# Methodological assessment and overall confidence in the results of systematic reviews with network meta-analyses in Endodontics

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## Author contribution

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**Methodological assessment and overall confidence in the results of systematic reviews with network meta-analyses in Endodontics**

**Abstract**

**Aim**: The aims of the study were to assess the methodological quality of systematic reviews with network meta-analyses (NMAs) in Endodontics using the "A MeaSurement Tool to Assess systematic Reviews" (AMSTAR 2) tool, and to evaluate the overall confidence in the results of the individual reviews included in the analysis.

**Methodology:** Systematic reviews with NMAs within the specialty of Endodontics published in English were identified from the PubMed, EbBSCOhost and SCOPUS databases from inception to July 2021. Two reviewers were involved independently in the selection of the reviews, data extraction, methodological quality assessment and overall confidence rating. Disagreements were resolved by discussion between the reviewers to achieve consensus; if disagreements persisted, a third reviewer made the final decision. The methodological quality of the included NMAs was appraised using the AMSTAR 2 checklist, which contains 16 items. The reviewers scored each item - 'Yes' – when the item was fully addressed, 'Partial Yes' – when the item was not fully addressed, or 'No' – when the item was not addressed. The overall confidence in the results of each review was classified as 'High', 'Moderate', 'Low' or 'Critically low' based on the criteria reported by the AMSTAR 2 developers.

**Results** Twelve systematic reviews with NMAs were included. All the NMAs adequately reported Item 1 ("*Did the research questions and inclusion criteria for the review include the components of PICO*?"), Item 8 ("*Did the review authors describe the included studies in adequate detail*?"), Item 9 ("*Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review*?") and Item 16 ("*Did the review authors report any*

*potential sources of conflict of interest, including any funding they received for conducting the review*?") , whereas only one NMA reported Item 10 adequately ("*Did the review authors report on the sources of funding for the studies included in the review*?"). The overall confidence in the results of eight reviews was categorised as "Critically low", one review was "Low", two reviews were "Moderate" and one review was "High".

**Conclusion** The overall confidence in the results for the majority of systematic reviews with NMAs in Endodontics was judged to be 'Critically low' as their methodological quality was below the necessary standard. AMSTAR 2 and PRISMA for NMA guidelines are available to guide authors to produce high quality systematic reviews with NMAs and for Editors and peer-reviewers when assessing submissions to journals.

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## Introduction

The systematic collection and analyses of research evidence to address specific clinical questions within the field of oral and dental health forms the basis of evidence-based Dentistry (Ismail & Bader, 2004). Systematic reviews and meta-analyses are effective in developing clinical practice guidelines, highlighting gaps in knowledge and prioritizing areas for future research (Moher et al., 2009, Gopalakrishnan & Ganeshkumar, 2013). In addition, the findings of systematic reviews and meta-analyses are being adopted increasingly by healthcare professionals wishing to provide up-to-date evidence-based care for their patients (Carrasco-Labra et al., 2015; Gopalakrishnan & Ganeshkumar, 2013). The pairwise comparison between an intervention (treatment) and a control is the fundamental role of a traditional meta-analysis. The comparative effectiveness of any two interventions can be analysed using a pair-wise meta-analysis from a head-to-head trial, that is, a single trial in which two interventions are compared (Jansen & Naci 2013; Kiefer et al., 2015). In situations where there are no head-to-head comparisons between two interventions or when more than two interventions are being compared, a pair-wise meta-analysis is limited in its utility (Jansen & Naci, 2013).

Unlike a pair-wise meta-analysis, a network meta-analysis (NMA) is able to analyse multiple interventions of interest from direct studies with head-to-head comparison or from indirect evidence with various interventions being compared against a common comparator (Buti et al., 2011; Lumley 2002). For example, NMAs comparing the efficacy of three local anaesthetic solutions (lignocaine, articaine and bupivacaine) in teeth with irreversible pulpitis. In this theoretical example, a range of randomised clinical trials may have reported comparative evidence of lignocaine versus articaine or lignocaine versus bupivacaine. However, a study has

not been conducted to compare articaine versus bupivacaine. In that situation, indirect evidence of articaine versus bupivacaine can be estimated through the known association of lignocaine versus articaine and lignocaine versus bupivacaine using lignocaine as the common comparator. An NMA provides two types of results, the relative magnitude of effect for each intervention in the network (a network is formed by a set of studies that can be used to link three or more interventions; https://training.cochrane.org/handbook/current/chapter-11 ) as well a ranking of the interventions relative to each other (Buti et al., 2011; Lumley, 2002; Salanti et al., 2014).

