Systematic Reviews in Dental Research. A Guideline.

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Background: *A systematic review aims to combine outcome data from published studies in a population. It is based on a number of steps and although there are numerous advantages in systematic review studies, dentists have been finding difficulties in performing them.* ***Objective:*** *Taking into account the misconceptions and difficulties in conducting this kind of study, this article aims to guide readers for understanding, performing, and interpreting comprehensive systematic reviews in dental research.*
Keywords: *systematic review, methodology, dentistry.*

INTRODUCTION

An evidence-based approach to provide medical care has been well accepted in other healthcare fields, and this method has also gained acceptance in dentistry.[1] It has significant advantages. First, it will serve patients using specific interventions supported by clinically relevant scientific evidence. Second, it will increase the standing of the profession because it will ensure that proven interventions are offered.[2] Evidence-based dentistry is an advance to oral healthcare that requires the integration of systematic assessments of clinically relevant evidence with the dentist's clinical expertise and the patient's treatment needs and preferences.[3]

Reviews that are not systematically undertaken may be based only on the partial review of the literature or reflect the personal values orviews of the authors. Systematic reviews are considered scientific investigations of primary studies and should be carried out according to a pre-defined plan in order to include all relevant articles, appropriate primary studies, and synthesized data.[4] They should be carried out using explicit methods to gather together high quality research evidence to minimize bias. By doing so, they provide quality comprehensive summaries of available evidence to base clinical treatment decisions.[5]

Data synthesis from existing primary research and well-conducted reviews is the main objective of systematic reviews and meta-analyses.[6] This type of analysis is a must for decision-making processes in healthcare and delivery, to implement new policies or uphold existing ones- These reviews will also help to develop new primary research,[7] reducing bias and enabling researchers to reduce the ever-increasing volume of both published and unpublished articles into manageable summaries relating to specific clinical questions.[8]

Although there are numerous advantages in systematic review studies, and taking into account the misconceptions and difficulties in conducting this kind of study, this article aims to assist readers in understanding, performing, and interpreting systematic reviews.

Preparing a Systematic Review

A systematic review is a methodologically prepared piece of primary research. First, authors must clearly state the question they are trying to answer and define the inclusion and exclusion criteria for individual studies.[4] In this case, the process of creating a systematic review should begin with a clear protocol describing the background, the hypothesis to be tested, and the methodology to be used, just like any other scientific study. The authors should discuss the strategy for conducting searches for all studies, trialsand databases how they will be identified, selected, and evaluated.[8]

The author can carry out the review following the steps presented below.

Step 1 – Formulation of a focused question

The most appropriate way of addressing any clinical question is through a systematic review of the relevant evidence.[9] The first step involves the formulation of important clinical questions that dental clinicians and their patients face in everyday practice. This focused question helps to clarify what the author really wants or needs to be answered. To choose an adequate question, there is a framework that breaks the question into four componentswith the acronym PICO/PECO format (Chart 1): 1- Patient/Problem, 2 –Intervention/ Exposition, 3 – Comparison, and 4 – Outcomes.[8] Breaking the question into its componentsmakes it easier to focus on answering the problem, and also makes it easier to design an efficient search.[10]

In summary, the first step in evidence-based dentistry is to design a well-built clinical question, taking into account the dilemmas in diagnosis, therapy, prognosis, and prevention issues.[8] A successful and rigorous systematic review starts with the development of a clear question structured using the PICO/PECO format (Chart 1).

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Chart 1. A stepwise approach to systematic reviews "PICO/PECO"

P Patient population – For which group do you need information?
EXAMPLE: Schoolchildren
I Intervention (or **E**xposure- in case of observational studies) – What medical intervention do you need to study?
EXAMPLE: Fluoride therapy
C Comparison - What is the evidence that the proposed intervention produces better or worse results than no intervention, or a different type of intervention?
EXAMPLE: Influence on the remineralization process
O Outcomes - What is the effect of the intervention?
EXAMPLE: Caries reduction

Note: Information based on Hassig[11] and modified by the present authors.

Step 2 – Determination of the inclusion and exclusion criteria

When designing a systematic review or its protocol, authors should discuss and develop a series of inclusion and exclusion criteria related with their review question. At this point, researchers should be cautious of any bias they might introduce into the review by adding certain eligibilitycriteria. The selected criteria should logically proceed from the focused question; it should define the population, the intervention/exposition, the comparisons, and sometimes the study design of interest.[7]

Researchers should bear in mind that a single failed eligibility criterion is sufficient for a study to be excluded from a review. In practice, therefore, eligibility criteria for each study should be assessed, and if case study does not meet one of these criteria, it should be excluded at this stage.[12] All the inclusion and exclusion criteria must be documented in the method section.

