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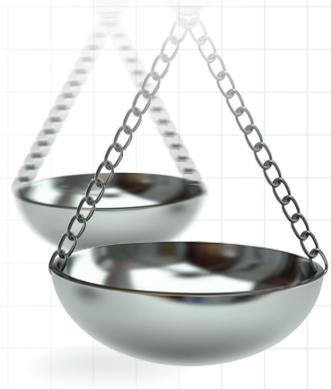

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Authors' lack of awareness and use of core outcome set on postoperative pain in children is hindering comparative effectiveness research

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Aim: To analyze awareness about and acceptability of core outcome set (COS) for pediatric pain recommended by the PedIMMPACT. **Methods :** We invited authors of systematic reviews and randomized controlled trials about interventions for postoperative pain in children to participate in a survey. **Results:** Only a third of surveyed authors of systematic reviews and randomized controlled trials about postoperative pain in children had heard about the PedIMMPACT COS for acute pediatric pain. Problems indicated as preventing them from using the COS were lack of awareness, difficulties with implementation, and lack of resources. **Conclusion:** Further discussions about the adequacy of COS for acute pediatric pain, as well as interventions to increase the uptake of COS may be warranted.

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A need for a greater attention to alleviation of postoperative pain in children has been recognized ever since Eland and Anderson published their seminal study in which they reported that children do not receive analgesics after major surgical procedures [1]. Different measures for postoperative analgesia in children were developed, therapies have been evaluated and practice has changed. However, many children and adolescents still suffer because of inadequate pain management [2,3].

Randomized controlled trials (RCTs) are a standard method for studying efficacy and safety of interventions in medicine. Standardization of outcome domains and outcome measures in RCTs and systematic reviews (SRs) from the field of pediatric pain would enable simpler design and review of research protocols, simplify and improve production of SRs and help clinicians in decision-making. To encourage clinical trials in pediatric population and enable easier interpretation and data collection in trials and reviews on pediatric pain, the Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (PedIMMPACT) was developed, and in 2008 published the recommended core outcome domains and measures for clinical trials to treat pain in children and adolescents [4].

The manuscript describing PedIMMPACT indicated that the COS was based on an SR of literature and consensus of experts, described as stakeholders representing *"academic research, government funding and regulatory agencies, and the pharmaceutical industry"* [4]. The consensus group that published the COS consisted of 26 authors who mainly had affiliations from the USA; three affiliations were from Canada and only three from Europe,

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including two from Sweden and one from the UK [4]. Finally, their findings were disseminated and reviewed by the international pediatric pain community consisting of clinicians and researchers from more than 45 countries, whose suggestions were included within the PedIMMPACT recommendations [4].

The PedIMMPACT initiative first reached consensus about domains that should be used for acute and chronic pain in age groups 3–6 years, and 7 years and older. Pain in neonates and infants was not included in their considerations due to considerable developmental differences between children in that age group and other age groups. Additionally, the PedIMMPACT did not consider pain in children with cognitive disabilities because of challenges associated with assessment of pain in that group of children. The next step was to assess adequate measures for each core outcome domain. The PedIMMPACT has finally recommended a core outcome set (COS) for analyzing acute and chronic pain in clinical trials and SRs about pediatric pain with the primary aim of standardizing outcomes in research from that field [4].

The COS for pediatric acute pain recommended by the PedIMMPACT includes the following six outcome domains: pain intensity, global judgement of satisfaction with treatment, symptoms and adverse events, physical recovery, emotional response and economic factors [4].

In our previous work, we systematically searched for SRs and RCTs about postoperative postoperative treatment of pain in children, and analyzed whether they use the COS suggested by the PedIMMPACT [5,6]. Analysis of COS in those SRs indicated that the use of the PedIMMPACT COS was insufficient and that some SRs did not even analyze pain intensity as an outcome domain [5,6].

