

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository:<https://orca.cardiff.ac.uk/id/eprint/148293/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Nagendrababu, Venkateshbabu, Abbott, Paul V., Boutsioukis, Christos, Duncan, Henry F., Faggion, Clovis M., Kishen, Anil, Murray, Peter E., Pulikkotil, Shaju Jacob and Dummer, Paul M.H. 2022. Methodological quality assessment criteria for the evaluation of laboratory-based studies to be included in systematic reviews within the specialty of Endodontology: a development protocol. *International Endodontic Journal* 55 (4) , pp. 326-333. 10.1111/iej.13682

Publishers page: <https://doi.org/10.1111/iej.13682>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



Methodological quality assessment criteria for the evaluation of laboratory-based studies to be included in systematic reviews within the specialty of Endodontology: a development protocol

Venkateshbabu Nagendrababu¹, Paul V. Abbott², Christos Boutsoukis³, Henry F Duncan⁴, Clovis M. Faggion Jr⁵, Anil Kishen⁶, Peter E. Murray⁷, Shaju Jacob Pulikkotil⁸, Paul M.H. Dummer⁹

¹Department of Preventive and Restorative Dentistry, College of Dental Medicine, University of Sharjah, Sharjah, UAE; ²UWA Dental School, University of Western Australia, Nedlands, Australia; ³Department of Endodontology, Academic Centre for Dentistry Amsterdam (ACTA), University of Amsterdam and Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; ⁴Division of Restorative Dentistry, Dublin Dental University Hospital, Trinity College Dublin, Dublin, Ireland; ⁵Faculty of Dentistry, Department of Periodontology and Operative Dentistry, University Hospital Münster, Münster, Germany; ⁶Faculty of Dentistry, University of Toronto, Toronto, Ontario, Canada; Mount Sinai Hospital, Toronto, Ontario, Canada; ⁷Private Consultant, Fort Lauderdale, FL, USA; ⁸School of Dentistry, International Medical University, Kuala Lumpur, Malaysia, ⁹School of Dentistry, College of Biomedical and Life Sciences, Cardiff University, Cardiff, UK.

Corresponding author

Venkateshbabu Nagendrababu

Department of Preventive and Restorative Dentistry, College of Dental Medicine, University of Sharjah, Sharjah, UAE.

E mail: hivenkateshbabu@yahoo.com, vnagendrababu@sharjah.ac.ae

Keywords: Endodontology, laboratory study, methodological quality, root canal, systematic reviews

Running title: Methodological quality criteria for laboratory-based studies

Funding: The authors declare that there no funding was received.

Ethical statement: The study did not require ethical approval.

Conflict of Interest: The authors deny any conflicts of interest related to this study.

Author contribution

Study conception and design – VN, PD

First draft of the manuscript - VN, PA, CB, HD, CF, AK, PM, SP, PD

Final approval of the manuscript - VN, PA, CB, HD, CF, AK, PM, SP, PD

ORCID ID

Venkateshbabu Nagendrababu -0000-0003-3783-3156

Paul V Abbott - 0000-0001-5727-4211

Christos Boutsoukis - 0000-0002-1347-1034

Henry F Duncan -0000-0001-8690-2379

Clovis M. Faggion Jr - 0000-0001-8323-909X

Anil Kishen- 0000-0002-6953-2633

Peter E. Murray-0000-0002-5874-2926

Shaju Jacob Pulikkotil - 0000-0001-5727-8255

Paul M.H. Dummer - 0000-0002-0726-7467

Methodological quality assessment criteria for the evaluation of laboratory-based studies included in systematic reviews within the specialty of Endodontology: a development protocol

Abstract

High quality systematic reviews in the field of Dentistry provide the most definitive overarching evidence for clinicians, guideline developers and healthcare policy makers to judge the foreseeable risks, anticipated benefits, and potential harms of dental treatment. In the process of carrying out a systematic review, it is essential that authors appraise the methodological quality of the primary studies they include, because studies which follow poor methodology will have a potentially serious negative impact on the overall strength of the evidence and the recommendations that can be drawn. In Endodontology, systematic reviews of laboratory studies have used quality assessment criteria developed subjectively by the individual-authors as there are no comprehensive, well-structured, and universally accepted criteria that can be used objectively and universally to individual studies included in reviews. Unfortunately, these subjective criteria are likely to be inaccurately-defined, unreliably-applied, inadequately-analysed, unreasonably-biased, defective, and non-repeatable. The aim of the present paper is to outline the process to be followed in the development of comprehensive methodological quality assessment criteria to be used when evaluating laboratory studies (research not conducted *in vivo* on humans or animals) that should be included in systematic reviews within Endodontology.