Differences between patients, interventions, or outcome measurements, as well as the quality of the individual trials, constitute the main reasons for heterogeneity between the studies. In these cases, the authors should try to determine why it is occurring and make a decision about the eligibility criteria.[4,8]

Different types of systematic reviews can be found in dental literature and in accordance with the aims of the review; one can search for diagnostic, prevalence, etiology, prognosis, prevention, treatment modalities among many others. Three examples of published selection criteria for studies to be included and excluded in a systematic review in dentistry are presented below:

Example 1 – Treatment Study

In a systematic review developed by Antonio *et al* [13] the authors tested the efficacy of xylitol candies and lozenges in preventing caries among individuals. Only controlled clinical trials (CCTs) and randomized controlled clinical trials (RCTs) of at least 1 year's duration.

To be eligible, the studies must have had the following characteristics: (a) the subjects must have consumed candies or lozenges containing xylitol; (b) there were no restrictions on study populations; (c) the control group included subjects who had not received any kind of intervention or who had received a placebo (e.g., sorbitol), or had received any preventive procedures (such as sealants, supervised tooth brushing with fluoride dentifrices, oral health instructions); and (d) the study provided concurrent comparisons of incremental percentages of dental caries according to decayed, missing, and filled surface (DMFS) scores (World Health Organization criteria). In addition, articles of trials not performed on humans, or on experimental group exposed to products other than candies or lozenges containing xylitol (such as chewing gum and chlorhexi-dine) were excluded.

Example 2- Prevalence Study

Tannure *et al,*[14] in a prevalence study, aimed to assess whether individuals born with non-syndromic oral clefts display a higher frequency of dental anomalies. Observational controlled study designs composed of non-syndromic forms of oral clefts matched for dental anomalies in primary and/or permanent teeth were included without language restrictions. Textbooks, dissertations, case reports, case series, review articles, and abstracts were excluded.

Example 3 – Prognosis study

In a study by Marquezan *et al* [15] the influence of bone mineral density on the primary stability of dental implants was investigated. The inclusion criteria comprised observational clinical studies conducted in patients who received dental implants for rehabilitation; studies that evaluated the association between bone mineral density (prognostic factor) and implant primary stability (outcome); bone density assessment performed by measurement of Hounsfield units using cone bean computed tomography; and dental implant primary stability evaluated by implant stability quotient value (Ostell, Integration Diagnostics, Gothenburg, Sweden), Periotest value value (Periotest, Medizintechnik Gulden, Modautal, Germany) or insertion torque measurement. Studies that evaluated implant stability and bone density but did not verify their association were excluded from this systematic review.

In summary, the inclusion/exclusion criteria must be applied to all the studies retrieved by the searches through a well-defined search strategy. Firstly, the decisions are usually made using the titles and abstracts of the articles retrieved. Those that are clearly irrelevant or do not fulfill the inclusion criteria should be promptly excluded at this stage. Only the full text of relevant studies must be obtained, read, and classified according to its methodological quality, and redefined as adequate or not to be included in the review. This process is frequently represented using a flow diagram.[16]

Step 3- Search Strategy

After the research question has been defined, the search strategy must be determined, taking into account inclusion and exclusion criteria. This search should also be based on the acronym PICO/PECO format, and should be developed in consultation with librarians or someone experienced in searches. Search strategies are usually iterative and may benefit from: (1) trial searcher using various combinations of search terms or key words derived from the research question; (2) preliminary searches aimed at both identifying existing systematic reviews and assessing the volume of potentially relevant studies; and (3) consultations with experts in the studied field.[17,18]

An exhaustive search is performed to find all possibly relevant studies. A general approach is to break down the question

into individual facets such as: population, intervention, outcomes, study designs, and others. This is followed by drawing up a list of synonyms, abbreviations, and alternative spellings without language restrictions.[18]

Many electronic databases can be searched using subject terms assigned by indexers. The most commonly used are Medline or PubMed, Embase, Metapress,Web of Science, Biosis, Scirus, eTblast, Google Scholar, Cochrane databases of randomized trials or systematic reviews, DARE (Database of Abstracts of Reviews of Effectiveness, HTA (Health Technology Assessment Database),as well as language-specific databases, such as LILACS (Literatura Latino Americana e do Caribe emCiências da Saúde).[8,17]

