized evidence from SRs of randomized controlled trials (RCTs) on interventions for NeuP and found that evidence about efficacy and safety of analyzed interventions for NeuP is frequently inconclusive or completely lacking [5].

As inconsistent use of recommended outcome domains and outcome measures can prevent comparing different studies in the same field and hinder decision making [6], outcome domains and outcome measures used in those SRs were further investigated, and insufficient adherence to the IMMPACT-recommended COS and COMs for chronic pain in NeuP interventional reviews was found [7].

Therefore, we decided to look for the reasons for insufficient uptake of the IMMPACT-recommended COS and COMs for chronic pain among authors of SRs and RCTs conducted in the field of NeuP. Currently it is not known whether those authors are familiar with the IMMPACT-recommended COS and core measures for COS assessment, whether they intentionally used it while conducting their studies, whether there are any challenges preventing the acceptance of COS and COMs, whether there are the currently proposed outcome domains and outcome measures within the core set relevant and appropriate to SR and RCT authors, and if there are other outcome domains and measures that should be included in the core set. We aimed to answer those questions in this study via survey of authors.

Methods

Study design

This was a cross-sectional survey.

Study participants

Authors of published SRs and RCTs about interventions for NeuP identified in the previous overview of SRs were included. A systematic literature search was performed and 97 SRs published between 1995 and 2015 about pharmacological, surgical and multiple interventions for the management of NeuP were identified, of which 7 SRs were without included RCTs [5]. Therefore, two authors (ZN, BI) extracted a list of 772 unique RCTs from 90 SRs, 112 duplicate corresponding authors were removed, and extractions were checked by a third author (SD).

E-mail addresses of corresponding authors from the SRs and RCTs were obtained from published manuscripts and from the Internet if necessary, and authors were invited to participate in the survey via e-mail. We also made an effort to obtain e-mail addresses of other authors of included SRs to increase the number of potential participants. In cases where a valid e-mail address was not indicated in the manuscript or could not be found online, the survey could not be delivered to those authors. Two authors of this study (ZN, BI) collected authors' names, affiliations and email addresses, which was checked by a third author (SD).

Survey

A 24-item survey was designed in English (Supplementary Information 1). It was piloted by five persons during the testing phase, including a psychologist and four methodologists, and modified based on the received feedback.

Outcome domains and outcome measures listed in the survey were selected from the IMMPACT-recommended core domains [3] and core measures [4], and supplemented by the most frequent outcomes identified in the authors' study, which analyzed outcome domains and measures used in 90 SRs of RCTs on efficacy and safety of interventions for NeuP [7]. General questions covering participant characteristics were first presented. The participants were then asked about their awareness of IMMPACT-recommended COS and COMs. They were asked to state the number of core outcome domains; and to identify core domains and measures recommended by IMMPACT from the list of offered outcome domains and measures. For authors whose studies were published before January 2005 (before IMMPACT recommendations), the answer 'not applicable' was offered to a question of the use of the COS and

COMs in their manuscripts. January 2005 was used as a cut-off date to separate published studies into pre- and post-IMMPACT cohorts, to account for a time delay in the publication of the manuscripts.

Subsequently, the participants were asked to rate the relevance of the COS and COMs, as well as outcome domains and measures outside the IMMPACT recommendations, on a 1–9 scale: we interpreted scores 1–3 as a domain of limited importance for participants, 4–6 an important domain and 7–9 a critically important domain. We used this scoring because, previously, consensus on whether an outcome should be included in the COS was defined as 70% or more of the respondents scoring it 7–9 and <15% as 1–3 [2].

Additional questions were asked about the previous and future use of the IMMPACT COS and COMs, difficulties associated with using IMMPACT COS and COMs, domains and measures which should be included in a COS for chronic pain, and possible reasons for improving their adherence to IMMPACT-recommended COS and COMs. The participants had the possibility to leave comments they might have about the study topic and to skip questions.

Survey administration

The survey was constructed using the online survey software (SurveyMonkey, Inc, CA, USA). We did not collect IP addresses of the respondents to secure anonymity. The survey was open for participation between 19 March 2018 and 20 October 2018. After an initial e-mail invitation, up to two subsequent reminders were sent to each participant.

Ethics

Study protocol was approved by the Ethics Committee of the University of Split School of Medicine before commencing the study. Participants received information about the study and provided their informed consent before answering the survey questionnaire.

Statistics

Microsoft Excel (Microsoft Corp., WA, USA) was used for descriptive analyses. Data were described using frequencies, percentages and weighted averages. We calculated percentages of responses based on the number of participants who took part in each question.

