**PRISMA ITEMS: EXPLANATORY NOTES**

**Page 83**

**Item 1: Title.**

**Identify as meta-analysis or systematic review.**

**Explanation:** Search filters have been developed to identify systematic reviews, but inclusion of the words ‘‘systematic review’’ or ‘‘meta-analysis’’ in the title may improve indexing and the yield from electronic searching. We advise authors to use informative titles that make key information easily accessible to readers. Ideally, a title reflecting the PICOS approach (Participants, Interventions, Comparators, Outcomes, and Study design) may help readers as it provides key information about the scope of the review.

**Item 2: Abstract.**

**Include a structured abstract.**

Specific guidance on Abstract reporting within SRs have been developed:

Beller EM et al. PRISMA for Abstracts: Reporting systematic reviews in journal and conference abstracts. PLoS Med Apr 2013;10(4):e1001419.

**Page 84**

**Item 3: Rationale.**

**Give the rationale for the review in the context of what is known and what uncertainty exists.**

**Explanation:** Authors should clarify whether their report is new or an update of an existing review. Authors might define the importance of the review question from different perspectives (eg, public health, individual patient, or health policy) and mention the current state of knowledge and its limitations.

A possible sequence might be to:

-define the importance of the review question from different perspectives (eg, public health, individual patient, or health policy).

-briefly mention the current state of knowledge and its limitations.

-clearly state what the review aims to add.

-discuss the extent to which the limitations of the existing evidence base may be overcome by the review.

**Item 4: Objectives.**

**Provide a clear statement of questions being addressed, ideally using a PICOS format (Participants, Interventions, Comparisons, Outcomes, Study design).**

The aims of this study were therefore to compare 1-step (Intervention) and 2-step (Comparison) bonding procedures with respect to attachment failure rates and time taken to place attachments (Outcomes) in patients undergoing full-arch, fixed orthodontics (Participants).

**Item 5: Protocol and registration.**

**Indicate whether a protocol exists and, if so, where it can be accessed**

**Explanation:** A protocol is important because it pre-specifies the objectives/methods of the review and may prevent data-dredging. Registration may possibly reduce the risk of multiple reviews addressing the same question, reduce publication bias, and provide greater transparency when updating systematic reviews. Changes to the protocol after its submission might be warranted, but selective outcome reporting is associated with bias.

See the PROSPERO International Prospective Register Of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO/).

**Item 6: Eligibility criteria.**

**Provide study and report characteristics used as eligibility criteria. These should include PICOS and length of follow-up, years considered, and language and publication status.**

**Explanation:** Knowledge of the eligibility criteria is essential in appraising the validity, applicability, and comprehensiveness of a review. Carefully defined eligibility criteria influence the development of the search strategy and ensure that studies are selected in a systematic and unbiased manner.

**Items 7, 8, and 9: Information sources, search strategy, and study selection.**

**Give information sources outlining the most recent search date, provide full strategy for at least one electronic database.**

**Outline the process for selecting studies.**

**Explanation:** As a minimum, for each database searched, the database, platform, or provider (eg, Ovid, Dialog, PubMed) and the start and end dates for the search should be made clear. Authors should also report who developed and conducted the search. In addition, the use of supplementary approaches to identify studies, such as hand searching of journals, checking reference lists, searching trials registries or regulatory agency web sites, contacting manufacturers, or contacting authors, should be outlined. Authors should also report if they attempted to acquire any missing information (eg, on study methods or results) from investigators or sponsors.

Authors are encouraged to report the full electronic search strategy for at least one major database. Apart from the keywords used to identify or exclude records, any additional limitations relevant to the search, such as language and date restrictions (see also Item 6, Eligibility criteria), should be reported.

Methods of screening the retrieved records (typically a title and abstract) should be made clear, with detail on the number of full texts reviewed, and if any types of record (eg, letters to the editor) were excluded. Authors are encouraged to use the PRISMA flow diagram to summarize study selection processes.

Efforts to enhance objectivity and avoid mistakes in study selection are important. Thus, authors should report whether each stage was carried out by one or several people, who these people were, and, when multiple independent investigators performed the selection, what the process for resolving disagreements was. The use of at least two investigators may reduce the possibility of rejecting relevant reports. The benefit may be greatest for topics where selection or rejection of an article requires difficult judgments.

**Items 10 and 11: Data collection process and data items.**

**Describe methods of data extraction (including piloting and duplicate extraction).**

**List variables for which data were sought, eg, PICOS and funding sources.**

**Explanation:** The authors should describe these methods, including any steps taken to reduce bias and mistakes during data collection and data extraction. Reviewers extract information from each included study so that they can critique, present, and summarize evidence in a systematic review. They might also contact authors of included studies for information that has not been reported. If individual patient data were sought, this must be described. We advise authors to describe any steps they used to avoid double counting and piece together data from multiple reports of the same study (duplicate publications). It is advised that review authors be as explicit as possible in the description of these methods, even if some of the data has to be presented in the Appendix.