The aim of this study was to analyze awareness and acceptability of COS for acute pediatric pain recommended by the PedIMMPACT among authors of RCTs and SRs about interventions for postoperative pain in children.

Methods

Based on a previous overview of SRs, we identified 48 SRs with data from a total of 576 unique RCTs [5,6]. These SRs were published between 2003 and 2017 and analyzed interventions for postoperative pain in children. Analyzed interventions were both pharmacological and nonpharmacological; any intervention and comparator were eligible for inclusion [5,6].

We downloaded full text articles of all those studies, extracted email addresses of corresponding authors of those SRs and RCTs and sent them an email with an invitation to participate in our survey. Since there were only 48 SRs, we also searched the internet to find email addresses of other SR authors in order to increase the number of potential participants. For RCTs we contacted only corresponding authors; if the email address was not indicated we tried to find it online, and if we could not find it, we were not able to contact those authors in this study.

Survey

For the purpose of this study we designed an eight-item survey in English language. The survey was designed by the authors of the study, which are methodologists and clinicians.

The participants were asked about their awareness of PedIMMPACT COS. Then we asked for the number of outcomes recommended by the COS, and which core outcomes were recommended by the PedIMMPACT. For this the authors were shown a list of outcome domains of which six belong to the PedIMMPACT COS, and the other six do not. The non-COS domains that we used were outcome domains that were most frequently used in the SRs used for this study [5].

The study participants were asked which of the shown domains belong to the PedIMMPACT COS. Participants had the possibility to skip question about reasons for personally not using the COS, in case their study was published before the PedIMMPACT COS was published and this is why they are not aware of it.

In the second set of questions, participants were asked to rate the relevance of the PedIMMPACT outcome domains and other non-PedIMMPACT outcome domains we found in the SRs on the topic [5,6], whether they used the PedIMMPACT COS for preparing their review, any difficulties associated with using the PedIMMPACT COS, their personal opinion about outcomes that should be included in COS for pediatric pain and any comments they might have about the study topic.

Survey administration

The survey was administered via SurveyMonkey, a web-based survey software (SurveyMonkey Inc., CA, USA). The survey was set as anonymous and we did not collect IP addresses of the responders. The email invitations for

Table 1. Respondents' recognition of the PedIMMPACT core outcomes.

Outcomes	Responses of SR authors, n (%) of 12‡	Responses of trial authors, n (%) of 18
Pain intensity†	12 (100)	17 (94)
Global judgment of satisfaction with treatment†	6 (50)	9 (50)
Symptoms and adverse events†	10 (83)	13 (78)
Physical recovery†	10 (83)	10 (56)
Emotional response†	9 (75)	11 (61)
Economic factors†	3 (25)	7 (39)
Sleep	7 (58)	8 (44)
The duration of postoperative analgesia	6 (50)	10 (56)
Additional analgesia	5 (42)	12 (67)
Role functioning	4 (33)	4 (22)
Pain free	4 (33)	8 (44)
Additional opioid analgesia	4 (33)	7 (39)
Outcome specific only for certain interventions	2 (16)	4 (22)
Pharmacokinetics	1 (8)	5 (28)

†These six outcomes are recommended by the PedIMMPACT as the core outcome set for acute pediatric pain.
‡The participants had option to skip questions; this question was answered by 12 authors of SRs.
SR: Systematic review.

participation in the study were sent from April to July 2017. Each participant received initial invitation and four subsequent reminders.

Ethics

The study was approved by the Ethics Committee of the University of Split School of Medicine. Before accessing the survey, the participants were provided information about the study and asked to click on a dedicated button on the SurveyMonkey page indicating that they are giving their informed consent and are willing to proceed with the survey.

Statistics

Descriptive statistics was performed using the Microsoft Excel (Microsoft Inc., WA, USA).

Results

SR authors

We sent 114 email invitations. Of these, 20 email invitations bounced back as not deliverable. 15 authors (16%) of SRs completed our survey.