Results

Systematic review authors

We sent 283 email invitations to SR authors, of which 19 could not be delivered. Although 39 of the 264 remaining SR authors gave the informed consent for participating in the survey, 34/264 (13%) took part in the survey. One author informed us that he had decided not to participate in the survey because he did not feel confident to express an opinion. Some participants did not respond to all questions.

Most of the surveyed SR authors were men, clinicians by profession, with >10 years of experience in the specific chronic pain area. Five of 34 (15%) SR authors participated in the development of a COS in a specific research area (either IMMPACT or another organization). Eight of 34 SRs (24%) were conducted before January 2005 and around a half (19/34) of SR authors had published *a priori* protocol of their SR.

Core outcome domains

24 out of 33 (73%) SR authors indicated they were familiar with the IMMPACT COS for assessing the efficacy and safety of interventions for chronic pain, and 16/20 (80%) could correctly identify the number of core domains it contains (others skipped the question). Almost all surveyed SR authors (27/28, 96%) correctly identified pain, physical functioning and emotional functioning as domains that belong to the IMMPACT COS. The other three COS domains were correctly chosen by over 75% of SR authors. The list of offered outcome domains also included domains that are not a part of the COS, and role functioning and sleep were most frequently mistakenly identified as COS domains (Table 1).

Next, the SR authors judged the appropriateness of the offered outcome domains for inclusion in a COS for assessing interventions for chronic pain. Pain (weighted average 8.2/9) and physical functioning (weighted average 7.8/9) were rated highest. Other domains with weighted average of greater than or equal to seven were symptoms and adverse events, emotional functioning, participant ratings of global improvement and satisfaction with treatment, and role functioning. Biological markers (weighted average 3.8/9), clinician or surrogate ratings of

Table 1. Participants' knowledge of Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials core outcome domains.

Outcome domain	SR authors, n (% of 28 total)	RCT authors, n (% of 15 total)
Pain†	27 (96)	15 (100)
Physical functioning†	27 (96)	13 (87)
Emotional functioning†	27 (96)	13 (87)
Participant ratings of global improvement and satisfaction with treatment†	21 (75)	11 (73)
Symptoms and adverse events†	25 (89)	11 (73)
Participant disposition†	21 (75)	8 (53)
Role functioning	10 (36)	11 (73)
Interpersonal functioning	8 (29)	6 (40)
Pharmacoeconomic measures and healthcare utilization	2 (7.1)	2 (13)
Biological markers	2 (7.1)	4 (27)
Coping	5 (18)	7 (47)
Clinician or surrogate ratings of global improvement	1 (3.6)	5 (33)
Neuropsychological assessments of cognitive and motor function	2 (7.1)	3 (20)
Suffering and other end-of-life issues	2 (7.1)	3 (20)
Additional analgesia	7 (25)	7 (47)
Being pain free	7 (25)	5 (33)
Sleep	9 (32)	11 (73)

The number of respondents varied as those who were not familiar with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials core outcome set could skip the question.
†Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials core outcome set.
RCT: Randomized controlled trial; SR: Systematic review.

global improvement, and neuropsychological assessments of cognitive and motor function domains were judged to be of lowest importance (Table 2). According to this group of SR authors, consensus on whether an outcome domain should be included in the core set would be reached for five of six IMMPACT-COS domains: pain, physical functioning, emotional functioning, participant ratings of global improvement and satisfaction with treatment, and symptoms and adverse events; and one non-COS domain: role functioning.

Only 3 of 28 (11%) SR authors indicated that they used the full COS, and 14 (50%) indicated they used the core set partially while preparing their SR, although their SR was conducted after publication of the IMMPACT-recommended COS.

As reasons for not using the IMMPACT COS and/or problems someone else may experience while trying to implement COS, the SR authors most frequently stated lack of awareness of the recommended COS (13/28, 46%), lack of proposed COS domains in RCTs (12/28, 43%) and lack of mandatory use of a COS during protocol registration or manuscript publication (11/28, 39%).

Subsequently, in an open-ended question, the SR authors were asked to name outcome domains they consider essential for inclusion in the COS for assessing interventions for chronic pain. One of the 23 SR authors stated that they would endorse the IMMPACT-recommended core outcome domains, while others proposed one to four outcome domains of their choice. The most frequently named domains were physical functioning (6/23, 26%) and symptoms and adverse events (5/23, 22%). Surprisingly, pain was only in the third place and chosen by 4/23 (17%) of SR authors (Supplementary Table 1).