It is important that the reviewers describe what information was sought from each study, even if this was not available in the end. Variables that were not planned in the protocol can be added but must be described accordingly. Any assumptions made about missing or unclear data should also be reported.

Authors are advised to tell readers who extracted what data, whether any extractions were completed in duplicate, and if so, whether duplicate abstraction was done independently and how disagreements were resolved. Published reports of the included studies may not provide all the information required for the review. Reviewers should describe any actions they took to seek additional information from the original researchers. The description might include how they attempted to contact researchers, what they asked for, and their success in obtaining the necessary information. Authors should also tell readers when individual patient data were sought from the original researchers and indicate the studies for which such data were used in the analyses.

**Item 12: Risk of bias in individual studies.**

**Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis. The likelihood that the treatment effect reported in a systematic review approximates the truth depends on the validity of the included studies, as certain methodological characteristics may be associated with effect sizes.**

**Explanation:** There has been a recent transition from the assessment of the “quality” of a study to the assessment of the risk of bias of a study. There is a difference between the terms *quality* (ie, “did the authors do their best”?) and *bias* (ie, “should I believe their results”?). Bias can also occur in well-conducted studies, while not all methodological flaws introduce bias. Authors should report how they assessed risk of bias: whether it was in a blind manner, whether assessments were completed by more than one person, and if so, whether they were completed independently.

For RCTs, the Cochrane Risk of Bias Tool is considered the gold standard in the assessment of risk of bias. It is important that the threshold level of bias or quality permitting inclusion in quantitative assessment is defined.

For nonrandomized studies a variety of assessment tools exists, including checklists, individual components, and scales (though use of the latter should be avoided).

**Page 85**

**Items 13 and 14: Summary measures and Synthesis of results.**

**State the principal summary measure (eg, mean difference, relative risk).**

**Describe how data will be handled and results combined (eg, outlining methods of dealing with statistical heterogeneity).**

**Explanation:** The summary effect measure must be pre-specified for each of the primary/secondary outcomes. The most common summary effect measures include the risk ratio, odds ratio, or risk difference (for binary outcomes) and the mean difference or standardized mean difference (for continuous outcomes). For time-to-event outcomes, the hazard ratio is most widely used.

The standardized difference in means is used when the studies do not yield directly comparable data. Usually this occurs when all studies assess the same outcome but measure it in a variety of ways (eg, different scales to measure pain). Caution should be exercised when paired or clustered designs are included in the analysis. Ignoring matching in paired designs decreases the power of the analysis. Correct calculation of the estimates requires additional information such as the correlation coefficient between within-patient measurements. For clustered designs, such as multiple observations within patients (eg, multiple bracket failures), ignoring clustering may increase precision spuriously. An adjustment for the produced standard errors is required according to the correlation within patients (intracluster correlation coefficients) unless outcomes are provided at patient and not at tooth level.

Authors should report how they planned to evaluate between-study variability (heterogeneity or inconsistency). The consistency of results across trials may influence the decision to combine trial results in a meta-analysis.

When meta-analysis is done, authors should specify the effect measure (eg, relative risk or mean difference), the statistical method (eg, inverse variance), and whether a fixed- or random-effects approach or some other method (eg, Bayesian) was used. Ideally the statistical analysis should be pre-specified (before data extraction) and be based on clinical and statistical reasoning.

**Page 85**

**Item 15: Risk of bias across studies.**

**Outline methods of assessing publication bias or selective reporting.**

**Explanation:** Reviewers may examine results from the available studies for clues that suggest that there may be missing studies (publication bias) or missing data from the included studies (selective reporting bias). Authors should report in detail any methods used to investigate possible bias across studies.

**Also refer to GRADE assessment**

The GRADE assessment allows assessment of the quality of evidence and subsequent recommendations: http://www.gradeworkinggroup.org/publications/jce\_series.htm.

**Reference:** Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008 Apr 26;336:924–926.

**Item 16: Additional analyses.**

**Describe any additional analyses (eg, sensitivity or subgroup analyses).**

**Explanation:** Authors may perform additional analyses to help understand whether the results of their review are robust, all of which should be reported. Such analyses include sensitivity analysis, subgroup analysis, and meta-regression. It is important to inform readers whether these analyses were performed, their rationale, and which were pre-specified.

