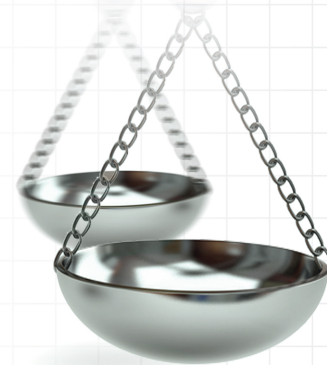




Reasons and factors associated with inconclusiveness of systematic reviews about interventions for neuropathic pain

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Svjetlana Dosenovic^{*,1} , Andria Dujmic² , Danijela Nujic^{3,4} , Ivana Vuka⁵ , Goran Tintor⁶, Antonia Jelcic Kadic⁷  & Livia Puljak⁸ 

¹Department of Anesthesiology & Intensive Care Medicine, University Hospital Split, Split, Croatia

²University of Split School of Medicine, Split, Croatia

³Department of Public Health, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Croatia

⁴Department of Public Health, Humanities & Social Sciences in Biomedicine, Faculty of Dental Medicine & Health, Josip Juraj Strossmayer University of Osijek, Croatia

⁵Laboratory for Pain Research, University of Split School of Medicine, Split, Croatia

⁶Department of Surgery, University Hospital Split, Split, Croatia

⁷Department of Pediatrics, University Hospital Split, Split, Croatia

⁸Center for Evidence-Based Medicine & Health Care, Catholic University of Croatia, Zagreb, Croatia

*Author for correspondence: sdosenovic@yahoo.com

Aim: Systematic reviews (SRs) are frequently inconclusive. The aim of this study was to analyze factors associated with conclusiveness of SRs about efficacy and safety of interventions for neuropathic pain (NeuP). **Materials & methods:** The study protocol was registered in the PROSPERO database (No. CRD42015025831). Five electronic databases (Medical Literature Analysis and Retrieval System Online, Cochrane Database of Systematic Reviews, Cumulative Index for Nursing and Allied Health Literature, Database of Abstracts of Reviews of Effects and Psychological Information Database) were searched until July 2018 for SRs about NeuP management. Conclusion statements for efficacy and safety, and characteristics of SRs were analyzed. Conclusiveness was defined as explicit statement by the SR authors that one intervention is better/similar to the other in terms of efficacy and safety. Methodological quality of SRs was assessed with the AMSTAR (A Measurement Tool to Assess systematic Reviews) tool. **Results:** Of 160 SRs, 37 (23%) were conclusive for efficacy and/or safety. In the SRs, conclusions about safety were missing in half of the analyzed abstracts, and a third of the full texts. Conclusive SRs included significantly more trials and participants, searched more databases, had more authors, conducted meta-analysis, analyzed quality of evidence, and had lower methodological quality than inconclusive SRs. The most common reasons for the lack of conclusiveness indicated by the SR authors were the small number of participants and trials, and the high heterogeneity of included studies. **Conclusion:** Most SRs about NeuP treatment were inconclusive. Sources of inconclusiveness of NeuP reviews need to be further studied, and SR authors need to provide conclusions about both safety and efficacy of interventions.

Lay abstract: Systematic reviews (SRs) analyze the evidence from research studies to provide recommendations on the efficacy and safety of medical interventions. Clear conclusions whether an intervention is efficacious and safe are important for patients, clinicians and policymakers, to enable informed decisions. Neuropathic pain (NeuP) is caused by the injury to the nerves. In this study factors associated with conclusiveness of SRs about efficacy and safety of interventions for the treatment of NeuP were analyzed. Our results showed that the majority of analyzed SRs do not provide a definitive answer, more so if reviews were conducted by higher methodological standards. Conclusive reviews included significantly more trials and patients. Sources of inconclusiveness of NeuP reviews need to be further studied.

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Systematic reviews (SRs) are frequently inconclusive, which is the usual reason why more randomized controlled trials (RCTs) or other types of primary studies are suggested in order to reach a definitive conclusion. Several research groups analyzed the conclusiveness of Cochrane SRs from various areas of research such as physiotherapy [1], pediatric gastroenterology [2], nutrition [3], neonatal themes [4], gynecological malignancy [5] and palliative care of cancer [6]. However, studies that involve both Cochrane and non-Cochrane SRs are needed, to explore reasons for inconclusiveness and factors associated with it.