Shea et al. (2007) developed a validated critical appraisal tool for use by health professionals and policy makers - "A MeaSurement Tool to Assess systematic Reviews" (AMSTAR). AMSTAR consists of 11 items and can be used to reproducibly assess the methodological quality of systematic reviews. A revised new AMSTAR 2 tool with 16 items, includes a more comprehensive user guide, and can be used to rate the overall confidence in the results of a review as "High", "Moderate", "Low", or "Critically low" based on seven critical and nine non-critical domains (Shea et al., 2017).

In Medicine, several studies have appraised the methodological quality of systematic reviews with NMAs in the fields of drug interventions, acupuncture and moxibustion, and Chinese Medicine. They reported that the NMAs had serious methodical flaws in areas such as: explanations of study design, status of publications, lists of excluded studies, sources of funding and assessment of publication bias, that needed to be corrected in future (Tonin et al., 2019; Yang et al., 2018; Yuan et al., 2021;). Gao et al. (2019) concluded that the overall methodological quality of NMAs available in the Cochrane library was 'low'. The overall confidence in the results of systematic reviews in the specialty of spine surgery (Dettori et al., 2020) and exercise therapy for chronic non-specific low back pain (Almeida et al., 2020) were assessed using the AMSTAR 2 tool; both studies concluded that the overall confidence in the results of these reviews were "Critically

low". Obviously, NMAs with methodological flaws result in biased and invalid conclusions (Gao et al., 2019).

Lee and Shin (2018) concluded that the reporting quality of systematic reviews with NMAs within Dentistry was 'low'. In recent years, the number of systematic reviews with NMAs have gradually increased in the field of Endodontics, but there is no evidence to confirm whether they were performed well from a methodological perspective. As a consequence, it is essential and timely to undertake an analysis of the overall confidence in the results of systematic reviews with NMAs in Endodontics with the aim of identifying methodological flaws, which can be corrected in future. Hence, the aims of the current study were to assess the methodological quality of systematic reviews with NMAs in Endodontics using the AMSTAR 2 tool, and to evaluate the overall confidence in their results.

## Methods

*Literature search*

The reviews were retrieved from the PubMed, EbBSCOhost and SCOPUS databases from inception to July 2021 using the following search strategy ((((((((((pulp) OR ("root canal")) OR (Endodontic)) OR (Endodontology)) OR ("periapical surgery")) OR ("periradicular surgery")) OR (apicoectomy)) OR (apicectomy)) OR (pulpotomy)) OR (pulpectomy)) AND ("network meta-analysis")) OR ("indirect meta-analysis"). Grey Literature was searched in OpenGrey (opengrey.eu). Additional searches were performed by screening the reference lists of the included reviews.

*Selection criteria*

All systematic reviews with NMAs in the specialty of Endodontics published in English were included.

*Study selection*

The study selection process was performed by two independent reviewers (VN,SJ). Disagreements were resolved by discussion between the reviewers to achieve consensus. If disagreements persisted, a third reviewer (PD) made the final decision.

*Data extraction*

Data extraction was performed independently by two reviewers (VN, SJ). Disagreements were resolved by discussion between the reviewers until consensus was achieved. If disagreements persisted, a third reviewer (PD) made the final decision. A data extraction form was created with the following items: name of the first author, country of the corresponding author, year of publication, name of the database where the protocol of the review was registered, number of authors, name of the journal, specialty field of the journal, impact factor of the journal, and journal adherence to PRISMA guidelines.

*Methodological quality*

The methodological quality of the included NMAs was appraised using AMSTAR 2 checklist, which contains 16 items. Two reviewers (VN, SJ) independently scored each item - 'yes' – when the item was fully addressed, 'partial yes' – when the item was partially addressed, or 'no' – when the item was not addressed. Disagreements were resolved by discussion between the reviewers until consensus was achieved. If disagreements persisted, a third reviewer (CF) made the final decision. Unclear or missing information was identified, and the corresponding authors of each

review were contacted with a request to provide the information. The AMSTAR 2 scores were shared with the corresponding authors of the individual reviews to avoid any possible misinterpretation and to confirm the scores awarded.