Five SR authors (33%) indicated that they heard about the PedIMMPACT initiative. When asked how many core outcome domains for pediatric pain are recommended by the PedIMMPACT initiative, three SR authors chose six domains, while one chose eight domains.

When asked which of the listed core outcome domains for pediatric pain are recommended by the PedIMMPACT initiative, all SR authors marked the outcome 'pain intensity' as a recommended outcome. The other five domains were chosen by 25–83% of the SR authors (Table 1). From the list of six outcome domains that do not belong to the COS for acute pediatric pain, the majority chose 'sleep', while only one author chose 'pharmacokinetics' (Table 1).

From the list of the offered outcome domains, the SR authors rated as the most appropriate outcomes 'pain intensity', 'symptoms and adverse events' and 'sleep'. They marked 'economic factors' and 'pharmacokinetics' as the least appropriate outcomes for inclusion in a COS for assessing intervention for pediatric pain (Table 2).

Seven (70%) SR authors answered that they did not use the PedIMMPACT COS while preparing their SR; 30% answered that they used the COS partially. No one indicated that they used full recommended outcome set.

Seven SR authors provided problem/reason that may have prevented them to use the PedIMMPACT COS. They stated lack of information about the PedIMMPACT initiative, complained that the COS has too many domains and that they lack resources needed to use the COS. Some of the SR authors stated that they published their SRs before the COS was created or that RCTs that they analyzed did not include those outcomes.

Table 2. Systematic review authors' opinion about appropriateness of the listed outcome domains for acute pediatric pain.

Outcomes	1: Totally inappropriate	2: Inappropriate	3: Neutral	4. Appropriate	5: Totally appropriate	Rating average	Response count
Pain intensity†	0	0	1	2	7	4.60	10
Global judgment of satisfaction with treatment†	0	2	2	4	2	3.60	10
Symptoms and adverse events†	0	0	0	5	5	4.50	10
Physical recovery†	0	0	2	5	4	4.18	11
Emotional response†	0	0	2	3	6	4.36	11
Economic factors†	1	5	2	2	0	2.50	10
Sleep	0	0	0	6	5	4.45	11
Additional analgesia	0	1	1	3	5	4.20	10
Role functioning	1	1	4	2	1	3.11	9
Pain-free	2	2	2	2	2	3.00	10
Additional opioid analgesia	0	2	0	6	3	3.91	11
Outcome specific only for certain interventions	1	1	3	2	3	3.50	10
Pharmacokinetics	2	2	5	0	1	2.60	10

†These six outcomes are recommended by the PedIMMPACT as the core outcome set for acute pediatric pain.

When asked whether they can indicate some problems/reasons that somebody else might experience, which may prevent consistent use of all COS domains that are recommended by the PedIMMPACT, the SR authors listed the same reasons as in the previous question.

Finally, the SR authors were asked to select one or more outcome domains from the list of offered domains that they personally feel that should be part of the COS for assessing the efficacy and safety of interventions in pediatric pain (in children aged 3 years and older). None of the outcome domains that are in the PedIMMPACT COS for acute pediatric pain were chosen by all the SR authors.

Most of the SR authors (77%) indicated that outcomes 'symptoms and adverse events' and 'sleep' should be part of the COS. These were followed by 'pain intensity', 'additional analgesia' and 'physical recovery' that were chosen by 67% of the SR authors. 'Emotional response' and 'additional opioid analgesia' were another two outcome domains that were selected by more than 50% of the SR authors (Table 3).

RCT authors

Among 300 email invitations that were sent, 32 bounced back as undelivered. Twenty-seven (10%) authors of RCTs completed our survey.

Nine (35%) RCT authors answered that they have heard about the PedIMMPACT COS for acute pediatric pain.

Six (66%) RCT authors indicated that PedIMMPACT COS has six domains, two respondents chose four domains while one respondent answered that it has eight domains.