In this study, the conclusiveness of SRs about interventions using neuropathic pain (NeuP) as the case study was analyzed. Pain relief is considered a basic human right [7]. Therefore, effective and safe pain therapies are of high public health significance. However, it is known that certain types of pain, such as NeuP, are still difficult to treat [8]. Hence, it is important to have conclusive evidence about the efficacy and safety of interventions for NeuP. The following main hypotheses regarding SRs about interventions for NeuP were tested: the majority of the SRs are inconclusive; conclusive SRs have included more participants, more studies, they are more commonly non-Cochrane SRs and they have higher methodological quality compared with inconclusive ones; the most common reason for inconclusiveness is the low number of participants; and the majority of conclusions presented in the SR abstract are concordant with conclusions presented in the full text.

Materials & methods

Study design

This was a methodological study based on a systematic search of the literature. Secondary data analysis was conducted only; no patient data were included in the study. The study was registered in the PROSPERO database (No. CRD42015025831).

Bibliographic search

Five electronic databases were searched: Cumulative Index for Nursing and Allied Health Literature (CINAHL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Medical Literature Analysis and Retrieval System Online (MEDLINE) and Psychological Information Database (PsycINFO) from the database inception to 17 July 2018. A combination of keywords for NeuP and systematic review/meta-analysis (search strategy was reported elsewhere [9]) was used, without language restrictions. Two authors (S Dosenovic and A Jelicic Kadic) independently conducted each of the following steps: screening of bibliographic records retrieved by search (titles and abstracts) and screening of potentially eligible full-text manuscripts. Discrepancies in judgments were resolved via discussion or involvement of a third author (L Puljak).

Inclusion criteria

SRs of RCTs on efficacy and safety of interventions for the treatment of NeuP that were published as a full text in a peer-reviewed journal were included. The definition of NeuP by the International Association for the Study of Pain (IASP) was used, which postulates that “*Pain caused by a lesion or disease of the somatosensory nervous system.*”, and all the accompanying notes regarding this definition were also taken into account [10]. SRs with participants of any age and gender were eligible if the participants suffered from NeuP according to the IASP definition [9]. SRs about any type of therapeutic intervention and any type of comparator were included. In terms of outcomes, SRs of RCTs that analyzed pain intensity, with or without other outcome measures were eligible for inclusion. SRs published in any language and year were included. Articles were not excluded based on the methods used; all eligible articles that were self-identified as SRs were included.

Exclusion criteria

SRs of nonrandomized studies; SRs published as conference abstracts or gray literature; and SRs of diagnostic accuracy, prognosis, prevention, epidemiology, cost-effectiveness and guidelines were excluded.

SRs with participants presenting with disorders that did not satisfy the IASP criteria, for example, participants suffering from fibromyalgia, complex regional pain syndrome type 1, low back pain without radicular pain and atypical facial pain, were excluded. Also, SRs where participants suffered from painful conditions that may be attributed to both neuropathic and nociceptive mechanisms (i.e., pain caused by multiple sclerosis, pain related to cancer and pain associated with stroke) were excluded, unless study authors categorized it as neuropathic. SRs

with trials that included participants suffering from a combination of NeuP and noneligible conditions and SRs in which pain was assessed only as a composite score were also excluded.

Data extraction & categorization

The following data were extracted: year of publication, number of authors and databases searched, number of included studies, number of included patients, if the quality or risk of bias of included RCTs was assessed (yes/no), whether a meta-analysis was performed (yes/no), if the quality of body of evidence in SRs was graded (yes/no), referral to the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) [11] guideline for selecting outcomes (yes/no), and whether it was Cochrane or a non-Cochrane SR (yes/no). The information about conclusiveness about efficacy and safety of the analyzed interventions presented in the abstract conclusion, as well as in the conclusion from the full text, was also collected. SRs were classified as conclusive (the authors explicitly stated that one intervention is better than the other, or one intervention is similar to the other in terms of efficacy and safety) or inconclusive (the SR authors indicated there were insufficient data, the available data are of low or inadequate quality or that further research is needed to make conclusions). If either efficacy or safety conclusion statement from the abstract or the full text was inconclusive, the whole SR was categorized as inconclusive. If both efficacy and safety were conclusive or efficacy was conclusive, and a safety conclusion was not reported, the SR was categorized as conclusive. For SRs that investigated multiple interventions, if at least one intervention was found to be inconclusive, the whole SR was rated as such.