Sophisticated search strings can then be constructed using Boolean AND's and OR's in the electronic databases, but this is not sufficient. Other sources of evidence must also be searched (sometimes manually) including: reference lists from relevant primary studies and review articles; grey literature such as System for Information on Grey Literature in Europe Archive (SIGLE); conference proceedings; research registers and the internet. In addition, it is important to emphasize that although review articles are excluded from the search, the reference lists of review articles can help to identify additional primary studies to be reviewed by a member of the review team. As additional references are identified, they should be added to the citation manager software (e.g., Reference Manager or TrialStat's SRS) with an indication of where they were located,[19] or they can be manually added to the group of references still selected.[18]

Standardized subject terminologies can be useful in retrieving articles that may use different words to describe the same concept and they can provide information beyond that which is simply contained in the words of the title and abstract.

Once the searches have been run, repeated references should be removed, and all references are assigned a number identifying the study. Careful citation counts are made at each step along the way. These citations counts are important for final reporting, when all identified citations must be accounted for (i.e., whether they were duplicated, screened out by reviewers, or were ultimately included in the review).[19] Also, a flow chart showing the number of studies/papers remaining at each stage is a simple and useful way of documenting the study selection process (Figure 1).[16]

Systematic reviews are quite work-intensive and search methodology must be based on research about retrieval practices. Expert searchers are an important part of the systematic review team, and are crucial throughout the review process, from the development of the proposal and research question to publication.[19] After the selection of possible articles to be included in the review, the next step involves the review of the titles alone to select the manuscripts that will be included in the systematic review. This should be done by two reviewers working independently, using the selection criteria previously developed, Then, the results of the two reviewers are compared.

Titles should be discarded only if the two reviewers agree that the title is irrelevant; if either feels the study may be eligible, then the title should be retained for the next step.

The next stage is to review all abstracts of each selected title. This is again performed by two reviewers working independently, taking into account a checklist of pre-specified study inclusion

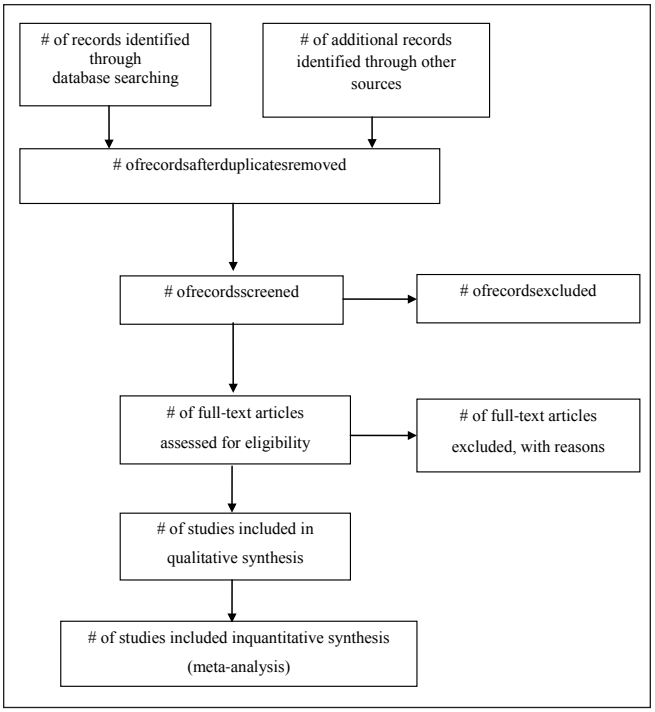

Figure 1. PRISMA Flow Diagram[16]

criteria, as well as reasons for exclusion should also be kept. When this is completed, both lists are compared. Abstracts that both reviewers consider ineligible are discarded, while all other studies should be retained for full-text review.[17]

Step 4- Defining quality assessment and the risk of bias

Quality assessment is an integral part of any systematic review. If the results of a study are biased and an assessment of quality was not performed during its synthesis, then the systematic review will be also biased and deficient.[20] Although almost all scientific studies are flawed in some way, the most important task is to determine whether the flaws, which are inevitable, actually invalidate the findings of the study.[21] Nevertheless, to make a decision based on evidence, all the evidence needs to be acknowledged not just the most easily accessed. It is imperative that expert attention should be given to the synthesis and quality grading of every study as it is a part of the body of evidence concerning an issue.[5] Therefore, quality is a multifactorial concept involving the design, conduct, and analysis of a trial, its clinical relevance, or quality of report.[22] For the success of a systematic review, it is essential to perform an assessment of the quality of individual studies to be included in terms of potential bias and lack of applicability.[20]