When offered outcome domains to choose those that belong to the PedIMMPACT COS for acute pediatric pain, 17 (94%) RCT authors chose the outcome 'pain intensity'. The second most commonly chosen outcome (78%) was 'symptoms and adverse events' (Table 1). As the most appropriate for the COS for pediatric pain, RCT authors rated 'pain intensity', 'symptoms and adverse events' and 'additional analgesia'. 'Economic factors' was rated as the least appropriate (Table 4).

Nine (47%) RCT authors answered that they did not use the PedIMMPACT COS while preparing their trial, while 42% answered that they used the set partially. Two respondents used the full recommended outcome set to prepare their trial.

Table 3. Authors' opinion about outcome domains that should be part of the core outcome set for assessing the efficacy and safety of interventions in pediatric pain (in children aged 3 years and older).

Outcomes	Responses of SR authors, n (%) of 9	Responses of trial authors, n (%) of 18
Pain intensity†	6 (67)	15 (83)
Global judgment of satisfaction with treatment†	3 (33)	6 (33)
Symptoms and adverse events†	7 (78)	12 (67)
Physical recovery†	6 (67)	11 (61)
Emotional response†	5 (55)	10 (56)
Economic factors†	3 (33)	5 (28)
Sleep	7 (78)	10 (56)
Additional analgesia	6 (67)	15 (83)
Role functioning	1 (11)	4 (22)
Pain-free	2 (22)	12 (67)
Additional opioid analgesia	5 (55)	13 (72)
Outcome specific only for certain interventions	1 (11)	6 (33)
Pharmacokinetics	0 (0)	8 (44)

†These six outcomes are recommended by the PedIMMPACT as the core outcome set for acute pediatric pain.
SR: Systematic review.

Table 4. Trial authors' opinion about appropriateness of the listed outcome domains for acute pediatric pain.

Outcomes	1: Totally inappropriate	2: Inappropriate	3: Neutral	4. Appropriate	5: Totally appropriate	Rating average	Response count
Pain intensity†	1	0	1	3	14	4.53	19
Global judgment of satisfaction with treatment†	1	1	1	8	8	4.11	19
Symptoms and adverse events†	1	0	2	5	11	4.32	19
Physical recovery†	0	1	4	5	9	4.16	19
Emotional response†	0	1	7	5	6	3.84	19
Economic factors†	1	4	8	4	2	3.11	19
Sleep	0	1	6	5	7	3.95	19
Additional analgesia	0	0	1	5	13	4.63	19
Role functioning	0	1	9	2	5	3.65	17
Pain-free	0	2	4	1	12	4.21	19
Additional opioid analgesia	0	1	4	4	10	4.21	19
Outcome specific only for certain interventions	0	2	4	5	6	3.88	17
Pharmacokinetics	0	1	1	6	10	4.39	18

†These six outcomes are recommended by the PedIMMPACT as the core outcome set for acute pediatric pain.

As problems that they have experienced and that may have prevented consistent use of all COS domains, the RCT authors indicated a lack of information about COS. One person indicated that more presentations on this topic should be conducted among scientific population. Two RCT authors consider that domains are complicated and difficult to implement in practice. One author wrote that their RCT was published before the COS was published.

As a major problem that might prevent use of all COS, the RCT authors indicated lack of human resources and time. They also stated that the COS is too complicated and difficult to implement in practice.

'Pain intensity' and 'additional analgesia' were chosen by 83% of the RCT authors when they were asked to select one or more outcome domains from the list of offered domains that they personally feel that should be part of the

COS for assessing the efficacy and safety of interventions in pediatric pain (in children aged 3 years and older). 'Additional opioid analgesia', 'pain-free', 'symptoms and adverse events' and 'sleep' were other outcome domains that were chosen by more than half participating RCT authors (Table 3).