For inconclusive reviews reasons for the lack of conclusiveness were extracted and categorized. Data extractions were done independently in duplicate (I Vuka and D Nujic; G Tintor and A Dujmic) and discrepancies were resolved by another author (S Dosenovic).

Methodological quality appraisal

The methodological quality of SRs was analyzed with the AMSTAR (A Measurement Tool to Assess systematic Reviews) checklist [12]. Before the quality assessment, the items on both scales were discussed, and a calibration exercise was performed on ten included SRs. Two authors independently rated each SR (I Vuka, D Nujic) and discrepancies were resolved by the involvement of a third author (S Dosenovic).

Analyses

The year of publication, number of studies and patients, number of authors and databases searched; the number of SRs which assessed the quality or risk of bias of RCTs, performed a meta-analysis, graded the quality of evidence, and referred to IMMPACT guideline for selecting outcomes; the frequency of Cochrane and non-Cochrane reviews, and methodological quality of SRs in conclusive versus inconclusive reviews were compared. Concordance between conclusions presented in the abstracts of SRs and conclusions presented in the full texts was also analyzed. 'Empty reviews', in other words, SRs without included RCTs were analyzed separately.

The data were presented as frequencies, percentages, and median and interquartile range (IQR). Normality distribution of data was tested with the Kolmogorov–Smirnov test. The Mann–Whitney test was used for differences in continuous data because data were not normally distributed, and chi-square test was used for differences in proportions. IBM SPSS Statistics for Windows software, version 19.0.0 (IBM Corp., NY, USA), was used for statistical analyses. Statistical significance was defined at $p < 0.05$, two sided.

Results

After screening titles and abstracts of 4644 items retrieved from the five bibliographic databases, 3824 items were excluded. Subsequently, 468 full-text manuscripts were retrieved for detailed eligibility assessment. Further 300 manuscripts were excluded because they did not fit inclusion criteria. Thus, 168 SRs of RCTs about interventions for NeuP were found. However, of those 168, there were eight empty reviews. They were analyzed separately. Therefore, 160 SRs were included in the main analysis. The characteristics of those SRs are presented in [Supplementary Table 1](#).

Of the 160 SRs with included RCTs, 37 (23%) had conclusive statements about efficacy and/or safety ([Table 1](#)). All of the 160 SRs contained conclusions about efficacy, but 93 (53%) SRs did not provide any conclusions about the safety of the analyzed intervention(s) in the abstract; while that number was lower in the full texts ($n = 62$; 34%).

Table 1. Characteristics of neuropathic pain systematic reviews with conclusive versus inconclusive results.

Variable	All SRs (n = 160)	Conclusive SRs for efficacy and/or safety (n = 37)	Inconclusive SRs (N = 123)	p-value
Patients enrolled (n), median (IQR)	817 (353–1817.5)	1596 (478–2938.5)	728 (317–1410)	U = 1146; p < 0.001 [†]
RCTs included (n), median (IQR)	10 (5–17)	12 (7–24)	9 (5–16)	U = 1630.5; p = 0.009 [†]
Authors (n), median (IQR)	5 (3–6.75)	6 (4–7.5)	5 (3–6)	U = 1739; p = 0.028 [†]
Databases searched (n), median (IQR)	4 (3–6)	4 (3–5)	5 (3–6)	U = 2879.5; p = 0.013 [†]
Reference to IMMPACT guideline for selecting outcomes, n (%)	32 (20)	5 (14)	26 (21)	X ² = 1.620; p = 0.445
Meta-analysis performed, n (%)	122 (76)	36 (97)	86 (70)	X ² = 11.786; p = 0.003 [†]
Quality or RoB of RCTs assessed, n (%)	151 (94)	33 (89)	118 (96)	X ² = 3.688; p = 0.158
Quality of evidence in SRs assessed, n (%)	60 (38)	8 (22)	52 (42)	X ² = 6.143; p = 0.046 [†]
Year of SR publication, median (IQR)	2014 (2011–2016)	2014 (2010.5–2016)	2014 (2011–2016)	U = 2274; p = 0.997
Cochrane reviews, n (%)	44 (28)	4 (11)	40 (33)	X ² = 6.724; p = 0.010 [†]
Methodological quality, AMSTAR score, median (IQR)	7 (6–9)	6 (5–7.5)	8 (6–10)	U = 3125; p < 0.001 [†]

[†] Statistically significant results.