Taking all these aspects into account, to evaluate the quality of studies using different designs, questions were developed to answer a general concept and instructions provided specific examples to assist the reviewer. For example, two general questions about validity and reliability are included to assess the potential problems with outcome measurement. For a randomized trial, failure to blind observers or interviewers would result in a limitation of outcome measure validity. For a paper with a time-series design eg. An epidemiological study in which measurements of the same variables are taken at different points in time (e.g. study of social trends); blinding would not be considered in assessing the validity of the outcome

measure, but other issues relevant to validity would be considered. For all questions in the quality of execution section (e.g. method for randomization, initial assembly of comparable or control group, calibration of examiners), if the quality issue, relevant to the study design, is not reported in the systematic review, then the study is limited in that respect.[23]

Quality refers to internal and external validity of the included studies, because its interpretation depends on design, conduction, and analysis (internal validity), as well as on populations, interventions, and outcomes measures (external validity).[7] Careful consideration and appraisal of the methodological characteristics of the primary studies are essential in systematic reviews.[24] However, it is important to balance judgments about such critical reviewing carefully, to avoid excessive criticism that may inappropriately reject valuable clinical evidence.[8]

Internal validity of a review is threatened by bias. Bias can be defined as a systematic error or deviation in results or inferences. It can arise from selection, performance, detection, and attrition.[8,25] As proposed by Hartlig *et al* [24] for interventional studies, the risk of a bias tool is usually based on the following six domains: (1) sequence generation (e.g. a computer-generated list of random numbers, which is generally used for allocation of the participants); (2) allocation concealment – the procedure for protecting the randomization process so that the treatment to be allocated is not known before the patient is entered into the study; (3) blinding (e.g. the experimenter being unaware of which are treatments and which are controls); (4) incomplete outcome data (e.g. missed data about drop-outs; participant's outcome is not available); (5) selective outcome report; and "other sources of bias". Critical assessments of the risk of bias (high, moderate, low – according to the number of bias) should be made separately for each domain (e.g. study conduct bias, detection bias, follow-up bias and others).[24] By selecting only certain trials to include, the authors can introduce a selection bias in their systematic review.[4] In order to avoid a publication bias, unpublished data is important and should be searched by contacting experts in the field, as "negative" studies or those where the treatment shows no significant benefit are less likely to be published.[4]

It is often difficult to critically assess the quality of any one study, particularly if it has a complex methodology or it presents contradictory results.[5] In some cases, the obvious explanation of a study may not be correct due to the presence of confounding factors and flawed interpretations.[21]

Quality assessment can be used to judge the need for further studies; if a systematic review is based on several high-quality studies, the estimated effect of the intervention is likely to be correct and there will be little need for further studies. On the other hand, if there are only low-quality studies, the estimates of effect might be incorrect and there is a need for additional studies of higher quality.[17] The information gained from quality assessment is the basis for determining the strength of inferences, and of assessing scores to recommendations generated within a systematic review with or without a meta-analysis.[7]

The checklists for quality assessment focus on identifying flaws in reviews that might bias the results.[7] Checklists come in a wide variety of forms and can make the assessment of research simpler and more repeatable. Using a checklist to assess a number of publications means that the same questions will be asked about each study, and answers will be expressed in comparable terms.[21] Checklists will also vary depending upon the type of study being assessed and different questions may arise in accordance with the study design (experimental or observational, for instance).[21] Standardized published checklists such as Quadas (Quality Assessment tool for Diagnostic Accuracy Studies),[20] Newcastle-Ottawa (checklist for cohort and case-control studies),[26] National Institute for Health and Clinical Excellence from United Kingdom,[27] Cochrane checklist,[12] among others, and additional quality criteria, such as the Consort (Consolidated Standards of Reporting Trials),[28] Strobe (Straightening the Reporting of Observational Studies in Epidemiology),[29] and Prisma (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[16] should ideally be used in order to improve the systematic review reliability.