Core outcome measures

The majority (18/25, 72%) of SR authors were aware of the IMMPACT-recommended COMs for assessing efficacy and safety of interventions for chronic pain. When asked to identify COMs from a list with various measures offered, 24 of 25 (96%) correctly chose Patient Global Impression of Change (PGIC), and 22 of 25 (88%) correctly chose 11-point Numeric Rating Scale (NRS). At least one of the core measures was correctly chosen by each participant. The majority (15/25, 60%) of SR authors had incorrectly chosen the Visual Analog Scale as a COM (Table 3).

Subsequently, the SR authors were asked to judge the appropriateness of the offered outcome measures for inclusion in a COS for assessing interventions for chronic pain. The highest rated scales were the PGIC (weighted

Table 2. Systematic review authors' ratings of importance of offered outcome domains for inclusion in a core outcome set for chronic pain on a 1–9 scale (1 = not important, 9 = critically important).

Outcome domain	1 (Not important)	2 (Slightly important)	3 (Somewhat important)	4 (Of low average importance)	5 (Of average importance)	6 (Of high average importance)	7 (Very important)	8 (Highly important)	9 (Critically important)	Total	Weighted average
Pain†	0	0	0	0	0	2	3	11	12	28	8.18
Physical functioning†	0	1	0	0	0	1	7	10	9	28	7.79
Emotional functioning†	0	0	1	1	0	2	8	11	5	28	7.43
Participant ratings of global improvement and satisfaction with treatment†	0	0	1	1	1	3	9	7	6	28	7.25
Symptoms and adverse events†	0	0	0	1	2	1	10	5	9	28	7.54
Participant disposition†	0	2	0	0	3	6	7	5	5	28	6.75
Role functioning	0	0	0	4	0	1	11	10	2	28	7.04
Interpersonal functioning	0	1	0	2	2	7	8	6	2	28	6.57
Pharmacoeconomic measures and healthcare utilization	1	1	2	7	6	3	5	3	0	28	5.14
Biological markers	6	5	2	5	4	1	2	2	1	28	3.82
Coping	0	2	1	1	2	6	8	7	1	28	6.36
Clinician or surrogate ratings of global improvement	5	2	2	3	8	4	2	2	0	28	4.32
Neuropsychological assessments of cognitive and motor function	1	3	5	4	2	6	4	3	0	28	4.86
Suffering and other end-of-life issues	1	2	2	3	4	6	4	3	3	28	5.64
Additional analgesia	2	1	5	0	4	7	4	4	1	28	5.36
Being pain free	2	2	4	1	4	3	5	3	4	28	5.54
Sleep	0	1	0	1	0	9	7	7	3	28	6.86

†Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials core outcome set.
SR: Systematic review.

Table 3. Participant knowledge of Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials core outcome measures.

Outcome measure	N of SR authors (% of 25 total)	N of RCT authors (% of 11 total)
11-point numerical rating scale†	22 (88)	6 (55)
Usage of rescue analgesics†	14 (56)	4 (36)
Verbal rating scale†	11 (44)	8 (73)
Multidimensional Pain Inventory Interference Scale†	12 (48)	4 (36)
Brief Pain Inventory interference items†	19 (76)	7 (64)
Beck Depression Inventory†	17 (68)	4 (36)
Profile of Mood States†	11 (44)	3 (27)
Patient Global Impression of Change†	24 (96)	6 (55)
Passive capture of spontaneously reported adverse events and symptoms and use of open-ended prompts†	10 (40)	2 (18)
Detailed information regarding participant recruitment and progress through the trial†	9 (36)	1 (9.1)
The Short-Form McGill Pain Questionnaire	8 (32)	5 (45)
Visual Analog Scales for Pain Intensity	15 (60)	6 (55)
The 36-Item Short Form Health Survey SF-36	8 (32)	5 (45)
Gracely Pain Scale	0 (0)	0 (0)
West-Haven Yale Multidimensional Pain Inventory	3 (12)	2 (18)
Neuropathic Pain Scale	8 (32)	2 (18)
Neuropathic total symptom score 6	0 (0)	0 (0)
The 12-Item Short Form Health Survey	0 (0)	0 (0)
EuroQol 5 dimensions questionnaire	0 (0)	0 (0)
State-Trait Anxiety Inventory	0 (0)	0 (0)
Global Perceived Effect	0 (0)	0 (0)
Clinical Global Impression of Change	6 (24)	3 (27)
Sickness Impact Profile	2 (8)	2 (18)
Hospital Anxiety Depression Scale	0 (0)	0 (0)
Need for surgery as efficacy measure for conservative treatments	0 (0)	0 (0)
Recurrence rate	0 (0)	0 (0)

The number of respondents varied as those who were not familiar with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials core outcome set could skip the question.
†Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials core outcome measures.
RCT: Randomized controlled trial; SR: Systematic review.

average 7.8/9) and 11-point NRS (weighted average 7.6/9). Conversely, Gracely Pain Scale (weighted average 3.8/9) was judged to be of least importance (Supplementary Table 2). Consensus whether an outcome measure should be included in the core set was reached for two IMMPACT-recommended COMs: PGIC and 11-point NRS, and one non-IMMPACT outcome measure EuroQol 5 dimensions questionnaire (EQ-5D).