X² = Chi square test; AMSTAR: A Measurement Tool to Assess systematic Reviews; IMMPACT: Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials; IQR: Interquartile range; RCT: Randomized controlled trial; RoB: Risk of Bias; SR: Systematic review; U: Mann–Whitney U-test.

Factors associated with conclusiveness

SRs that were conclusive for efficacy and/or safety enrolled more patients compared with inconclusive ones (median, IQR: 1596 [478–2938.5] vs 728 [317–1410], p < 0.001). Likewise, SRs with conclusive evidence included significantly more RCTs (median, IQR: 12 [7–24] vs 9 [5–16], p = 0.009). There was also a significant association between conclusiveness of SRs and performed meta-analysis (X² = 11.786, p = 0.003), and the quality level of a body of evidence assessment (X² = 6.143, p = 0.046).

Inconclusive SRs had significantly higher methodological quality than conclusive SRs on the AMSTAR checklist (median, IQR: 8 [6–10] vs 6 [5–7.5], p < 0.001). Significantly higher number of Cochrane SRs was found among inconclusive SRs (n = 40; 33%), compared with conclusive SRs (n = 4; 11%; p = 0.010).

Other statistically significant factors associated with conclusiveness were the number of authors and the number of databases searched (Table 1).

Publication date, analyzed quality or risk of bias of RCTs, and the reference to IMMPACT guideline for selecting relevant outcomes in chronic pain trials were not associated with conclusiveness (Table 1).

Reasons for inconclusiveness

SR authors indicated 27 different reasons for the lack of conclusiveness. The six most common reasons were: small number of included participants; small number of included studies; high heterogeneity of included studies, such as different doses and different duration of treatment, heterogeneous population, etc.; insufficient information about methodology or poor methodology; missing, inconsistent or partial data about safety; and low quality of evidence (Table 2). Conclusion statements about the efficacy and safety of analyzed NeuP interventions and categorizations are shown in Supplementary Table 2.

Concordance between conclusions in the abstract & main text of SRs

Concordance between 155 (97%) SR abstract and full-text conclusions was found. Only five pairs of abstracts/full texts were discordant in efficacy conclusion [13–17]. In all five cases the abstract was conclusive, and in the full text the authors indicated inconclusiveness.

Empty reviews

There were eight SRs without included RCTs (Supplementary Table 3). As such, they were inconclusive for both efficacy and safety. All of them were Cochrane reviews.

Table 2. Reasons provided by authors to explain lack of conclusiveness for efficacy and/or safety of reviews in neuropathic pain.

Reason	n (%) of SRs
Small number of participants	63 (51)
Small number of RCTs	51 (41)
High heterogeneity of included studies (different interventions, methodologies and population)	43 (35)
Insufficient information about methodology or poor methodology	43 (35)
Missing, inconsistent or partial data about safety; low number of events	42 (34)
Low/very low quality of evidence	38 (31)
Lack of long-term outcome assessment/insufficient information	36 (29)
Inadequacy of outcome measures/lack of relevant outcomes	28 (23)
High risk of bias for at least one domain	27 (22)
Heterogeneity of outcome measures	19 (15)
Selection bias: issues with randomization and allocation concealment	17 (14)
Performance bias: issues with blinding of participants and personnel	16 (13)
Lack of adequate comparisons	15 (12)
Attrition bias: lack of participant follow-up or inadequate follow-up, attrition not reported and high withdrawal rate of participants	13 (11)
Detection bias: problems with blinding of outcome assessors	12 (10)
Publication bias, language bias, relevant trials potentially missed	10 (8)
Cross-over trials, wash-out period in cross-over trial inadequate or not reported	6 (5)
Reporting bias: selective reporting of outcomes	6 (5)
Insufficient data; lack of available literature	5 (4)
Lack of clear diagnostic criteria/inconsistent diagnostic criteria	4 (3)
Large placebo responses	3 (2)
Geographically limited area, no ethnic diversity	2 (2)
Unclear inclusion and exclusion criteria	2 (2)
Commercial bias	2 (2)
Limited external validity and generalizability	2 (2)
Insufficient information about quality of drugs/interventions	1 (1)
Lack of direct evidence about efficacy, only surrogate outcomes	1 (1)