Discussion

Only a third of surveyed authors of SRs and RCTs about postoperative pain in children had heard about the PedIMMPACT COS for acute pediatric pain. Most of them showed lack of knowledge about six domains of that COS, and the majority did not use the COS while preparing their studies. Problems indicated as preventing them from using the COS were lack of awareness, difficulties with implementation and lack of resources. When asked to indicate which outcome domains should be part of the COS for acute pediatric pain, they chose domains that only partly overlap with outcome domains of the PedIMMPACT for acute pain.

A limitation of our study is low response rate. Even after five email messages, only 16% of SR authors and 10% of RCT authors participated in the survey. A minority of emails bounced back as undelivered, so lack of willingness of authors to participate in such survey may also be an indication about insufficient awareness about the COS.

To our best knowledge, this is the first study that analyzed the knowledge, utilization and opinion of SR and RCT authors about the PedIMMPACT COS for acute pediatric pain. It has been reported that adherence to the IMMPACT COS for pain in adults is also insufficient [7]. In 2015, Mulla *et al.* published analysis of 156 trials about opioids for chronic noncancer pain. They found that reporting of the IMMPACT recommended COS was very variable, ranging from 99% for 'pain' to 7% for 'interpersonal functioning'. They also conducted regression analysis to study factors that could be associated with using recommended IMMPACT outcome domains. Identified factors were associated with reporting of certain individual outcome domains, not the COS [7].

The PedIMMPACT was published in 2008, and it is the only published recommended COS for acute pediatric pain [4]. Ten years later, we found out that SR and RCT authors have not been using this COS since it was published [6]. We hypothesized that there could be two explanations; either the authors do not find the PedIMMPACT COS appropriate, or they are not aware of it. Therefore, we decided to test these hypotheses, and we found that both explanations are part of the story. One of the study participants indicated that the PedIMMPACT COS was complicated and difficult to implement. The participant did not elaborate this further. It is possible that the participant is referring to the fact that the PedIMMPACT COS recommended some outcome domains which did not have validated measures [4].

The consensus required was not reported in the manuscript that described the PedIMMPACT COS. We agree that any consensus involves the possibility that not all of the authors agree, and that also not all the authors will agree with the suggested COS. For this reason we studied whether they find it appropriate.

Developing a COS is a complex process that involves multiple steps [8]. However, developing a COS is only the first step. It has been recommended that the COS should be reviewed periodically, as a very important part of validation of a COS. Such periodic evaluations can ensure that the outcome domains in a COS are still relevant, to review the possibility of adding new outcomes, to analyze whether implementation of the COS was successful and to make sure that new stakeholders are engaged when appropriate [8]. Our study can be considered as part of this periodic evaluation of the PedIMMPACT COS for acute pediatric pain. Based on our findings, implementation of that COS was not successful, and this situation calls for different actions and interventions.

New studies in this field could focus on other stakeholders as well, not only published authors, to see whether there is a need for revision of the COS. We plan to submit these results to the developers of the PedIMMPACT COS so that they can be used for audit and potential update of the COS, as recommended by the experts in the field of COS development and the COMET handbook [9].

In 2013, Kirkham *et al.* published analysis of outcome measures used in trials about rheumatoid arthritis (RA) over the period of 50 years, and within the study they contacted authors of trials published after publication of the RA COS in 1994. Their study had different aims than ours. They asked trialists whether they were aware of COS during designing of their study and choosing outcome domains, and whether they would consider using the RA COS in their future trials. They also included a small sample of authors. Among the 38 authors that responded, 13 did not use the full RA COS, and the majority of them indicated that they were not aware of it at the time they designed their study [10]. In this study we did not intend to ask the same questions; instead, we mainly wanted to know whether authors of SRs and trials in a particular field were aware of the relevant COS and did they find it appropriate; only one question was about whether they used the COS for their study.