The development of new methodological quality assessment criteria for appraising the laboratory-based studies included in systematic reviews within Endodontology will follow a three-stage process. First, a steering committee will be formed by the project leaders to develop a preliminary list of assessment criteria by

modifying and adapting those already available, but with the addition of several new items relevant for Endodontology. The initial draft assessment criteria will be reviewed and refined by a Delphi Group (n=40) for their relevance and inclusion using a nine-point Likert scale. Second, the agreed items will then be discussed in an online or face-to-face meeting by a group of experts (n=10) to further refine the assessment criteria. Third, based on the feedback received from the online/face-to-face meeting, the steering committee will revise the quality assessment criteria and subsequently a group of authors will be selected to pilot the new system. Based on the feedback collected, the criteria may be revised further before being approved by the steering committee. The assessment criteria will be published in relevant journals, presented at national and international congresses/meetings, and will be freely available on a dedicated website. The steering committee will update the assessment criteria periodically based on feedback received from end-users.

Keywords: Endodontology, laboratory study, methodological quality, root canal, systematic reviews

Methodological quality assessment criteria for the evaluation of laboratory-based studies included in systematic reviews within the specialty of Endodontology: a development protocol

Introduction

Systematic reviews of the primary research literature are essential to summarize evidence relating to the efficacy, effectiveness, and safety of health care interventions, accurately and reliably (Liberati et al., 2009). A systematic review is based on a clearly formulated question, identifies relevant primary studies, appraises their quality, summarizes the evidence using an unbiased objective methodology and interprets the results accordingly (Khan et al., 2003). It is the systematic methodological approach that distinguishes systematic reviews from biased subjective narrative reviews and commentaries (Akobeng 2005). Unfortunately, the clarity and transparency of many systematic reviews is not optimal with poor methodological quality diminishing their value (Ho et al., 2021, Wasiak et al., 2017).

It is fundamental that authors use accurately-defined, reliably-applied, adequately-analysed, unbiased, objective, non-defective, consistent, repeatable and generalisable assessment criteria to appraise the methodological quality of primary studies that are included in a systematic review. This is because a flawed analysis destroys the validity of their conclusions. These serious problems can increase the risks of creating defective recommendations with the potential to harm patients (Hartling et al., 2009). Authors must rigorously apply assessment criteria to screen the quality of the primary studies that are to be included within a systematic review. Importantly, authors of systematic reviews should use appropriate analytic criteria when assessing the quality of the individual studies they include and then consider the findings of the resultant quality assessments when summarising and interpreting the overall results of their review (Shea et al., 2007, 2017). Unfortunately, the most common pitfalls in systematic reviews

submitted to the leading Endodontic journals is that the authors fail to consider two key elements of the AMSTAR 2 tool (AMSTAR: A MeaSurement Tool to Assess systematic Reviews; Shea et al., 2017) when assessing the quality of the primary studies they include (V. Nagendrababu, P.M.H Dummer, Unpublished data), that is:

1. “If meta-analysis was performed did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis?”
2. “Did the review authors account for risk of bias in individual studies when interpreting/ discussing the results of the review?”

A high-quality primary study has a well-designed methodology and evidence of meticulous objectivity, accuracy, reliability, and complete and unbiased data analysis and interpretation that produces consistent, repeatable and generalisable results. The internal validity of a study can be destroyed because of an uncontrolled risk of bias which distorts the results or through analytical errors that distort and misrepresent the results (Whiting et al., 2017). The applicability of the results of a specific study to other contexts influence its external validity, which is often referred to as its “generalisability”. The need to objectively report adequately-analysed data is the third important quality parameter of a review, which is directly related to its reproducibility. In general, the more objective, accurate, and reliable the reporting, the greater is the likelihood that a review will be reproducible (Pieper et al., 2021).

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) (<https://gradepro.org>) approach can be used for undertaking systematic reviews, because it is a transparent and structured process used to rate the quality of the clinical evidence from the

primary studies as “High”, “Moderate”, “Low”, and “Very Low”. When using the GRADE approach, the risk of bias is one of the key domains that helps to define the quality of evidence and is evaluated along with several other domains, including inconsistency, indirectness, imprecision, and publication bias (Guyatt et al., 2008). The methodological quality assessment of primary studies that are included within systematic reviews can provide an indication of the strength (reliability and repeatability) of the evidence on which the conclusions of the review are based (Higgins & Green, 2011). However, GRADE; is unsuitable for the analysis of laboratory studies because its endpoints are focussed solely on clinical treatment interventions.