RCT: Randomized controlled trial; SR: Systematic review.

Discussion

The analysis of 160 SRs about NeuP indicated that the majority of SRs had inconclusive statements regarding results about the efficacy and/or safety. A small number of included participants was the most commonly stated reason by the SR authors to explain inconclusive results. Conclusiveness of evidence was associated with SRs that included more participants, more RCTs, searched more databases, had more authors, conducted meta-analysis and analyzed the quality of evidence. On the other hand, inconclusive SRs had a higher methodological quality.

The conclusiveness of results in SRs is important for patients, clinicians and policymakers, to enable informed decisions and save time when searching for definitive information. The results of this study indicated that the majority of analyzed SRs in the field of NeuP do not provide a definitive answer, even more frequently if reviews were published by Cochrane.

In SRs about NeuP, a higher number of included participants and studies were found to be associated with conclusiveness. Larger trials with many patients will contribute more toward the estimate of the magnitude of effect [18], and subsequently to the more conclusive results in evidence syntheses. The most common reasons for inconclusiveness that the SR authors provided were the low number of participants, stated in half of SRs, followed by a small number of included RCTs, stated by 41% of SRs.

Heterogeneity of the included studies, as a reason for inconclusiveness, is another important cause for concern. Nonstandardized interventions, methodologies and population were stated as the third most common reason for the lack of conclusiveness, together with issues related to the methodological quality of RCTs, each stated by a third of SR authors. Arguments about including primary studies of low quality and with a low number of patients in SRs are ongoing, with valid arguments on both sides of the discussion [19,20].

Inconclusive SRs had significantly higher methodological quality compared with the conclusive ones; the difference was 2 out of 11 AMSTAR points. This finding might indicate that authors of higher-quality reviews may be more critical toward evidence they are analyzing.

Another finding of this study is that inconclusive SRs more frequently rated the quality of evidence in a systematic and transparent manner, such as using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [21]. In line with this finding, low/very low quality of evidence was frequently stated as a cause for inconclusiveness by authors of SRs in this sample. However, it also needs to be emphasized that the focus of this study was analysis of conclusiveness as explicitly reported by SR authors at the end of the abstract and full text; past results indicate that authors may report conclusive statements about effects of an intervention, despite having a GRADE assessment in which primary outcome was rated less than high quality [22].

SRs should be used as a guide for justifying the conduct of new clinical trials, otherwise, a trial may represent waste in research [23]. The current study indicated a high prevalence of inconclusiveness of available SRs in the field of NeuP, which would imply a need for conducting many new trials in this field. Some of the hypotheses, which were based on the prior research findings in the field, were confirmed, while others were not. These previous results were reported in a number of methodological studies that analyzed the conclusiveness of Cochrane reviews in various research fields [1–6,24] and most of those studies, except two [1,6], found that the majority of analyzed Cochrane SRs had conclusive evidence. A high prevalence of inconclusive Cochrane reviews was observed in a study by Momosaki *et al.*, which found 94.3% of physiotherapy Cochrane reviews to be inconclusive [1]. Zhang *et al.* showed that less than half of Cochrane reviews in palliative and supportive care for cancer were conclusive [6]. Conclusiveness of SRs varied with different research areas.

A difference in the proportion of Cochrane and non-Cochrane reviews among the SRs with conclusive evidence was found, in other words, nine in ten Cochrane reviews about NeuP treatment were inconclusive. A part of the reason for this finding might be that Cochrane reviews in various fields [25–29], including NeuP [30], were found to have higher methodological quality.