*Overall confidence rating*

The overall confidence in the results of each review was classified as 'High', 'Moderate', 'Low' or 'Critically low' based on the criteria reported by the AMSTAR 2 developers (Shea et al., 2017). First, the research team identified and selected critical domains (*a priori* protocol registration, adequacy of the literature search, rationale for excluding studies, risk of bias from individual studies being included in the review, appropriateness of meta-analysis methods, considering risk of bias when interpreting the results of the review, and publication bias) and then two reviewers (VN, SJ) applied the criteria independently to rate the overall confidence in the results of each review (Shea et al., 2017). The larger the number of non-critical and critical weaknesses that were identified meant there was less confidence in the results of a review; any disagreements were resolved by a third reviewer (CF).

## Results

*Literature search*

The literature search process is shown in Figure 1. The initial literature search identified 393 publications and after screening the titles and/or abstracts 381 publications were excluded because they did not satisfy the inclusion criteria. Following full text reading, 12 systematic reviews with NMAs were included.

*Characteristics of the included reviews*

The characteristics of the included studies are set out in Table 1. The corresponding authors of the reviews were from Bahrain, Brazil, Canada, Egypt, Italy, Malaysia, and Taiwan. The number of authors in each review ranged from 3 to 11 (median = 6). The reviews were published between 2014 and 2021 in the *International Endodontics Journal* (n=2), *Journal of Endodontics* (n=3), *Australian Endodontic Journal* (n=1), *Journal of Evidence-Based Dental Practice* (n=1), *Journal of Dentistry* (n=1), *Journal of Dental Anaesthesia and Pain Medicine* (n=1), *The Open Dentistry Journal (n=1), Brazil Oral Research* (n=1) and *Materials* (n=1).

Among the 12 reviews, the protocols of 6 reviews were registered in the PROSPERO database (https://www.crd.york.ac.uk/prospero/), and 1 review was registered in the INPLASY database (https://inplasy.com ); the other 5 reviews were not registered.

Among the 12 reviews, ten were clinical trials, and two were laboratory-based studies. The software used to conduct the individual NMAs were WinBUGS (Lin et al., 2014), STATA (Nagendrababu et al., 2019a, 2019b), program R (Zabjir et al., 2019, 2020), MetaXL (Sivaramakrishnan et al., (2019) and R version (Almuthhin et al., 2020).

*Methodological quality*

All the reviews reported the following items adequately:

Item 1 (*Did the research questions and inclusion criteria for the review include the components of PICO?*),

Item 8 (*Did the review authors describe the included studies in adequate detail?*),

Item 9 (*Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?*), and

Item 16 (*Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?*).

Only one review (Khater *et al.* 2021) reported item 10 adequately (Did the review authors report on the sources of funding for the studies included in the review?).

*Overall confidence*

The overall confidence in the results of the reviews is described in Table 2. The overall confidence in the results of eight reviews were categorised as "Critically low" (Almuthhin et al., 2020; de Souza Matos et al., 2021; Dioguardi et al., 2021; Lin et al., 2014; Sivaramakrishnan et al., 2019; Tedesco et al., 2021; Zanjir et al., 2019; 2020), one review was "Low" (Nagendrababu et al., 2019b), two reviews were "Moderate" (Nagendrababu et al., 2019a; Pulikkotil et al., 2018), and one review was "High" (Khater et al., 2021).

**Discussion**

A NMA can provide evidence on the relative effectiveness of various interventions to aid clinical decision-making when head-to-head comparison clinical trials are not available (Buti et al., 2011; Lumley 2002; Salanti et al., 2014). Indeed, Leucht et al., (2016) proposed that NMAs should be considered as the highest level of evidence in the hierarchy of treatment guidelines. Several studies have appraised the methodological quality of NMAs in Medicine, but the current study is the first to appraise the methodological quality of systematic reviews with NMAs in Endodontics. A total of 12 NMAs were appraised using the AMSTAR 2 tool, which suggests that the use of NMAs in the specialty is still in the initial stages, but with a trend for a gradual increase in numbers in recent years.

All the included NMAs in the current study reported the PICO component (population, intervention, control and outcome). PICO is the format commonly used to develop the research question in a systematic review where authors should describe the PICO in detail (Shea et al., 2017). Information on a 'timeframe' (e.g. following a pulpotomy, the effect of a material was observed after *six months*) should be included if this is important in deciding the likelihood of a trial capturing relevant clinical outcomes. The inclusion of studies in a review and their suitability to be combined in a meta-analysis can be appraised by the PICO component and allows readers to evaluate the appropriateness of the results (Shea et al., 2017).