Four of 24 (17%) SR authors from a post-IMMPACT cohort (after 2005) used the COMs while preparing their SR, and 11 (46%) used them partially. Only one (11%) SR author indicated their SR was conducted before publication of the IMMPACT-recommended COMs.

As main reasons for not using the IMMPACT-recommended COMs and/or problems someone else may experience while trying to implement recommended measures, the SR authors most frequently stated that proposed COMs were not available in included RCTs (12/25, 48%) and there was no obligation to use COMs during protocol registration or manuscript publication (11/25, 44%). Many SR authors also (10/25, 40%) stated that other outcome measures were more relevant for their research.

The SR authors were then asked to name one or more outcome measures that should be included in COMs for assessing interventions for chronic pain. One of 19 SR authors again stated that he would endorse the IMMPACT recommendations, while the others specified from one to six outcome measures. The most frequently stated outcome measures were 11-point NRS for pain intensity, PGIC and Depression, Anxiety and Stress Scale each suggested by three SR authors.

The majority of surveyed SR authors (15/25, 60%) would consider using the COS and COMs while designing future SRs, while others stated they might adhere to the IMMPACT recommendations. Easier conduction of a systematic review/meta-analysis due to homogeneous outcomes (16/25, 64%), easier comparison of results from different studies (15/25, 60%) and reduction of outcome reporting bias (15/25, 60%) were main reasons that would encourage the SR authors to use the COS of domains and COMs recommended by the IMMPACT initiative for chronic pain when conducting their future SRs.

RCT authors

We sent 337 email invitations of which 117 were undeliverable. One author responded that he had already participated in the survey sent to SR authors, and one did not participate due to a potential conflict of interest as he is a co-chair of IMMPACT. 19 of 218 contacted RCT authors consented to participate in the survey (19/218, 8.7%), one left the survey immediately after, and some left certain questions unanswered; therefore the number of responses to different questions varied.

Most of the surveyed RCT authors were men (males: 13; females: 5), clinicians by profession (12/18, 67%), with >10 years of experience in the specific chronic pain area. Nine of 18 (50%) RCT authors participated in the development of a COS in a specific research area (either IMMPACT or other organization). The majority of authors (14/18, 78%) indicated their RCT was conducted before January 2005, and more than half (11/18, 61%) had published *a priori* protocol.

Core outcome domains

Ten of 18 (56%) RCT authors indicated they were familiar with the IMMPACT COS for assessing the efficacy and safety of interventions for chronic pain, and 6 out of 8 (75%) could correctly identify the number of core domains it contains (11 skipped the question). Seven of ten respondents familiar with the IMMPACT COS were involved in the development of a COS in a specific research area.

All RCT authors (15/15) correctly identified pain, and 13 out of 15 (87%) identified physical functioning and emotional functioning as domains that belong to the IMMPACT COS. From domains which are not a part of IMMPACT COS, role functioning and sleep were chosen as COS domains by 11/15 (73%) of RCT authors (Table 1).

The RCT authors subsequently judged the appropriateness of the offered outcome domains for inclusion in a COS for assessing interventions for chronic pain. Pain (weighted average 7.1/9) and physical functioning (weighted average 7.1/9) were rated as the most appropriate outcome domains for inclusion in a COS for chronic pain interventions. On the contrary, biological markers (weighted average 4.6/9) were judged to be the least appropriate for inclusion in a chronic pain COS (Table 4). Consensus whether an outcome domain should be included in the core set was not reached for any domain, either COS or non-COS domain. Nine of 15 (60%) RCT authors have not used COS at all and 4 (27%) used at least one of the COS domains while preparing RCTs, which were conducted after IMMPACT-recommended COS was published.

The most common reasons for not using the IMMPACT COS for chronic pain and/or problems someone else may experience while trying to implement it were the lack of awareness of the recommended COS (6/15, 40%), participant burden, other domains were more relevant and other reasons (each selected by 5/15, 33% RCT authors). Other reasons were that RCT was conducted before IMMPACT recommendations (n = 3), 'NIH core measures' were used (n = 1) and 'excessive burden' (n = 1).

12 RCT authors responded to an open-ended question to name outcome domains that they consider essential for inclusion in the COS for assessing interventions for chronic pain (Supplementary Table 1). The most frequently named domains were pain (6/12, 50%) and 'function' (5/12, 42%).