Sensitivity analyses are used to explore the degree to which the main findings of a systematic review are affected by changes in its methods or in the data used from individual studies (eg, study inclusion criteria, results of risk of bias assessment). Subgroup analyses address whether the summary effects vary in relation to specific (usually clinical) characteristics of the included studies or their participants. Meta-regression extends the idea of subgroup analysis to the examination of the quantitative influence of study characteristics on the effect size. Meta-regression also allows authors to examine the contribution of different variables to the heterogeneity in study findings. Readers of systematic reviews should be aware that meta-regression has many limitations, including a danger of overinterpretation of findings. Even with limited data, additional analyses are possible; however, the appropriate analysis depends on the aims of the review.

**Items 17 and 18: Study selection and characteristics.**

**Give details of number of studies included, ideally using a PRISMA flow diagram.**

**Provide details of characteristics recorded for each study (eg, sample size, PICOS, follow-up).**

**Explanation:** Authors should report, ideally with a flow diagram, the total number of records identified from electronic bibliographic sources (including specialized database or registry searches), hand searches of various sources, reference lists, citation indices, and experts.

Authors should also note the presence of duplicate or supplementary reports so that readers understand the number of individual studies compared to the number of reports that were included in the review.

For readers to gauge the validity and applicability of a systematic review’s results, they need to know details of the included studies including PICOS and specific information relevant to the review question. Authors should present enough detail to allow readers to make their own judgments about the relevance of included studies. Authors should avoid, whenever possible, assuming information when it is missing from a study report (eg, sample size, method of randomization).

**Item 19: Risk of bias within studies.**

**Present data on risk of bias from individual studies and outcome level assessments, if available.**

**Explanation:** Reviewers should assess the risk of bias in the included studies using a standard approach with defined criteria. The results of any such assessments should be reported in detail (ideally explicitly reporting the methodological features evaluated for each study) and not purely providing summary data (eg, ‘‘two of eight trials adequately concealed allocation’’).

The Cochrane Collaboration’s new tool for assessing the risk of bias also suggests that authors substantiate these assessments with any relevant text from the original studies.

**Items 20, 21, and 23: Results of individual studies, meta-analyses, and additional analyses.**

**Present outcomes from individual studies with 95% CIs and combined estimates with CIs, ideally with a forest plot.**

**Outline results of additional analyses (eg, sensitivity analysis or meta-regression).**

**Explanation:** Publication of summary data from individual studies allows the analyses to be reproduced and other analyses and graphical displays to be investigated. Additionally, because data extraction errors in meta-analyses are common and can be large, the presentation of the results from individual studies makes it easier to identify errors. For all included studies (and for all included outcomes, if possible) it is important to present the estimated effect with a confidence interval. This information may be incorporated in a table showing study characteristics or may be shown in a forest plot.

If authors have conducted one or more meta-analyses, they should present the results as an estimated effect across studies with a confidence interval (ideally in a forest plot).

Authors should also provide, for each meta-analysis, a measure of the consistency of the results from the included studies such as I-squared. If no meta-analysis was performed, the qualitative inferences should be presented as systematically as possible (eg, with a forest plot without a summary estimate) with an explanation of why meta-analysis was not done. Any deviations from the planned analysis should be reported.

Information on harms is only rarely reported in systematic reviews, even when it is available in the original studies. Selective omission of harms results biases a systematic review and decreases its ability to contribute to informed decision making.

Authors should report any subgroup or sensitivity analyses and whether or not they were pre-specified (Items 5 and 16). For analyses comparing subgroups of studies (eg, fixed or removable functional appliances), the authors should report any tests for interactions, as well as estimates and confidence intervals from meta-analyses within each subgroup. Similarly, meta-regression results (see Item 16) should not be limited to *P* values, but should include effect sizes and confidence intervals, as the first example reported above does in a table. The amount of data included in each additional analysis should be specified if different from that considered in the main analyses. This information is especially relevant for sensitivity analyses that exclude some studies; for example, those with high risk of bias.

**Also add GRADE assessment.**

Present a GRADE Summary of Findings (SoF) table. The quality of evidence may be scored as high, medium, low, or very low. Consider reasons for downgrading the quality of evidence (study limitations, indirectness, inconsistency, imprecision, and publication bias) or for upgrading the quality of evidence (magnitude of effect, dose-response effect, or absence of residual confounding).

For further guidance on GRADE:

1. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008 Apr 26;336(7650):924–926.

2. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011 Apr;64(4):383–394.

**Page 86**

**Fig 1. PRISMA flow diagram showing the process of identifying and selecting eligible studies for the systematic review.**

**Explanation:** The flow diagram is divided in 5 parts: (1) the identification of studies from the literature search and the removal of duplicates, (2) the exclusion of ineligible studies on the basis of the title/abstract, together with reasons, (3) the exclusion of ineligible studies on the basis of the full-text, together with reasons, (4) the inclusion of studies in the qualitative synthesis (systematic review), and (5) the inclusion of studies in the quantitative synthesis (meta-analysis), if appropriate. The flow diagram is an integral part of transparent reporting for systematic reviews, enabling a quick overview of the review’s procedures.