The protocol of a systematic review must be developed before starting the review process (Abuabara et al., 2019) and should be registered in a database (e.g. PROSPERO (https://www.crd.york.ac.uk/prospero/), Open Science Framework (OSF) (https://osf.io/prereg/)). The Preferred Reporting Items for Systematic review and Meta-Analyses for Protocols (PRISMA-P) 2015 statement helps authors to prepare and report a robust protocol (Moher et al., 2015). Any deviation from the protocol during a review must be reported and explained fully in the manuscript (Shea et al., 2017). In Dentistry, a positive association was observed between those protocols that were registered *a priori* and the reporting quality of the resultant article (Dos Santos et al., 2020). Furthermore, adherence to the original protocol may reduce the risk of bias in a review (Shea et al., 2017). Due to the importance of *a priori* protocol registration, the *International Endodontic Journal* recently endorsed the policy of mandatory prospective protocol registration for systematic reviews (Nagendrababu et al., 2021a).

In the present study, only 17 % of the NMAs reported Item 3 adequately. Authors must explain the selection of the included study designs (randomised controlled trials or non-randomised studies, or both) in their systematic review and should justify the selection of a

particular study design as being suitable to answer the research question; for example, restriction to only randomized controlled studies. The combination of non-randomized and randomized trials can be rationalized when insufficient information can be derived from only randomised studies and when non-randomized can provide supplementary evidence (Shea et al., 2017). In the present study, two NMAs, were laboratory-based studies, and authors are expected to provide the rationale for conducting such non-clinical systematic reviews.

Authors are advised to perform a comprehensive literature search to identify relevant studies in at least two electronic databases (e.g., EMBASE, MEDLINE), supplemented by searching in the reference lists of published reviews/included studies, trial registers (e.g. ClinicalTrials.gov), include or consult the experts in the particular field of study, and the grey literature (Shea et al., 2017). In the present study, most of the reviews did not search the grey literature. Grey literature is evidence not published in commercial publications (e.g., theses, research and committee reports, conference papers), but they can provide important contributions to a systematic review by reducing publication bias, increasing the comprehensiveness of a review and providing a balanced overview of all the available evidence (Paez, 2017). The grey literature can be searched in databases such as OpenGrey (www.opengrey.com).

During a systematic review, two individuals should perform the study selection process independently, which includes screening the title/abstract, reading the full text and extracting data from the included studies. A consensus process should be described when disagreements arise between the two reviewers. In general, disagreement can be resolved by a third reviewer or following a team discussion. If only one reviewer performed the study selection or data extraction, a second reviewer should do so in a sample of representative studies and achieve a kappa agreement of more than 0.80 (Shea et al., 2017). In the current study, 50 % of NMAs

reported item 7 adequately, that is: 'After reading the full text, a list of excluded studies must be reported in the manuscript with explanations for all exclusions'. The unjustified exclusion of studies will bias a review (Shea et al., 2017). The complete reporting of the search/selection process will likely increase the chances of reproducibility (Faggion et al., 2018a; Pieper et al., 2021). If authors believe that details of this process will increase the length of the manuscript beyond acceptable word limits, it can be accommodated in supplementary files (Faggion 2015).

The description of subjects, interventions, controls, outcomes, study design and analysis of the studies must be provided (Item 8). This item helps judgments to be made on the extent to which the studies were appropriately chosen in regard to the PICO format. Authors can provide all this information in Tables. Item 8 has been reported to be the most consistently adequately reported among the AMSTAR items across disciplines (Faggion 2015, Wasiak et al. 2016, Wasiak et al., 2017, Faggion et al., 2018b), which is similar to the current study.