Core outcome measures

The majority (6/11, 55%) of RCT authors were unaware of the IMMPACT-recommended COMs for assessing efficacy and safety of interventions for chronic pain. When asked to identify COMs from a list with various measures offered, 8 of 11 (73%) correctly selected Verbal Rating Scale and 7 of 11 (64%) Brief Pain Inventory interference items. Around a half (6/15, 55%) of RCT authors had incorrectly chosen Verbal Rating Scale as a COM, followed by the Short Form McGill Pain Questionnaire (SF-MPQ) and 36-Item Short Form Health Survey (SF-36) (Table 3).

Table 4. Randomized controlled trial authors' ratings of importance of offered outcome domains for inclusion in a core outcome set for chronic pain on a 1–9 scale (1 = not important, 9 = critically important).

Outcome domain	1 (Not important)	2 (Slightly important)	3 (Somewhat important)	4 (Of low average importance)	5 (Of average importance)	6 (Of high average importance)	7 (Very important)	8 (Highly important)	9 (Critically important)	Total	Weighted average
Pain†	0	1	1	1	0	2	1	3	6	15	7.07
Physical functioning†	0	0	1	0	2	3	2	1	6	15	7.13
Emotional functioning†	0	0	0	1	3	5	1	1	4	15	6.67
Participant ratings of global improvement and satisfaction with treatment†	1	0	1	2	1	3	2	3	2	15	6.07
Symptoms and adverse events†	1	0	0	1	1	5	3	2	2	15	6.33
Participant disposition†	0	0	0	2	3	4	4	1	1	15	6.13
Role functioning	0	0	0	1	1	6	1	4	2	15	6.8
Interpersonal functioning	0	0	0	1	3	3	6	2	0	15	6.33
Pharmacoeconomic measures and healthcare utilization	0	1	2	2	6	3	0	1	0	15	4.8
Biological markers	1	2	1	3	2	3	3	0	0	15	4.6
Coping	0	0	2	1	3	2	1	3	3	15	6.33
Clinician or surrogate ratings of global improvement	1	1	0	3	4	3	2	1	0	15	5
Neuropsychological assessments of cognitive and motor function	0	1	2	5	2	3	2	0	0	15	4.67
Suffering and other end-of-life issues	0	1	1	3	2	2	3	3	0	15	5.6
Additional analgesia	0	1	2	0	6	1	3	1	1	15	5.47
Being pain free	3	2	1	1	2	1	0	3	2	15	4.8
Sleep	0	0	1	0	3	2	3	3	3	15	6.8

†Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials core outcome set.

The Brief Pain Inventory Interference Items (weighted average 5.7/9) was rated as the most appropriate, while Sickness Impact Profile (weighted average 3.5/9) was the least appropriate outcome measure for inclusion in a COS for assessing interventions for chronic pain (Supplementary Table 3). Among the surveyed RCT authors, consensus whether an outcome measure should be included in the core set was not reached for any of the listed outcome measures (core and other).

Only one of eight (13%) RCT authors from a post-IMMPACT cohort (after 2005) used COMs in RCT, and additional three RCT authors (38%) used them partially. Three RCTs were conducted before IMMPACT-recommended COMs were introduced. As main reasons for not using the IMMPACT-recommended COMs and/or problems someone else may experience while trying to implement recommended measures, the RCT authors most frequently selected similar reasons as for core outcome domains: the lack of awareness (6/11, 55%), participant burden and existence of other, more relevant outcomes, each selected by 5 out of 11, 46% of RCT authors.

Eight RCT authors responded to a question to name one or more outcome measures, which should be included in COMs for assessing interventions for chronic pain. Two RCT authors named PGIC, one EQ-5D and one McGill Pain Questionnaire (MPQ), while others wrote outcome domains without specific outcome measures for their assessment. The majority of RCT authors (7/11, 64%) would consider using the COS and COMs while designing future RCTs. Simplified design of new studies and easier conduction of a systematic review/meta-analysis due to homogeneous outcomes were most often stated reasons that would encourage implementation of IMMPACT recommendations for chronic pain.

At the end of the survey RCT authors were asked to leave comments, if applicable. One RCT author commented 'another organization that is also working hard to standardize the outcome measures such as International Consortium for Health Outcomes Measurement (ICHOM)'. The other RCT author wrote that survey authors have bias in the perception of COS since 'assumed only benefits of core sets and did not ask about potential downsides for recommending consistent measures'.