Appropriate outcomes should be selected while designing clinical trials in order to allow the direct comparison of the analyzed interventions. Measuring and reporting relevant outcomes is one of the fundamental features of comparative effectiveness research [31]. The standardized core outcome set and outcome measures are selected for specific research areas to reduce this heterogeneity [32]. Heterogeneity of outcomes was stated as one of the reasons behind inconclusiveness by 15% of SRs in the sample. Several studies have previously shown that recommended core outcome set and core measures are insufficiently utilized in pain research [33–37]. In the analyzed sample there was no significant difference in the conclusiveness of SRs based on the date of publication, analyzed quality or risk of bias of included RCTs and the reference to IMMPACT guideline for selecting relevant core outcomes in chronic pain trials [11].

It is worrying that every other SR did not have a conclusion about the safety of analyzed interventions in the abstract. Readers of scientific literature often rely only on abstracts to get quick information whether an intervention works and is it safe, so this is a limitation of the published literature. Furthermore, a third of the full-text manuscripts did not contain a safety conclusion. Safety outcomes were frequently missing from RCTs; a third of SR authors indicated that data about safety outcomes were missing, inconsistent or partial.

This study, although based on a large sample of SRs that were systematically searched without language restrictions, had several limitations. First, unpublished (gray) literature was not included. Second, the search was limited to SRs published by mid-2018; however, the purpose of the study was not to summarize the most current literature about the treatment of this chronic condition, but to look behind reasons for the lack of conclusive evidence. Additionally, the association between the reporting quality of SRs, using a tool such as the Preferred reporting items for systematic reviews and meta-analyses checklist [38], and conclusiveness of NeuP SRs was not assessed. It would be interesting to investigate whether there is any association between reporting quality and statements about conclusiveness of SRs.

In our study we have depended on the authors' reporting of conclusiveness, without going deeply into the definition of conclusiveness. Currently, there are no consensus guidelines regarding the criteria that would define a conclusive review, and few studies have addressed that issue. This has important implications on decisions such as whether a SR needs an update and whether new primary studies are needed, and potentially preventing research waste. Cochrane, for example, has labeled some of their reviews as 'stable', meaning that they are not in a need of updating, but it has been shown recently that justifications for stabilizing a Cochrane review were often not clear and transparent [39]. Thus, further studies regarding conclusiveness of SRs are needed.

Conclusion

In conclusion, the insufficient number of participants and studies are among the most commonly indicated reasons for the inconclusiveness of results in SRs about interventions for NeuP. The performed analyses confirmed the association of conclusiveness with the number of included participants and RCTs, as well as with the methodological quality of SRs, evidence synthesis and rated quality of evidence by SR authors, the number of searched databases, and the number of authors. Sources of inconclusiveness of SRs need to be further studied and authors of SRs need to provide conclusions about both efficacy and safety of analyzed interventions.

Summary points

- This study analyzed factors associated with conclusiveness of systematic reviews (SRs) about efficacy and safety of interventions for neuropathic pain (NeuP).
- Five electronic databases were searched for SRs about NeuP management.
- Of 160 included SRs, only 37 (23%) were conclusive for efficacy and/or safety.
- A small number of included participants was the most commonly stated reason by the SR authors to explain inconclusive results.
- Conclusiveness of evidence was associated with SRs that included more participants, more randomized controlled trials, searched more databases, had more authors, conducted meta-analysis and analyzed the quality of evidence. Inconclusive SRs had a higher methodological quality.
- Every other SR did not have a conclusion about the safety of analyzed interventions in the abstract, as well as a third of the full-text manuscripts.
- A high prevalence of inconclusiveness of available NeuP SRs would imply a need for conducting many new trials in this field.
- Authors of SRs need to provide conclusions about both efficacy and safety of analyzed interventions.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2020-0165

Author contributions

S Dosenovic and L Puljak provided substantial contributions to the conception or design of the work, analysis and interpretation of data for the work, and drafting of the manuscript. S Dosenovic, A Dujmic, D Nujic, I Vuka, G Tintor and A Jelcic Kadic contributed to the acquisition of data for the work. All authors contributed to the revision of manuscript critically for important intellectual content, final approval of the version to be published and agreement to be 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.

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