Confidence in the accuracy of the overall evidence from a systematic review can be evaluated based on the assessment of the risk of bias of the included studies (Guyatt *et al.* 2011). Authors should follow a systematic approach to conduct the risk of bias assessment, preferably with a properly developed rating instrument, and provide an explicit explanation based on RoB if it impacts on the recommendation for clinical care or guidelines (Shea et al., 2017). AMSTAR 2 recommends consultation with the Cochrane Handbook for adequate assessment of risk of bias for reviews restricted to randomised clinical trials. The most commonly used tool for assessing risk of bias in randomised trials is the Cochrane risk-of-bias tool (Sterne et al., 2019). For non-randomised studies of interventions, the following parameters should be considered: confounding, selection bias, bias in measurement of exposures and outcomes, and selective reporting of analyses or outcomes, or both (Shea et al., 2017). If a systematic review combines randomised clinical trials of varying quality, the authors should assess the impact of this by

regression analysis, or by estimating pooled effect sizes using only studies at low risk of bias. In the case of non-randomized studies of interventions authors should estimate pooled effect sizes while including only studies at low or moderate risk of bias, and/or only those at low risk of bias (if there are any). This evaluation should be further extended to clarify if the inclusion of studies with variable quality and study designs could explain the difference in results among studies (Shea et al., 2017). In the present study, most of the reviews included clinical trials, whereas two reviews were laboratory-based.

It is interesting to note that only one of the NMAs in the current study reported the sources of funding for the studies included in their review (Khater et al., 2021). The literature confirms that research sponsors and authors can create bias in the design of studies towards support for the products of the sponsors (Lexchin, 2012, Lundh, 2012). Therefore, it is essential for authors to report sources of funding for each study included in their review (Shea et al., 2017). Also, the authors of systematic review should declare all potential conflicts of interest, including any funding they received for conducting the review (Nagendrababu et al., 2021b). All the NMAs included in the present study reported conflicts of interest.

A meta-analysis may provide a clear and valid result on the effectiveness of an intervention for patient management. The rationale and the principles for the conduct of a meta-analysis should be explained in the protocol that is registered before the start of the review. The report of the rationale and principles will allow the reader to understand whether the meta-analysis was conducted appropriately, considering the heterogeneity of studies. The combination of randomised and non-randomised trials in a meta-analysis should be considered carefully as there is a substantial possibility of heterogeneity due to the differing study designs (González-Castro & Tovilla-Zárate 2014; Haidich 2010; Shea et al., 2017). As in a pair-wise meta-analysis, heterogeneity may be a sensitive issue in a network meta-analysis where heterogeneity among

studies in one specific comparison can affect the other comparisons in the network (Chaimani et al., 2021). Additionally, authors should discuss the impact of any heterogeneity on their conclusions (Shea et al., 2017).

Small studies tend to have less robust methodological quality and are likely to be influenced by publication and selection bias, which can result in 'small study effects' whereby smaller studies report larger treatment effects, that is greater differences between interventions (Sterne et al., 2000). However, it must be appreciated that large studies can be flawed in other ways. Authors of systematic reviews must investigate publication bias adequately (e.g., statistical test or graphical display). If they are positive, authors must discuss its likely impact on the results of the review (Shea et al., 2017). However, the evaluation of publication bias is challenging in NMAs and is based on the availability of a common comparator. The 'comparison-adjusted funnel plot' assesses the "small study effects" based on the common comparator as the denominator (Chaimani & Salanti, 2012). Studies based on interventions are compared in this modified funnel plot. As recommended by Cochrane, at least 10 studies are necessary for a valid interpretation of such funnel plots (https://handbook-5-1.cochrane.org/chapter_10/10_4_3_1_recommendations_on_testing_for_funnel_plot_asymmetry.htm ). The basis for the combination of comparisons and ranking should be decided in a non-statistical manner, i.e., by assessing how clinically homogeneous or how heterogeneous are the trials included in the NMA. The availability of non-published studies for all the pair-wise comparisons in the network should be appraised by the authors of a review (https://training.cochrane.org/handbook/current/chapter-11) .

The AMSTAR 2 developers suggested that combining the individual ratings of each item of AMSTAR 2 into an overall score was not appropriate. The individual items provide information on the limitations in the respective quality domains while an overall score might conceal the

impact of the individual critical and non-critical weaknesses. Instead of providing an overall quality score, AMSTAR 2 recommends a rating of the overall confidence in the results (Shea et al., 2017), which involves careful analysis of critical and non-critical domains. The assessment of weaknesses in the critical and non-critical domains should be adopted by the reviewers and appraisers of each systematic review during its peer-review and prior to publication (Shea et al., 2017). The AMSTAR 2 developers suggested that the decision of the importance of the items should be made by authors of systematic reviews, considering the specific research carried out (Shea et al., 2017). In the present study, 67% of the NMAs were rated as "Critically low" confidence in the results.