Assessment of trials quality is still a controversial issue. Quality scales vary considerably in dimensions and complexity, and combine information from several features in a single numerical value.[25] Although composite quality scales may provide an useful overall assessment according to Jüni *et al* [22] such scales should generally not be used to identify trials of apparent quality or high quality in a given systematic review. For these reasons, as proposed by Cochrane's guidelines, as the component approach examines key dimensions individually, without calculation of a score, should be preferentially chosen.

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) is a valuable tool for developing and presenting summaries of evidence for systematic reviews and recommendations for healthcare bodies. It is an appropriate and helpful method, regardless of the evidence rating, ranging fromvery low to high. It can be used for a wide range of clinical questions, including diagnosis, screening, prevention, therapy, and can also be applied to public health and health systems questions. GRADE begins with an explicit question, including specification of all important outcomes. After the evidence is collected and summarized, it provides explicit criteria for rating its quality, which includes study design, risk of bias, imprecision, inconsistency, indirectness and magnitude or effect.[30]

As observed by Fledstein,[4] systematic reviews are only as good as their included studies. The combination of poorly performed and biased studies will cause misleading and biased results.

Steps 5 and 6 - Tabulation and Data Extraction

This is the process by which the reviewers gather the information from reports of their primary research findings. A data extraction form should be produced to introduce a consistent and systematic element to this procedure. The design of such a form should be undertaken carefully and should be directly related to the question(s) posed for the review. It should include some general information such as the name of the reviewer, bibliographic details of the paper, and the source of the paper. More specific information on the form should include details of the population characteristics, methodological quality of the study, as well as the interventions and the outcomes used. Detailed information on the outcome of the study should contain the number of drop-outs, length of follow up, missing data, information on discrete data (e.g. events, total numbers, *p*-values), and continuous data (e.g. mean, standard error, standard deviation, numbers and *p*-values) and effect measures (e.g. effect size, standardizing response mean).[31]

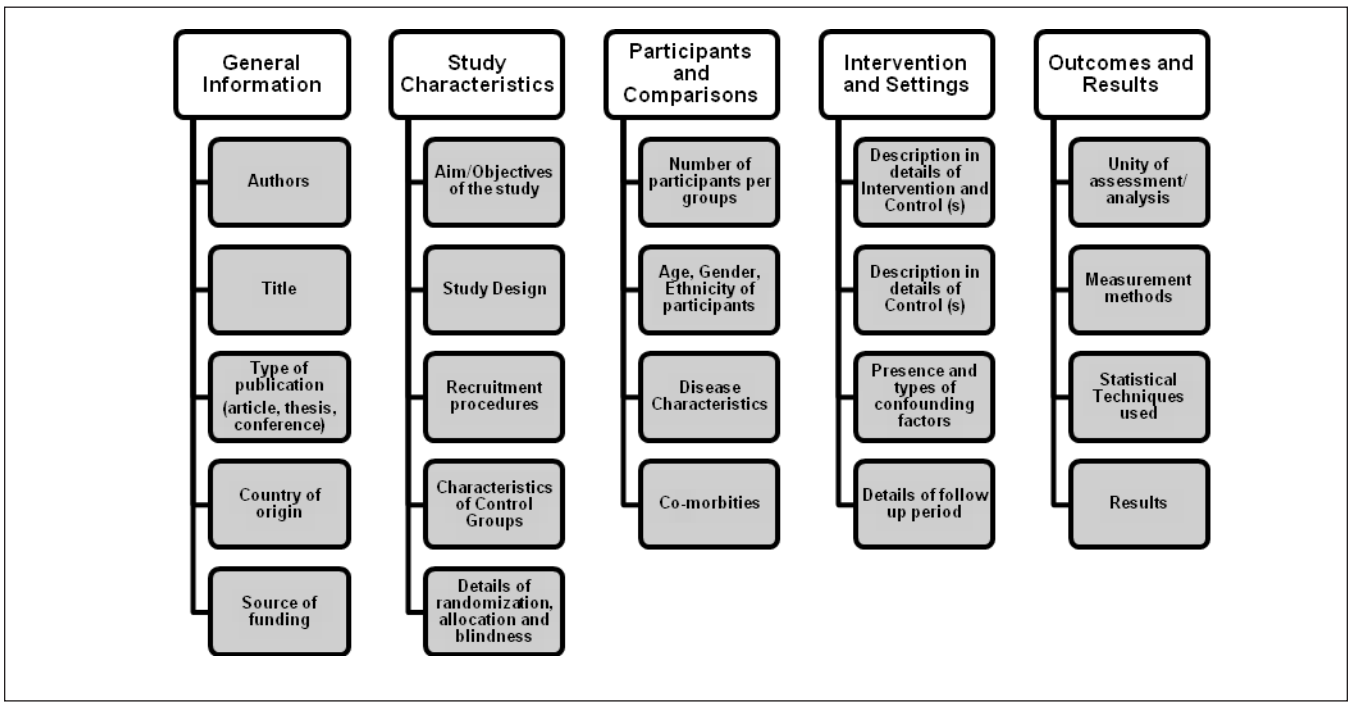

Figure 2. Example of information for data extraction from a treatment effect study