Discussion

This study was the first to assess the awareness and acceptability of the IMMPACT-recommended core set of outcome domains and COMs for chronic pain among authors of SRs and RCTs about interventions for management of NeuP. The knowledge of existing COS for chronic pain among surveyed authors was suboptimal; 73% of surveyed SR authors and 56% of trialists were familiar with the IMMPACT core set of domains, which was first developed in 2003 [3], and around three-quarters of respondents could also correctly identify the number of domains it contains. All RCT authors correctly identified pain, and almost all SR authors identified pain, physical functioning and emotional functioning as domains that belong to the IMMPACT COS. This shows that the majority of respondents are aware of the existence of the COS and domains it contains to some extent, and indicates at other problems preventing consistent and complete use of IMMPACT-recommended COS for chronic pain among NeuP authors.

Importantly, SR authors agreed that five of six IMMPACT-proposed outcome domains should be included in the core set (except participant disposition), as well as one additional outcome domain (role functioning), which is currently not a part of IMMPACT COS. Although such consensus could not be reached among RCT authors, the majority of respondents, represented by SR authors, acknowledge the critical importance of IMMPACT-proposed core outcome domains for chronic pain.

The knowledge of the core set of outcome measures, first published in 2005 [4], differed among SR and RCT authors. Less than half of trialists were familiar with IMMPACT-recommended COMs for chronic pain and consensus for inclusion of any of the listed outcome measures in a core set could not be reached among RCT authors. On the contrary, the majority of SR authors were aware of the IMMPACT-recommended COMs and almost all could identify PGIC as one of the core measures. Consensus among SR authors for inclusion in the core set was reached for two IMMPACT-recommended COMs (PGIC and 11-point NRS), and one non-IMMPACT outcome measure (EQ-5D). This shows that surveyed SR authors feel that EQ-5D is a critically important outcome measure and should be considered for inclusion in a core set of outcome measures.

In the original manuscripts describing analyzed COS and COMs, it was not reported how consensus needed to include outcome domains and measures in the core set during IMMPACT consensus meetings was reached [3,4]. Therefore, we do not know the exact proportion of specialists that voted for inclusion of each outcome domain and measure into a COS. Although the choice of thresholds is somewhat subjective, it is generally accepted that if

70% or more of the respondents score an outcome as critically important and <15% as of limited importance, it should be included in a COS [2], which was the criterion we used as well.

Despite existence of relevant COS and COMs, our results point out at inconsistent adoption of IMMPACT recommendations among surveyed authors, as neither SR nor RCT authors used the full COS and COMs while choosing outcome domains and measures in their studies, that is, when used, the majority used it only partially.

The lack of awareness of all COS domains was stated as the main perceived reason, which prevented the consistent use of all COS domains recommended by the IMMPACT among both groups of respondents. The main obstacle in consistent use of IMMPACT-recommended COMs among trialists was also the lack of awareness, and for SR authors it was the lack of proposed COMs in included RCTs. Both SR and RCT authors stated that the incentive for using recommended COS and COMs when designing future studies would be facilitated conduct of systematic reviews/meta-analyses due to homogeneous outcome domains and measures.

It is important to periodically review the proposed COS to ensure that agreed outcomes are still relevant, to supplement them with the new outcomes as needed, to check whether the process of implementation has been successful and to engage further stakeholders [2]. Our study can be used as a part of this periodic review of the proposed COS and COMs, and it identified an additional outcome domain and additional outcome measure for which respondents feel are critical for inclusion in the core sets.

In the published literature there are very few studies that have investigated the use and uptake of any COS. Kirkham *et al.* conducted a survey of the use of rheumatoid arthritis (RA) COS published after its introduction in 1994 among RA trialists. They showed the increase in the number of trials reporting on the COS over time [8,9], but also that some trialists did not measure the whole COS despite being aware of it [8]. It was postulated that the increased adherence to RA COS was encouraged by the introduction of regulatory guidance from the agencies such as the US FDA [10] and EMA [11] involved in ratifying the COS in that field. Perhaps a similar approach could be used in the field of chronic pain.

Another study by Kirkham *et al.* in 2017 [9] used the new method to analyze the uptake of the RA COS and recommended the use of the clinical trial registry information for assessing uptake of the COS because it was more reliable than citation analysis, and more efficient and up-to-date than assessing publications of the registered trials.

The implementation of Outcome Measures in Rheumatology (OMERACT) COS in hip and/or knee osteoarthritis trials [12,13] and gout [14] trials has also been reported as limited. Another example of low uptake of COS comes from trials on fall injury prevention in older people. Copsey *et al.* [15] appraised the use of The Prevention of Falls Network Europe (ProFaNE) COS for trials on fall injury prevention in older people and found only 1 of 34 studies that reported use of the full ProFaNE COS, as well as inconsistency in the outcome measures used.