This study was undertaken from the perspective of a reader and the analysis was based on what the authors reported in their studies. It is always possible that the authors of the NMAs used the correct methodology but failed to report it in the manuscript.

It is important to acknowledge that AMSTAR 2 was developed originally for systematic reviews with meta-analyses of clinical trials. However, because a standard tool to appraise the methodological quality of NMAs is not available, the current study used the AMSTAR 2 tool with several additional steps in an attempt to ensure the process was sound. For example, the scores of individual reviews were shared with the corresponding authors of each review to obtain their feedback on the scores awarded. In that way, the corresponding authors had the opportunity to assess the scores awarded and provide feedback on whether the assessment was accurate and fair. This additional step is likely to increase the accuracy of the scoring by allowing a greater number of reviewers to assess the methodological quality of these studies. In the process of obtaining feedback from the authors of the NMAs, the problems inherent in the use of

checklists (Faggion 2015) is minimized as it reduces the discrepancy between what was reported in the systematic reviews with NMAs and what was in fact conducted by the authors of the NMAs. In other words, it reduces the impact of poor reporting.

With such an approach, potential discrepancies with the assessment of the statistical component of NMAs is likely to be reduced and provides justification for the use of AMSTAR-2 to evaluate NMAs. Nevertheless, it is worth noting that AMSTAR 1 and AMSTAR 2 have been used previously to assess the methodological quality of systematic reviews with NMAs in child and adolescent psychiatry (Cortese et al., 2019), Chinese medicine (Yang et al., 2018) and acupuncture and moxibustion (Yuan et al., 2021). Interestingly, Goa et al. (2019) assessed the methodological quality of systematic reviews in NMAs published in the Cochrane library using AMSTAR 2. Among 16 items, in AMSTAR 2, only three items (Item 11: appropriate methods for statistical combination, Item 12: potential impact of risk of bias in individual studies on the results of the meta-analysis, item 15: investigation of publication bias) are related to the meta-analysis. However, it is generally acknowledged that the application of the remaining 13 AMSTAR 2 items that relate to the systematic review element of a NMA is less controversial, because all systematic reviews (with pair-wise or NMA) should observe the standards set out in these items.

The strengths of the current study include: a robust literature search using three electronic databases as well as the reference list of the reviews included and the grey literature. To reduce bias further, two individuals were involved in appraising each of the reviews. The number of systematic reviews with NMAs included in the current study was small. However, to provide a holistic overview in Endodontology, the current study

included NMAs with all types of study designs (e.g., clinical trials as well as laboratory studies) and all types of journals (e.g., both Endodontic specialty and non- Endodontic specialty journals).

*Future directions for research*

Tonin et al. (2019) investigated the methodological quality of NMAs and their compliance with reporting guidelines (PRISMA -NMA). They concluded that poor quality NMAs were due largely to poor methodology not reporting. Hence, a tool is required exclusively for assessing the methodological quality of NMAs that takes into account the specific assumptions of NMAs, for example: similarity, homogeneity, transitivity, and statistical key domains. As a consequence, such a tool should include a description of the statistical models, presentation of the network structure, descriptions of the network geometry, assessments of inconsistency, any additional analyses performed, and the presentation of ranking order (Tonin et al., 2019).

Due to the relatively small number of reviews included in the current study (n=12), it was not possible to assess the associations between article and journal characteristics with the overall confidence of each review. Future studies should be conducted to assess this association when a larger number of NMAs is available. A future study should also be conducted to assess the reporting quality of NMAs in Endodontics using PRISMA for NMA guidelines (Hutton et al., 2015).

**Conclusion**

Of the 12 systematic reviews with NMAs in Endodontics, the overall confidence in the results of eight reviews was “Critically low”. Improvements in systematic reviews with NMAs in

Endodontics is essential, especially in reporting of: *a priori* protocol registration, providing a list of excluded studies and describing sources of funding. Authors should ensure that AMSTAR 2 and PRISMA for NMA guidelines are followed strictly before submitting their manuscript for publication. Editors should endorse the PRISMA for NMA statement.