The use of an expert consensus to develop structured and objective analytical criteria for the methodological quality assessment for systematic reviews has the advantage that it will allow more reliable and consistent quality assessments to evaluate laboratory-based studies, irrespective of the authors or subject matter (Whiting et al., 2017).

Quality vs risk of bias

Confusingly, the terms “quality” and “bias” have been used interchangeably to grade the validity of the methodological conditions of the primary studies included within a systematic review. The overall quality of a study is mainly based on three factors: internal validity (risk of bias), external validity and reporting quality (Whiting et al., 2017). The methodological quality assessment determines how well a primary study was designed and executed to prevent systematic errors or bias. A risk of bias can arise from critical flaws in the methodological design, unreliable or non-reproducible methods, improper or incomplete data analysis, the faulty interpretation of the results, or improper or incorrect reporting of the conclusions (Hartling et al., 2009).

Internal validity vs external validity

The internal validity of a study describes the ability of the methodological design, methods, and data analysis to answer research questions with minimal bias. Whereas the external validity of a study describes the ability of the results to be generalized for all similar studies (Andrade, 2018). In the simplest of terms, internal validity measures how accurately a study can answer a research question, whereas external validity measures how accurately the findings can be applied universally. External validity has two concepts: generalisability and applicability. “When the concern is how confidently we can extend the results from a sample to the population from which the sample was drawn, the problem is one of *generalisability*. When the concern is how confidently I can use inferences drawn from study participants in the care of patients drawn from any populations, the problem is one of *applicability*” (Murad et al., 2018).

The methodological quality assessment criteria known as “critical appraisal tools” are widely used in the evidence-based literature within Medicine and Dentistry. The tools were specifically created for various study designs, such as cross-sectional studies, case control studies, cohort studies, case reports/series, and diagnostic accuracy studies (e.g. <https://jbi.global/critical-appraisal-tools>). These critical appraisal tools were created by the Joanna Briggs Institute, an international research organisation at the University of Adelaide, South Australia. The quality assessment criteria known as the “Newcastle Ottawa Scale,” is widely used to appraise the quality of nonrandomised studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The Newcastle Ottawa Scale was developed through a collaboration between the Universities of Newcastle, Australia and Ottawa, Canada.

Other popular assessment criteria that can be used to analyse the risk of bias, including the Cochrane risk of bias tool for randomised trials (RoB 2.0) (Higgins et al., 2016), the ROBINS-I

tool for assessing the risk of bias in non-randomized studies of interventions (Whiting et al., 2016), and the QUADAS-C tool for assessing risk of bias in comparative diagnostic accuracy studies (Yang et al., 2021).

Reporting quality

The use of quality guidelines for the reporting of studies can improve the accuracy, completeness and transparency of manuscripts describing primary research projects (Sarkis-Onofre et al., 2015). In general, reporting guidelines provide advice on scientific writing and what information should be included in a manuscript (Simera et al., 2010). Some examples include the Consolidated Standards of Reporting Trials (CONSORT), which is commonly used for reporting randomised clinical trials (<http://www.consort-statement.org>) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), which is widely used to improve the reporting quality of systematic reviews and meta-analyses (<http://www.prisma-statement.org>).

The Preferred Reporting Items for study Designs in Endodontology (PRIDE) is a suite of reporting guidelines developed for various study designs exclusively for the speciality of Endodontology including randomised trials, animal studies, laboratory studies and case reports (<https://pride-endodonticguidelines.org>). The guidelines can provide valuable assessment criteria for reviewers and editors of journals when they assess the suitability of manuscripts for publication within the speciality of Endodontology.

The Preferred Reporting Items for Laboratory studies in Endodontology (PRILE) 2021 guidelines (Nagendrababu et al., 2021) were developed to guide authors on how to select the

most appropriate experimental methods, how to analyse and interpret the results and how to report laboratory studies in Endodontology. However,, they were not developed to assess the overall quality of a study. Moreover, the authors of the present paper are unaware of any consensus-based methodological quality assessment criteria that can be used for the systematic review of laboratory-based studies exclusively for Dentistry, nor Endodontology.