A recent study surveyed the knowledge and appropriateness of the Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (PedIMMPACT)-recommended core outcome domains for acute pediatric pain among SRs and RCTs authors. The findings indicated that the majority of participating authors were not familiar with the six domains of PedIMMPACT COS for acute pediatric pain, did not use the COS while preparing their studies and gave preference to outcome domains, which do not completely overlap with PedIMMPACT COS [16]. Our results, based on the sample of respondents that published RCTs and SRs in the field of NeuP, show that although the authors are aware of the IMMPACT COS, its implementation has not been successful.

There are possible actions that should be taken in order to improve the use of COS among authors of RCTs and SRs. As proposed recently, researchers would more likely consider using COS if its use would impact the likelihood of getting their research funded and published, or have an effect on clinical policy or reimbursement [1]. That identifies several stakeholders who could be targeted to improve implementation of existing COS; such as research funders, journal editors, clinical guideline developers, health technology assessment organizations and payers [1]. An example of action of research funders can be found in guidance for applicants to the UK's National Institute for Health Technology Assessment [17], which states: 'where established Core Outcomes exist they should be included amongst the list of outcomes unless there is good reason to do otherwise. Please see The COMET Initiative website [18] to identify whether Core Outcomes have been established.'

Another way to increase the uptake is to require a statement of COS adherence while registering protocols of RCTs and SRs, and justification of exclusion of certain COS domains, if applicable. For example, the SPIRIT Statement (Standard Protocol Items: Recommendations for Interventional Trials) provides guidance for reporting protocols of clinical trials [19] in which, among other relevant items, trialists are encouraged to determine if a relevant COS exists, and if so, to include proposed outcomes in their trial.

As hypothesized previously, the introduction of guidance from regulatory agencies, which were involved in defining the COS for RA, such as the FDA and EMA, might have contributed to increased uptake of core outcomes among trialists in RA [8]. Such approach can be applied to other COS as well. A support for that approach stems from our finding that SR authors stated the lack of regulatory guidance as the third most common reason for not using the proposed COS.

As pointed out in a recent editorial, developers of COS should proceed with advanced stages of COS development to ensure that proposed COS is still relevant, with the ultimate goal of ensuring comparability of future trials and systematic reviews [6].

Patient and caregivers' involvement in the development of COS is especially relevant for comparative effectiveness research, where long-term patient-reported outcomes are the important end points, and has been noted in recent years [20]. Although patients represent key stakeholders, they were not included in the IMMPACT COS development. This might have affected participants' decision to use the IMMPACT COS, even though none of the participants indicated so when asked about reasons for inconsistent use of the IMMPACT COS.

Although not within the scope of this study, investigating participants' views of the COS development methodology would be the next step, which should be addressed in the process of investigating reasons for insufficient uptake of the proposed COS.

Limitations

Our results are based on a limited number of samples of SR and RCT authors; particularly low response rate was obtained from authors of RCTs. That is not surprising, considering that the cohort of RCTs whose authors we contacted were conducted much earlier than SRs, and therefore there is lower chance of successfully achieving contact with the authors. Furthermore, it is possible that our results are not generalizable to knowledge and opinions of all SR and RCT authors from this field, and that there was selection bias, with self-selected participants who might have been more motivated to participate in the study, with more knowledge about the field. Still, these results indicate that this bias can be considered minimal; as not all participants exhibited adequate knowledge about the questions they were served. Since we invited an entire group of SR authors to participate, it is possible that we obtained more than one response from the same group of SR authors. It would be interesting to analyze the impact on results, but we could not collect these data as we guaranteed anonymity to the survey participants.

Another limitation is provisional division of participants to authors of SRs and RCTs based on first identification of SR authors and subsequent exclusion of the same participants if they appeared to be on the list of RCT authors as well. That might have skewed the number of respondents in favor of SR authors.

Conclusion

The implementation of IMMPACT-recommended COS and COMs for chronic pain among surveyed authors of RCTs and SRs in the field of NeuP has not been successful. Neither SR nor RCT authors used the full COS and COMs while choosing outcome domains and measures in their studies, that is, when used, the majority used them only partially. If a relevant COS is not widely implemented, its benefits for comparative effectiveness research are not realized since comparability and generalizability of research findings are limited. Therefore, actions should be taken in order to improve the use of COS among authors of RCTs and SRs in the field of NeuP, or to reconsider their adequacy.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/cer-2018-0123

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, informed consent has been obtained from the participants involved and the participants could not access the survey without providing their informed consent.