Figure 1: Literature search process

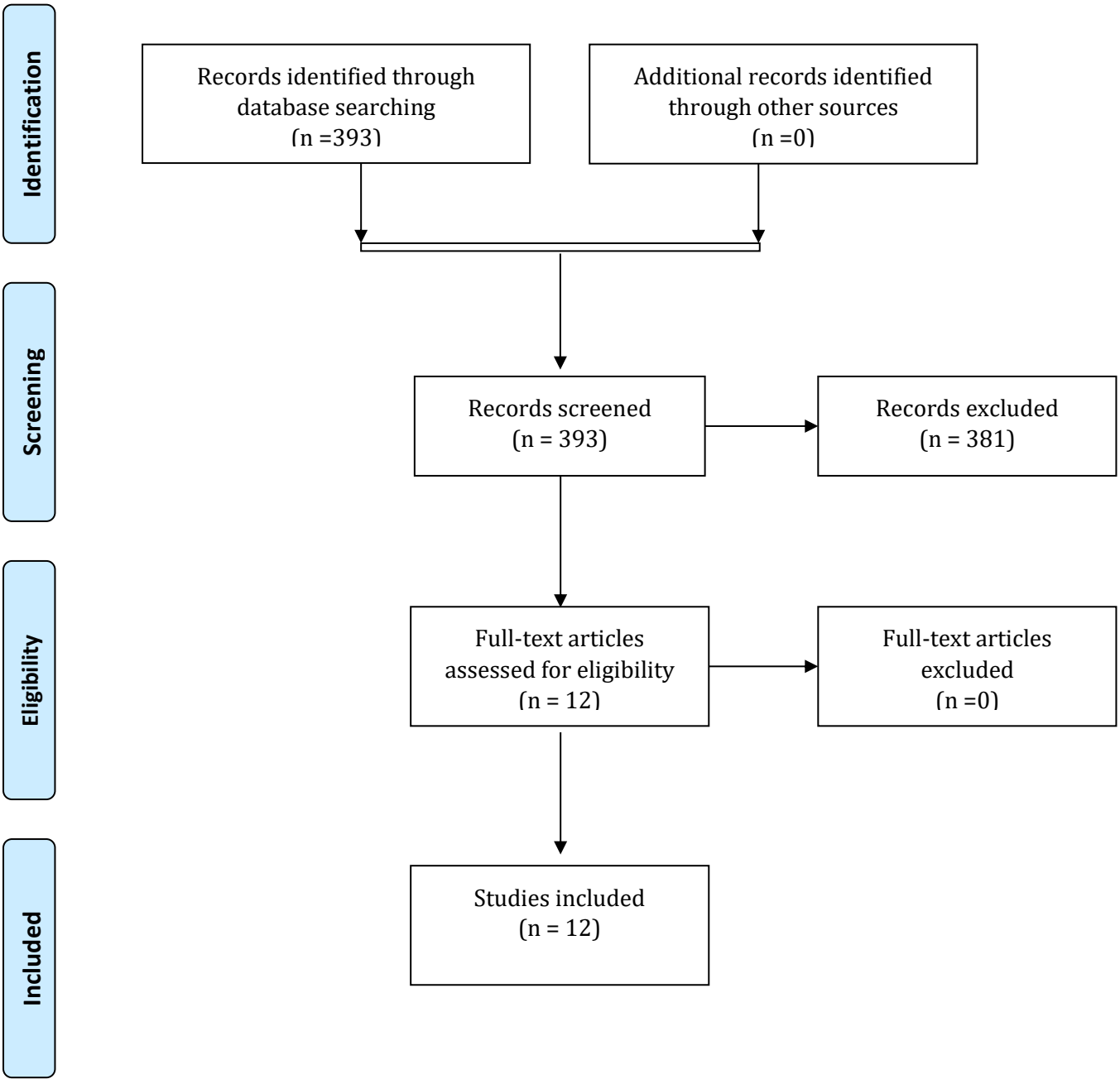

Table 1: Characteristics of the included network meta-analyses

| **Study** | **Country of the corresponding author** | **Name of the database where the protocol of the review was registered** | **Number of authors** | **Name of the Journal** | **Journal (Speciality vs non-speciality)** | **JCR Impact factor Journal** | **Journal adhered to PRISMA guidelines** |
|---|---|---|---|---|---|---|---|
| Lin et al., (2014) | Taiwan | Not Reported | 4 | *Journal of Dentistry* | Non Specialty | Yes | No |
| Pulikkotil et al., (2018) | Malaysia | PROSPERO | 5 | *International Endodontic Journal* | Specialty | Yes | Yes |
| Nagendrababu et al., (2019a) | Malaysia | PROSPERO | 6 | *International Endodontic Journal* | Specialty | Yes | Yes |
| Nagendrababu et al., (2019b) | Malaysia | PROSPERO | 6 | *Journal of Endodontics* | Specialty | Yes | No |
| Zanjir et al., (2019) | Canada | Not Reported | 6 | *Journal of Endodontics* | Specialty | Yes | No |
| Sivaramakrishnan et al., (2019) | Bahrain | PROSPERO | 3 | *Journal of Dental Anesthesia and pain medicine* | Non Specialty | No | Yes |
| Almuthhin et al., 2020 | Saudi Arabia | Not Reported | 9 | *The Open Dentistry Journal* | Non Specialty | No | Yes |
| Zanjir et al., (2020) | Canada | Not Reported | 7 | *Journal of Endodontics* | Specialty | Yes | No |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| de Souza Matos et al., (2021) | Brazil | PROSPERO | 7 | *Australian Endodontic journal* | Specialty | Yes | No |
| Dioguardi et al., (2021) | Italy | Not Reported | 11 | *Materials* | Non Specialty | No | Yes |
| Tedesco et al., (2021) | Brazil | PROSPERO | 9 | *Brazil Oral Research* | Non Specialty | No | Yes |
| Khater et al., (2021) | Egypt | INPLASY | 6 | *Journal of Evidence Based Dental Practice* | Non Specialty | Yes | No |

Table 2: Methodological quality assessment of the included network meta-analyses

| Study | Item1 | Item2 | Item3 | Item4 | Item5 | Item6 | Item7 | Item8 | Item9 | Item10 | Item11 | Item12 | Item13 | Item 14 | Item15 | Item16 | Overall confidence in the results of the review |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lin et al., (2014) | Y | N | N | PY | Y | Y | N | Y | Y | N | Y | N | N | Y | Y | Y | Critically Low |
| Pulikkotil et al., (2018) | Y | Y | N | PY | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Moderate |