**Page 88**

**Item 22: Risk of bias across studies.**

**Present results of any assessments for publication bias or selective reporting.**

**Explanation:** Authors should present the results of any assessments of risk of bias across studies. If a funnel plot is reported, authors should specify the effect estimate and measure of precision used. Authors should describe if and how they have tested the statistical significance of any possible asymmetry. Authors are advised to tell readers if any pre-specified analyses for assessing risk of bias across studies were not completed and the reasons (eg, lack of included studies).

**Item 24: Summary of evidence.**

**Summarize the main findings including the strength of the evidence. Relate the findings to key groups.**

**Explanation:** Authors should give a brief and balanced summary of the nature and findings of the review. The applicability of the findings to different patients, settings, or target audiences, for example, should be mentioned. Sometimes, authors formally rate or assess the overall body of evidence addressed in the review and can present the strength of their summary recommendations tied to their assessments of the quality of evidence (eg, the GRADE system).

Authors need to keep in mind that statistical significance of the effects does not always suggest clinical or policy relevance. Patients and health care providers may be primarily interested in which intervention is most likely to provide a benefit with acceptable harms, while policy makers and administrators may value data on organizational impact and resource utilization.

**Page 89**

**Fig 2. Summary of the risk of bias for the studies (in this instance RCTs) included in the systematic review.**

**Explanation:** According to the Cochrane risk of bias tool, the risk of bias for each RCT is judged based on seven domains (vertical columns) as “low risk of bias” (green plus sign), as “high risk of bias” (red minus sign), or as “unclear risk of bias” (yellow question mark). This figure enables the reader to quickly identify problematic aspects of the included studies that could introduce systematic errors (bias) in the trials’ results.

**Page 91**

**Fig 3. Forest plot presenting the meta-analysis results for the main outcome of the systematic review (bracket failure).**

**Explanation:** The forest plot can be divided in three regions: (1) the list of included studies, together with their raw data (here on the left side), (2) the graphical representation of each study’s results, together with the overall summary (here in the middle), and (3) the calculated effect size (here the odds patio [OR] and the 95% confidence interval [95% CI]) and the assigned weight for each study and for the overall summary. For each of the included studies (gray boxes with dots), if its 95% CI (black horizontal line) crosses the vertical no-effect line, then *P* value > 0.05 for this study. The overall summary (meta-analysis result) is given as a hollow blue diamond under the included studies, which includes both the pooled effect estimate (pooled OR) and the 95% CI. If the diamond crosses the vertical no-effect line, then *P* value > 0.05 for the pooled meta-analysis estimate. The blue horizontal lines of the diamond indicate the 95% predictive interval (95% PI) for the pooled estimate, not the 95% CI. The forest plot is integral to the transparent reporting of meta-analyses, as it presents the magnitude of the treatment effect for each study, which treatment group is favored, the homogeneity among the included studies, and the overall pooled estimate.

**Page 92**

**Fig 5. Forest plot presenting the sensitivity analysis for the meta-analysis of the main outcome.**

**Explanation:** In this kind of sensitivity analysis a single study is excluded for every line from the overall pooled summary (as indicated to the left), and the results are presented as pooled OR (open circle) and the corresponding 95% CI (dotted horizontal line). This analysis helps assess the relative contribution of each study to the overall pooled estimate. The more a single open circle deviates from the others, the more this study contributes to the meta-analysis.

**Fig 6. Forest plot presenting the meta-analysis results for the secondary outcome of the systematic review (time to bond).**

**Item 25: Limitations.**

**Discuss limitations at study and outcome level (eg, risk of bias, lack of relevant studies) and at review level (eg, incomplete retrieval of studies).**

**Explanation:** A discussion of limitations should address the validity (ie, risk of bias) and reporting (informativeness) of the included studies, limitations of the review process, and generalizability (applicability) of the review. Readers may find it helpful if authors discuss whether studies were threatened by serious risks of bias, whether the estimates of the effect of the intervention are too imprecise, or if there were missing data for many participants or important outcomes.

Limitations of the review process might include limitations of the search (eg, restricting to English-language publications) and any difficulties in the study selection, appraisal, and meta-analysis processes.

**Item 26: Conclusions.**

**Provide a general interpretation of the results in the context of other evidence together with implications for future research.**

**Explanation:** Conclusions drawn from systematic reviews should be explicitly formulated (not overly positive) and should consider both harms and benefits. If conclusions cannot be drawn because there are too few reliable studies or too much uncertainty, this should be stated. Authors are also advised to make clear recommendations for future research.

**Item 27: Funding.**

**Describe sources of funding and other support (eg, provision of data).**