Summary points

- This survey assessed the knowledge and adoption of Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)-recommended core outcome set (COS) and core outcome measures among neuropathic pain (NeuP) authors.
- Authors of NeuP systematic reviews (SRs) and randomized controlled trials (RCTs) were surveyed via SurveyMonkey (34 SR authors and 18 RCT authors took part in the survey).
- Over 70% of surveyed SR authors and around a half of RCT authors were familiar with the IMMPACT COS.
- The majority of respondents, represented by SR authors, acknowledge the critical importance of IMMPACT-proposed core outcome domains for chronic pain.
- Consensus for inclusion of domains in a COS was achieved among SR authors for five of six existing IMMPACT core domains (except participant disposition).
- One additional noncore outcome domain (role functioning) was rated as critically important for inclusion in COS by SR authors.
- Such consensus could not be reached among RCT authors.
- Neither SR nor RCT authors used the full COS and core outcome measures while choosing outcome domains and measures in their studies, and when used, the majority used it only partially.
- If relevant COS is not widely implemented, its benefits for comparative effectiveness research are not realized.
- Actions should be taken in order to improve the use of COS among authors of RCTs and SRs in the field of NeuP, or to reconsider their adequacy.

References

1. Tunis SR, Clarke M, Gorst SL *et al.* Improving the relevance and consistency of outcomes in comparative effectiveness research. *J. Comp. Eff. Res.* 5(2), 193–205 (2016).
2. Williamson PR, Altman DG, Blazeby JM *et al.* Developing core outcome sets for clinical trials: issues to consider. *Trials* 13, 132–132 (2012).
3. Turk DC, Dworkin RH, Allen RR *et al.* Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain* 106(3), 337–345 (2003).
4. Dworkin RH, Turk DC, Farrar JT *et al.* Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 113(1–2), 9–19 (2005).
5. Dosenovic S, Jelicic Kadic A, Miljanovic M *et al.* Interventions for neuropathic pain: an overview of systematic reviews. *Anesth. Analg.* 125(2), 643–652 (2017).
6. Puljak L, Dosenovic S, Boric K. Importance of consistent outcomes in randomized controlled trials and systematic reviews about anesthesiology and pain. *Pain Manag.* 8(4), 251–253 (2018).
7. 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* 34(7), 674–684 (2018).
8. Kirkham JJ, Boers M, Tugwell P, Clarke M, Williamson PR. Outcome measures in rheumatoid arthritis randomised trials over the last 50 years. *Trials* 14(1), 324 (2013).
9. Kirkham JJ, Clarke M, Williamson PR. A methodological approach for assessing the uptake of core outcome sets using ClinicalTrials.gov: findings from a review of randomised controlled trials of rheumatoid arthritis. *BMJ* 357 j2262 (2017).
10. The US FDA. Guidance for industry: clinical development programs for drugs, devices, and biological products for the treatment of rheumatoid arthritis (RA) (1999). www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071579.pdf
11. European Medicines Agency. Guideline on the clinical development of medicinal products intended for the treatment of pain (2016). www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-development-medicinal-products-intended-treatment-pain-first-version_en.pdf
12. Smith TO, Mansfield M, Hawker GA *et al.* Uptake of the OMERACT-OARSI hip and knee osteoarthritis core outcome set: review of randomized controlled trials from 1997 to 2017. *J. Rheumatol.* doi:10.3899/jrheum.181066 (2019) (Epub ahead of print).
13. Krsticevic M, Dosenovic S, Dimcea DA *et al.* Outcome domains, outcome measures and characteristics of randomized controlled trials testing non-surgical interventions for osteoarthritis. *J. Rheumatol.* doi:10.3899/jrheum.180985 (2019) (Epub ahead of print).

14. Araújo F, Cordeiro I, Branco JC, Falzon L, Buchbinder R, Ramiro S. Outcomes assessed in trials of gout and accordance with OMERACT-proposed domains: a systematic literature review. *Rheumatology (Oxford)* 54(6), 981–993 (2014).

15. Copsey B, Hopewell S, Becker C, Cameron ID, Lamb SE. Appraising the uptake and use of recommendations for a common outcome data set for clinical trials: a case study in fall injury prevention. *Trials* 17(1), 131 (2016).

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.* 7(5), 463–470 (2018).

17. NHS. National Institute for Health Research. Supporting information for applicants applying to the HTA programme (2018). www.nihr.ac.uk/funding-and-support/documents/current-funding-opportunities/hta/hta-supporting-information.pdf

18. COMET. Core outcome measures in effectiveness trials initiative (2017). www.comet-initiative.org/

19. Chan A-W, Tetzlaff JM, Gøtzsche PC *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 346, e7586 (2013).

20. Gorst SL, Gargon E, Clarke M, Blazeby JM, Altman DG, Williamson PR. Choosing important health outcomes for comparative effectiveness research: an updated review and user survey. *PLoS ONE* 11(1), e0146444 (2016).