Little or no consensus has arisen on how to assess the overall quality of the primary studies included in systematic reviews, because many authors of systematic reviews of dental laboratory studies have a history of developing their own methodological quality assessment criteria, or uniquely modifying existing criteria from *in vivo* studies or clinical trials (Tran et al., 2017). Confusingly, many manuscripts use the words “*in vitro*”, “*ex vivo*” and “laboratory” interchangeably, even though they have different meanings. In Latin, “*in vitro*” means ‘within glass’, which essentially means in test tubes, cell culture flasks, pipettes, and assay plates, In Latin, “*ex vivo*” means ‘out of the living’, which refers to experiments carried out in or on tissue explants or fluids collected from an organism, e.g. extracted teeth, saliva. The word ‘laboratory’ has a much broader meaning because it is used to describe any [study that was not conducted *in vivo* on human subjects or animals and is a better](#) term to use in order to capture all types of relevant studies. For example, “Tooth discoloration induced by different calcium silicate-based cements: A systematic review of *in vitro* studies” (Możyńska et al., 2017) should have referred to “laboratory” studies, rather than “*in vitro*” studies as the study were not carried out in test tubes.

The common criticism of systematic reviews of laboratory-based studies suggests that these studies are not *in vivo*, and therefore their limitations prevent them from producing any results or conclusions with a direct clinical relevance. This problem of clinical translation can also be described in another way: any systematic review of laboratory studies which reported a clinical relevance, has overgeneralized, and overemphasised its findings. Nevertheless, despite

these criticisms, systematic reviews of laboratory studies can have a major role in establishing the need for clinical studies and generating hypotheses to be tested (Elshafay et al., 2019).

Systematic reviews of laboratory studies on clinically relevant topics in Endodontology are beneficial, for example: to identify why some intra-canal medicaments are more effective than others for disinfecting root canal pathogens; to establish effectiveness of root canal irrigant activation devices, to establish appropriate parameters for effective irrigant activation, to prevent potential health hazards to human subjects from novel biomaterials, to examine the biological responses of dental pulp stem cells after treatment with new medicaments; to characterize the metallurgy of root canal instrument with its instrumentation efficiency and criteria for failure, to select rotary instruments that improve root canal centring to help prevent potential root perforations; to compare the preclinical effectiveness of irrigants to disinfect, debride, and to remove necrotic tissue from root canals. Some of these comparative tests are used for regulatory approvals while introducing newer products in the dental market.

Systematic reviews of laboratory studies not conducted *in vivo* on humans or animals have the potential to identify gaps in the clinical evidence-base, while highlighting the inconsistencies in methodology. For example, identifying the lack of knowledge on why some endodontic treatments are more prone to failure; why some instruments are more susceptible to fracture than others. What role does metallurgy and instrument design have on instrument fracture? Further, these studies may also highlight limitations in the design of clinical studies, such as heterogeneity, bias, poorly formulated research questions, or limitations for collecting optimum samples for analysis or improper comparisons etc. As a reflection of these advantages, during 2021, several systematic reviews of laboratory-based studies were published in Endodontology albeit with a range of methodologies (Bohrer et al., 2021, de Jesus Oliveira et al., 2021, Portela et al., 2021, Uzunoglu-Özyürek et al., 2021, Sanz et al., 2021, Tavares et al., 2021).

Currently, the methodological quality assessment criteria used for systematic reviews of laboratory-based studies in Endodontology, have modified and adapted the existing methodological tools from clinical trials (e.g. Cochrane tool, Joanna Briggs Institute Clinical Appraisal Checklist for Experimental Studies) to the specific requirements of the laboratory studies. For example, in the systematic review by Neelakantan et al., (2018) the authors assessed the methodological quality in laboratory-based studies by modifying and adapting the Cochrane criteria, whereas another laboratory-based systematic review (Yaylali et al., 2015) used the Joanna Briggs Institute Clinical Appraisal Checklist for Experimental Studies. Despite the logical enterprise of these authors, the application of clinical quality assessment tools is likely to be inappropriate when used for systematic reviews of laboratory-based studies because clinical specificity limits their use for the assessment of purely laboratory work, because the criteria are distinct and completely different.

Due to these fundamental problems and criticisms, there has been no consensus or guidance for authors of laboratory-based systematic reviews when using methodological quality assessment criteria. Therefore, the goal of this project is to develop methodological quality assessment criteria for the evaluation of laboratory-based studies included in systematic reviews within Endodontology,.