| Nagendrababu et al., (2019a) | Y | Y | Y | PY | Y | Y | Y | Y | Y | N | Y | Y | Y | N | Y | Y | Moderate |
| Nagendrababu et al., (2019b) | Y | Y | N | PY | Y | Y | Y | Y | Y | N | Y | N | N | Y | Y | Y | Low |
| Zanjir et al., (2019) | Y | N | N | Y | Y | N | Y | Y | Y | N | Y | Y | Y | Y | N | Y | Critically Low |
| Sivaramakrishnan et al., (2019) | Y | Y | N | PY | N | Y | N | Y | Y | N | Y | N | N | N | Y | Y | Critically Low |
| Zanjir et al., (2020) | Y | N | N | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | N | Y | Critically Low |
| Almuthhin et al., (2020) | Y | N | N | PY | Y | Y | N | Y | Y | N | Y | N | N | Y | N | Y | Critically Low |
| de Souza Matos et al., (2021) | Y | Y | N | Y | Y | Y | N | Y | Y | N | N | N | Y | Y | N | Y | Critically Low |
| Dioguardi et al., (2021) | Y | N | N | PY | Y | Y | N | Y | Y | N | Y | Y | Y | Y | N | Y | Critically Low |
| Tedesco et al., (2021) | Y | Y | N | PY | Y | Y | N | Y | Y | N | Y | Y | Y | Y | N | Y | Critically Low |
| Khater et al., (2021) | Y | Y | Y | PY | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | High |

Y – Yes; N – No, PY - Partial Yes. Note: "Item 1- Did the research questions and inclusion criteria for the review include the components of PICO? ; Item 2- Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? ; Item 3- Did the review authors explain their selection of the study designs for inclusion in the review?; Item 4- Did the review authors use a comprehensive literature search strategy?; Item 5- Did the review authors perform study selection in duplicate?; Item 6- Did the review authors perform data extraction in duplicate?; Item 7- Did the review authors provide a list of excluded studies and justify the exclusions? ; Item 8- Did the review authors describe the included studies in adequate detail? ; Item 9- Did the review authors use a satisfactory technique for; Item 10- Did the review authors report on the sources of funding for the studies included in the review?; Item 11- If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?; Item 12- If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?; Item 13- Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?; Item 14- Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?; Item 15- If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review; Item 16- Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? " (Shea et al., 2017).

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