According to Clarkson and Bonetti,[5] synthesizing and summarizing the evidence should be performed independently by two reviewers. They should then agree on a final version of data extraction. An example of information requirement for data extraction is demonstrated in Figure 2.

The first stage of any data extraction is to plan the type of analyses and list the tables that will be included in the report. This will help to identify which data should be extracted and included in the systematic review.[16] Moreover, it is important to emphasize that the extraction of data is linked to the assessment of the study quality; and both processes are often undertaken at the same time.[17]

Step 7- Results of a Systematic Review (Can a meta-analysis be performed?)

Pooling of data is usually narrative, and may or may not involve statistical pooling or meta-analysis,[8] which refers to a statistical analysis of the results from independent studies. Although such analysis usually aims to produce a single estimate of treatment effect,[4,8,32] there are meta-analyses that evaluate the quantitative pooling of data from studies of prevalence,[14] studies of prognosis,[33] and others. By combining the results from the selected studies, a meta-analysis can increase statistical power and provide a single numerical value of the overall research question.[32]

To interpret a meta-analysis, the reader needs to understand several concepts, including effect size, heterogeneity, the model used to conduct the meta-analysis, and the forest plot; a graphical representation of the results (Figure 3).[32] The effect size can be summarized as a measure with no units that indicate both direction and magnitude of the treatment, in case of studies of treatment effect.[12] Statistical heterogeneity occurs when the extracted data of a set of studies vary from one to another.[34]

Considering the models to conduct a meta-analysis, the most frequently used are the fixed- and random-effect models, of which the last one handles statistical heterogeneity differently. The fixed- and random-effects models differ in assumptions related to the observed differences among study results.[8] Therefore, it is important to emphasize that the selected studies (two or more studies) for meta-analysis should be homogeneous to provide an answer with greater accuracy.[35] Nevertheless, if the populations, interventions, conditions or outcomes in the different selected studies for the review are not similar, then the meta-analysis itself may use the referred random-effects methodologies.[17] Heterogeneity of studies, when it is assumed, is ideally explored through subgrouping or meta-regression. This allows those characteristics of studies, which alter the results, to be discerned – for example: a treatment may work better in older adults and poorly in young adults.[8]

In addition, the results of a meta-analysis are generally demonstrated through a forest plot as described above (Figure 3). This kind of graph presents the means and variance for the differencesbetween each study. The line represents the standard error of the difference, the box represents the mean difference and its size is proportional to the number of subjects in the study.[18] A forest plot may also be annotated with the numerical information indicating the number of subjects in each group, the mean difference and the confidence interval of the mean.[8]

In this way, a good meta-analysis does not simply report main effect and moderator tests. It also interprets these findings, and presents how they are consistent or inconsistent with the major hypotheses in the literature. Meta-analyses can greatly aid the literature providing a retrospective summary of what can be found in the existing literature. This should be followed by suggestions of what areas within the literature still need development. A good meta-analysis encourages rather than impedes future investigations.[36]

(Overall caries-preventive effect of xylitol candies/lozenges treatment studies by pooling the 95% confidence intervals. A1 = Alanen *et al* [37] – Group test with xylitol/maltitol candies (treatment