The development of high-quality methodological assessment criteria for systematic reviews and/or meta-analyses of laboratory-based studies will benefit authors, reviewers, readers, and ultimately help guide the future direction of clinical trials for the development of improved and more successful endodontic treatments. Hence, the present publication describes the process to be followed to develop comprehensive methodological quality assessment criteria

for laboratory-based studies included (studies not conducted *in vivo* on humans or animals) in systematic reviews within the specialty of Endodontology.

Methodology

The development of the new methodological quality assessment criteria for evaluating laboratory-based studies included in systematic reviews within Endodontology will follow a three-stage process (Whiting et al., 2017).

Stage 1: Initial steps

The project leaders (VN, PD) performed a comprehensive literature search in three electronic bases (PubMed, EbBSCOhost and SCOPUS) using a combination of the following key words: “root canal”, Endod*, “methodological quality”, quality, “risk of bias”, “systematic review”, “*in vitro*”, “*ex vivo*” and laboratory. No specific and dedicated assessment criteria were found for the evaluation of the quality of laboratory-based studies included in systematic reviews, exclusively for Endodontology. The project leaders formed a steering committee, consisting of individuals who satisfied at least one of the following criteria:

1. Published at least 25 laboratory-based studies (or) 10 literature reviews within the specialty of Endodontology;
2. Involved in developing one or more methodological/reporting guideline or quality assessment tool;
3. Published at least 5 articles related to methodological/reporting guidelines or quality assessment tools;
4. Served as an Editor-in-Chief or Associate Editor for an international, peer-review journal;

5. A minimum of 5 years of experience as a methodologist working on study designs.

In total, eight experts, including the project leaders (PA, CB, PD, HD, CF, AK, PM, VN) formed the steering committee. The initial focus of the steering committee will be to decide the scope and aims of the methodological quality assessment criteria to be developed (Whiting et al., 2017), that is:

1. Will this research project consider the impact of the methodological quality safeguards on the internal validity (risk of bias) of a laboratory study?
2. How will quality, risk of bias and other potential components be defined?
3. What type of structure will be adopted for the tool, e.g. simple checklist design or a domain-based approach?
4. How will quality of individual items be rated within the criteria?

Stage 2: Development of the quality assessment criteria

The steering committee will develop an initial draft of the quality assessment criteria by modifying and adapting the published criteria from other disciplines and include several unique criteria that are relevant for Endodontology. The steering committee will also evaluate the quality assessment criteria used in the published systematic reviews of laboratory-based studies in Endodontology and consider including any elements relevant to the new assessment criteria. Once the initial draft quality assessment criteria have been developed and agreed by the steering group, a consensus process involving a large group of experts (n=40) will be followed using an online Delphi system.

Eligibility criteria for the Delphi panel

The members of the Delphi panel will be selected based on whether they satisfy at least one of the following criteria:

- i. Experience of developing quality assessment criteria;
- ii. A minimum of 2 years of experience as a methodologist working on study designs;
- iii. Published at least five laboratory-based studies in Endodontology;
- iv. Published at least three literature reviews in Dentistry;
- v. Published at least 2 articles related to methodological/reporting guidelines or quality assessment criteria;
- vi. A minimum of 10 years of clinical/research/academic experience in Dentistry.

The steering committee will ensure the participants used to conduct the Delphi process will be balanced in terms of skills, knowledge and experience.

Online Delphi process

The Delphi panel (n=40) will engage in a structured Delphi consensus process to refine the checklist items/domains to be included in the new methodological quality assessment criteria using an iterative online process. An information document will be prepared by the steering committee and shared with the panel to explain the entire online Delphi process and highlight their role in building consensus on the inclusion or exclusion of the draft checklist list of items/domains. The panel will be asked to provide their views on the clarity and suitability of each checklist list of items/domains, independently using a dichotomous scale (yes or no) and a

9-point Likert scale (1-definitely not included to 9-definitely included) respectively. The panel members will be requested to provide feedback and comments on each item/domain and suggest additional items/domains. Items/domains that receive a score between 7 and 9 by at least 70% of large group members or items/domains with a score of 1-3 by less than 30% members will be included whereas, items/domains receiving a score between 1 and 3 by more than 70% of members or a score of 7 to 9 by less than 30% of members will be excluded (Agha et al., 2017, Nagendrababu et al., 2021). Where necessary, those checklist items/domains associated with feedback/comments by the panel will be revised by the steering group and included in a further round of the Delphi exercise. The same process will continue until all the items/domains achieve the set inclusion or exclusion standard and agreement (Nagendrababu et al., 2021).