Multiple surveyed authors indicated that they are not aware of the PedIMMPACT COS. This lack of knowledge could be addressed at several levels, but only before the study begins. Once the authors submit their manuscript to a journal is already too late because the study was completed and the authors cannot analyze new outcomes now from the beginning. First, education about the importance of COS can be added to research methodology courses, particularly in graduate schools. Second, members of ethics committees, or internal review boards should be aware of the COS and reject protocols for trials that do not use COS if they exist in a given research area. Third, research funders, both from industry and academia, should not fund trials or SRs that do not use relevant COS. As a commendable example, the UK's National Institute for Health Research has the following guidance in their guidance notes for applicants of full proposals: *"Where established Core Outcomes exist they should be included amongst the list of outcomes unless there is good reason to do otherwise"* [11].

Fourth, public registries of clinical trials such as Clinicaltrials.gov and PROSPERO for SRs should introduce relevant sections that ask whether the protocol uses relevant COS. Already in 2015, Clarke and Williamson proposed that trial registries *"should encourage researchers to note their use of the core outcome set and to specify each of the outcomes from the core set, as well as any additional outcomes, that they will measure"* [12].

Resources available via COMET initiative website should be used as a part of the solution [13]. The COMET is an initiative that brings together individuals that are interested in developing and applying agreed COSs. The initiative's website enables search of the COMET's database where studies about COS that are planned, ongoing or completed are collated [13]. Registries can provide links to the COMET website [13], where authors can check whether there are COS for any given research field, if they are not aware of it already. It is encouraging that the ISRCTN registry has already done this; on their website with instructions about primary outcome measures authors are instructed that they should refer to the COMET about the core outcome measures that should be used [14].

Furthermore, as one surveyed author suggested, interventions for raising awareness about the relevant COS in the academic community are necessary. This is the part of action defined as engaging new stakeholders when appropriate after development of COS [8]. All relevant stakeholders should be identified and included in discussion and action that will aim to improve awareness about and acceptance of the relevant COS. Industry is particularly important stakeholder in this respect because many trials are funded by producers of drugs and medical devices.

Although the number of authors participating in the study was low, this number is comparable with the overall number of authors that participated in the study of Kirkham *et al.*, which had 38 authors that responded to their email message about their usage of RA COS [10].

Furthermore, due to low number of SRs identified, we invited more than one author per SR to participate in the survey. It is likely that responses of authors that participated in the same SR were not the same, and therefore they would represent their personal opinion, and not representing the SR as the unit of analysis.

Despite the low response rate, our study still brings important message to the research community and developers of the PedIMMPACT COS. Since the authors do not use the COS, the studies are not comparable. Trials will use heterogeneous outcome domains, and SRs will have trouble synthesizing evidence if there are many outcome domains measured. Using standardized COS is in the interest of patients and entire research community to ensure that evidence can be justly compared and synthesized in SRs.

In conclusion, interventions are needed that will increase authors' awareness about the relevant COS. Additionally, further discussion about the most relevant outcome domains for pediatric pain may be warranted, considering that the majority of surveyed authors gave preference to outcome domains that do not completely overlap with PedIMMPACT COS. Insufficient use of the COS is hindering comparative effectiveness research because it is difficult to assess relative performance among competing interventions.

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Summary points

- This study analyzed awareness about the core outcome set (COS) for pediatric pain recommended by the PedIMMPACT initiative among researchers in this field.
- We surveyed authors of systematic reviews (SRs) and randomized controlled trials (RCTs) about interventions for postoperative pain in children.
- The survey was administered via SurveyMonkey, a web-based survey software.
- 15 authors of SRs and 27 authors of RCTs completed our survey.
- Only a third of the surveyed authors heard about the PedIMMPACT COS.
- Most of the authors showed lack of knowledge about six domains of that COS, and the majority did not use the COS while preparing their studies.
- When asked to recommend which outcome domains should be part of the COS for acute pediatric pain, the suggested outcome domains were partly different from the PedIMMPACT COS.
- Using standardized core outcome set is in the interest of patients and entire research community to ensure that evidence can be justly compared and synthesized in SRs.
- The PedIMMPACT COS should be revisited to make sure that it still contains the most relevant outcome domains for pediatric pain.

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, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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