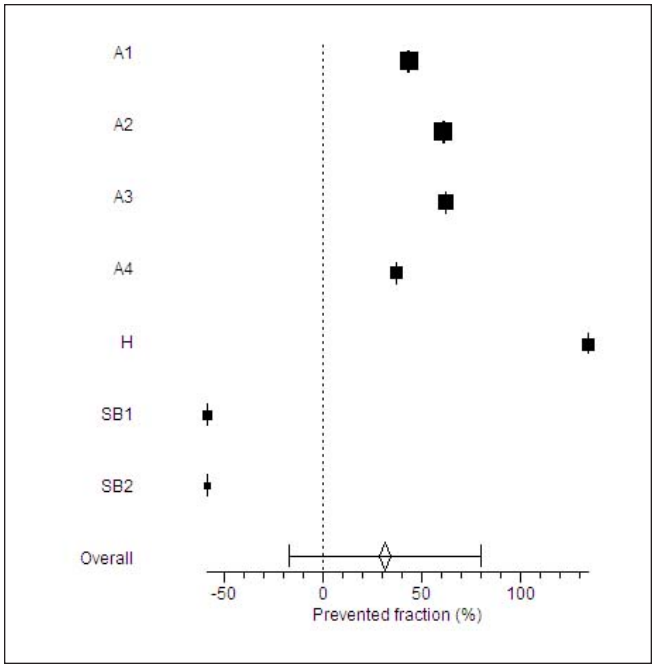

Figure 3: Unpublished plot provided by data from Antonio *et al* [13]

stopped after 2 years); A2 = Alanen *et al* [37] – Group test with xylitol/maltitol candies (treatment stopped after 3 years); A3 = Alanen *et al* [37] – Group test with xylitol/polydextrose candies (treatment stopped after 2 years); A4 = Alanen *et al* [37] – Group test with xylitol/polydextrose candies (treatment stopped after 3 years); H = Honkala *et al* [38] – Group test with xylitol; SB1 = Steckesén-Blicks *et al*.[39] – Group test with xylitol/sodium fluoride; SB2 = Steckesén-Blicks *et al* [38] – Group test with xylitol).

Step 8 – Recommendations

The final step of a systematic review involves interpreting the results, supporting and discussing the evidence and recommendations[40] and writing a succinct report in order to allow readers to judge the validity and implications of the review findings.[7]

Many studies aimed to develop systems to grade the strength of recommendations to assist clinicians in interpreting the strength of the recommendations.[40-42] Although guideline panels provide recommendations for the management of typical patients, treatment decisions involve a balance between benefits versus risks, burdens, and, potentially, costs for patients. For this reason, clinicians need to understand the basis for the recommendations that expert guidelines offer in order to integrate these recommendations with their own clinical judgment, and with individual patient values and preferences.[41] Therefore, recommendations must apply to specific settings and particular groups of patients. Four main factors should be considered when making a recommendation:[42]

- Taking into account the estimated size of the effect for the main outcomes, the confidence limits around those estimates, and the relative value placed on each outcome;
- The quality of the evidence;
- Translation of the evidence into practice in a specific setting, taking into consideration important factors that could be expected to modify the size of the expected effects, such as proximity to a hospital/clinic or availability of necessary expertise;
- Uncertainty about baseline risk for the population of interest.

It is very important to emphasize that although the strength of recommendations is used to give a balance between: -benefits and harms; - quality of evidence; - applicability, - and the certainty of the baseline risk,[42] the strength (or grade) of a recommendation for clinical practice is based on a body of evidence (more than one study). This body of evidence must take into account the level of evidence of individual studies, the type of outcomes measured by these studies (patient-oriented or disease-oriented), the number, the consistency, and mainly, the coherence of the evidence as a whole.[40]

To facilitate performing a systematic review, there is a chart containing a summary of all steps presented below (Chart 3).

DISCUSSION

Several types of structured reviews can be found in scientific literature. The narrative reviews are the most common, offering little criticism. They are sometimes subjective and biased. On the other hand, systematic reviews (based on a focused question, a specific search methodology, and a rigorous system of study quality and relevance) are created to identify the best evidence to clinical practice – based on critical analysis and discussion of results. Systematic reviews are superior to traditional narrative reviews because the latter generally provide a broad overview of a topic, with a source of evidence not usually specified, and with a biased selection of studies, which may lead to biased conclusions or recommendations.[4]

According to Clarkson *et al* [8], there are common misconceptions regarding systematic reviews: (1) they include only randomized, controlled trials; (2) they can be done without experienced information such as library support; (3) they necessarily involve statistical synthesis; and (4) they are only interested in disease outcomes. We do not agree with almost all the referred misconceptions because systematic review presupposes a systematic search of the highest quality methodological studies in order to identify the evidence for better practice. Taking these misconceptions we understand that all kinds of clinical studies could potentially be selected in order to answer a focused question (independent of its interventional or observational features). In this sense, one can search for diagnostic, prevalence, etiology, prognosis, prevention, treatment and other answers.