Online or face-to-face meeting

Following the online consensus process, not less than 10 individuals will be invited to attend an online or face-to-face meeting, to discuss and validate the items/domains (Whiting et al., 2017). The members of this group will be subject to the same eligibility criteria as the Delphi panel, with the possibility that some will participate in both groups. The project leaders will share the results of the online Delphi process, date and time of the meeting at least seven days before the event. The project leaders will present the results of the online Delphi process and facilitate a discussion on the outputs of the Delphi panel. The discussions will not attempt to agree the detailed wording of the final criteria but focus more on the scope and general format; they will also include the plans for disseminating the quality assessment tool, and a publication strategy. The steering committee will demand supporting evidence from the members should any new items/domains be proposed for inclusion at this stage. Further debate will centre around how feedback will be managed and the development of a dedicated website to support the project.

Draft quality assessment tool and guidance document

Based on the feedback received from the online/face-to-face meeting, the steering committee will revise and finalise the quality assessment criteria. Subsequently, the steering committee will develop clear guidance to explain each item/domain in the quality assessment criteria to improve understanding.

Piloting and refinement

The project leaders will identify individuals with a broad range of experience to pilot the new methodological quality assessment criteria in order to ensure it is fit for purpose. Once the criteria have been piloted, the steering committee will take account of any feedback and then finalise the methodological quality assessment criteria.

Stage 3: Dissemination of the methodological quality assessment criteria

The steering committee will disseminate the new methodological quality assessment criteria by:

1. Publishing two papers in a peer-reviewed journal that i. describe the process involved in developing the methodological quality assessment criteria, and ii. explain the rationale for each item/domain and elaborate further by providing examples;
2. Presenting the methodological quality assessment criteria at national and international conferences and meetings;
3. Conducting workshops and webinars to ensure the methodological quality assessment criteria become well-known to end-users;
4. Developing a dedicated website with relevant information and documents;
5. Translating the criteria into various languages;
6. Allowing feedback on the criteria to be posted through the website;

7. Updating/revising the criteria when necessary;
8. Contacting the Editors-in-Chief of relevant journals with a request for them to endorse the quality assessment criteria and include them in their instructions to authors.

References

Agha RA, Borrelli MR, Vella-Baldacchino M, Thavayogan R, Orgill DP; STROCCS Group (2017) The STROCCS statement: strengthening the reporting of cohort studies

in surgery. *International Journal of Surgery* **46**, 198–202.

Akobeng AK (2005) Understanding systematic reviews and meta-analysis. *Archives of Disease in Childhood* **90**, 845-8.

Andrade C (2018) Internal, external, and ecological validity in research design, conduct, and evaluation. *Indian Journal of Psychological Medicine* **40**, 498-9.

Bohrer TC, Fontana PE, Rocha RO, Kaizer OB (2021) Post-space treatment influences the bond strength in endodontically treated teeth: A systematic review and meta-analysis of in vitro studies. *Operative Dentistry* **46**, E132-57.

de Jesus Oliveira LS, de Bragança RM, Sarkis-Onofre R, Faria-e-Silva AL (2021) The effectiveness of the supplementary use of the XP-endo Finisher on bacteria content reduction: a systematic review and meta-analysis. *Restorative Dentistry & Endodontics* **46**, e37.

Elshafay A, Omran ES, Abdelkhalek M, et al. (2019) Reporting quality in systematic reviews of in vitro studies: a systematic review. *Current Medical Research and Opinion* **35**, 1631-41.

Guyatt GH, Oxman AD, Vist GE, et al. (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* **336**, 924–6.

Hartling L, Ospina M, Liang Y, Dryden DM, Hooton N, Seida JK, Klassen TP (2009) Risk of bias versus quality assessment of randomised controlled trials: cross sectional study. *BMJ* **19**, 339.

Higgins JPT, Sterne JAC, Savovic J et al. (2016) A revised tool for assessing risk of bias in randomized trials. *Cochrane Database of Systematic Reviews* **10** (Suppl. 1), 29–31.

Ho L, Ke FY, Wong CH, Wu IX, Cheung AK, Mao C, Chung VC (2021) Low methodological quality of systematic reviews on acupuncture: a cross-sectional study. *BMC Medical Research Methodology* **21**, 237.

Khan KS, Kunz R, Kleijnen J, Antes G (2003) Five steps to conducting a systematic review. *Journal of the Royal Society of Medicine* **96**, 118-21.

Liberati A, Altman DG, Tetzlaff J et al. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine* **21**, 6, e1000100.

Murad MH, Katabi A, Benkhadra R, Montori VM (2018) External validity, generalisability, applicability and directness: a brief primer. *BMJ Evidence-Based Medicine* **23**, 17 -19.

Możyńska J, Metlerski M, Lipski M, Nowicka A (2017) Tooth discoloration induced by different calcium silicate-based cements: A systematic review of in vitro studies. *Journal of Endodontics* **43**, 1593-601.

Nagendrababu V, Murray PE, Ordinola-Zapata R, *et al.* (2021). PRILE 2021 guidelines for reporting laboratory studies in Endodontology: A consensus-based development. *International Endodontic Journal* **54**, 1482-90.

Neelakantan P, Ahmed HM, Wong MC, Matinlinna JP, Cheung GS (2018) Effect of root canal irrigation protocols on the dislocation resistance of mineral trioxide aggregate-based materials: A systematic review of laboratory studies. *International Endodontic Journal* **51**, 847-61.

Pieper D, Heß S, Faggion CM Jr (2021) A new method for testing reproducibility in systematic reviews was developed but needs more testing. *BMC Medical Research Methodology* **21**, 157.

Portela NN, Rech JP, Marchionatti AM, Barasuol JC (2021) Techniques to address fractured instruments in the middle or apical third of the root canal in human permanent teeth: a systematic review of the in vitro studies. *Clinical Oral Investigations* **26**, 1-9.

Sarkis-Onofre R, Cenci MS, Demarco FF, Lynch CD, Fleming PS, Pereira-Cenci T, Moher D (2015) Use of guidelines to improve the quality and transparency of reporting oral health research. *Journal of Dentistry* **43**, 397-04.

Simera I, Moher D, Hoey J, Schulz KF, Altman DG (2010) A catalogue of reporting guidelines for health research. *European Journal of Clinical Investigation* **40**, 35-53.

Sanz JL, Guerrero-Gironés J, Pecci-Lloret MP, Pecci-Lloret MR, Melo M (2021) Biological interactions between calcium silicate-based endodontic biomaterials and periodontal ligament stem cells: A systematic review of in vitro studies. *International Endodontic Journal* **54**, 2025-43.

Shea BJ, Grimshaw JM, Wells GA, *et al.* (2007) Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology* **7**, 10.

Shea BJ, Reeves BC, Wells G, *et al.* (2017). AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* **21**, 358.

Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I (2016) ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* **12**, 355.

Tavares S, Pintor A, Mourão CF, *et al.* (2021) Effect of different root canal irrigant solutions on the release of dentin-growth factors: A systematic review and meta-analysis. *Materials*. **14**, 5829.

Uzunoglu-Özyürek E, Küçükkaya Eren S, Karahan S (2021) Contribution of XP-Endo files to the root canal filling removal: A systematic review and meta-analysis of in vitro studies. *Australian Endodontic Journal* Mar 13. doi: 10.1111/aej.12503. Online ahead of print

Wasiak J, Tyack Z, Ware R, Goodwin N, Faggion Jr CM (2017) Poor methodological quality and reporting standards of systematic reviews in burn care management. *International Wound Journal* **14**, 754-63.

Whiting P, Wolff R, Mallett S, Simera I, Savović J. (2017) A proposed framework for developing quality assessment tools. *Systematic Reviews* **6**, 1-9.

Whiting PF, Rutjes AW, Westwood ME, *et al.* (2011) QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of Internal Medicine* **155**, 529–36.

Yang B, Mallett S, Takwoingi Y, Davenport CF, Hyde CJ, Whiting PF, Deeks JJ, Leeflang MMG, QUADAS-C Group (2021) QUADAS-C: A Tool for Assessing Risk of Bias in Comparative Diagnostic Accuracy Studies. *Annals of Internal Medicine* **174**, 1592-99.

Yaylali IE, Kececi AD, Kaya BU (2015) Ultrasonically activated irrigation to remove calcium hydroxide from apical third of human root canal system: a systematic review of in vitro studies. *Journal of Endodontics* **41**, 1589-99.