Still regarding the methods, checklists are good providing a profile of the paper and alerting reviewers to its particular methodological strengths and weaknesses.[43] They are the most common way to assess the quality of dental studies. Although new approaches, such as GRADE, are being introduced in order to improve the quality assessment process in the medical area, systematic reviews in dentistry are still based on scores to evaluate such quality. The use of scores to evaluate studies requires a higher criticism and also expert analysis. For this reason, it could be more appropriate to use quality and risk of bias checklists based on component approach, mainly if it is followed by a summary. After pooling data, reviewers have the possibility to perform a meta-analysis if more than two similar studies have been selected.[4,8,17] Thus, there are no meta-analyses without previous and coherent systematic reviews concerning the selected theme. Furthermore, the validity of the meta-analysis

Chart 3. A step-by-step guide for a systematic review in dentistry.

STEPS	
1.	Formulation of a well-defined question – *focused question* – (ideally using the PICO/PECO strategy) is a critical part of the review.
2.	To determine well-defined and unambiguous study selection criteria, also using the PICO/PECO strategy.
3.	To define the databases in which the search will be performed (as many databases as possible, and preferably with no language restrictions). Hand search, gray literature assessment and contact with experts are also recommended. At this point, it is also important to decide which authors will perform the search (at least two authors in a separate way). The authors should make substantial effort to search all the literature relevant to the question posed.
4.	To make the first study selection by title and abstract. To exclude the inappropriate studies and include the ones that are in agreement with the idea of the proposed theme (at least two authors in a separate way). The selection of studies should be appropriated so to include studies that are useful and directly address the focused question.
5.	To assess the full texts and read their methodology. To table the methodological quality of studies based on methodological quality and risk of bias criteria previously defined. To establish the studies that will be included in the systematic review (based on the quality of their methods and evidence). The critical appraisal will help to identify high-quality reviews. At this point of the review, a consensus meeting may be needed and a third author opinion will be required.
6.	To extract the data (obtain the information) of the included studies, and also make a descriptive analysis of their results. In some cases, contact with article authors is important to request some missed data or further information. It is important to synthesize the data in one table of results, in which all included studies will be presented, considering their relevant data and outcomes.
7.	To assess the heterogeneity and, if appropriate, to perform a meta-analysis.
8.	To present the conclusions based on the level of evidence achieved (report recommendations).

depends on the quality of the systematic review. In case of heterogeneity, the robustness of the main findings should be explored using a sensitivity analysis. Meta-analyses, which combine the results from many randomized trials, have more power to detect small, but significant, clinical effects.

In addition, inborn risks and false conclusions have been made with meta-analysis. According to Thompson,[44] as meta-analysis becomes widely used as a technique for reviewing scientific evidence, an overly simplistic approach to its implementation needs to be avoided. Failure to investigate potential sources of clinical heterogeneity is one aspect of this. Such investigation can importantly affect the overall conclusions to be drawn, as well as the clinical implications of the review. Moreover, Eysenck[45] still affirmed that proponents of meta-analysis pride themselves on the inclusiveness of the method, rejecting the notion that bad studies should be excluded as "subjective." Thus, scientific judgments are as necessary in meta-analysis as they are in other forms of dental research, and skills in recognizing appropriate analyses and dismissing overly provisional interpretations need to be developed.

In summary, when we intend to make a systematic review (that will result in a meta-analysis or not) before making the protocol, authors should understand the design of this kind of study in order to be aware of its particularities. The next step is choosing a focused question and reviewing the literature to identify if there are potential articles that can be used in the review. At this time, if there are no articles related to the focused question, the systematic review will not be able to adequately answer the question. If we perceive that there are no studies answering the focused question (that could be included in our review), we do not have reasons to go on. At this point, it is time to rethink the focused question in order to find appropriate evidence based articles.

CONCLUSION

A great volume of systematic reviews and meta-analyses are available in journals of interest in the dental area, however, not all systematic reviews are of high quality, and it is important to critically assess their validity and applicability.[6] Cultivating a critical attitude to research studies is an essential skill in interpreting the current flood of publications. It is not necessary that each dentist is an expert in appraisal research,[21] but a basic knowledge about evidence-based dentistry will be invaluable.

The present authors believe that the eight key steps presented here should be followed in performing a systematic review. There is much data and information to be further studied. However, for those concerned with this theme, this guide is a comprehensive introduction into the universe of systematic reviews and meta-analysis for dental research.

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