MR. CLÓVIS MARIANO JUNIOR FAGGION (Orcid ID : 0000-0001-8323-909X)
DR. ALBERTO MONJE (Orcid ID : 0000-0001-8292-1927)

Article type : Other

Appraisal of systematic reviews on the management of peri-implant diseases with two methodological tools

Clovis Mariano Faggion Jr[1], Alberto Monje[2,3], Jason Wasiak[4]

[1] Department of Periodontology and Operative Dentistry, Faculty of Dentistry, University of Münster, Münster, Germany;

[2] Department of Oral Surgery and Stomatology, School of Dental Medicine, University of Bern, Bern, Switzerland;

[3] Department of Periodontology, Universidad Internacional de Cataluña, Barcelona, Spain

[4] Melbourne School of Health Sciences, Faculty of Medicine, University of Melbourne, Australia.

Corresponding author: Clovis Mariano Faggion Jr

Faculty of Dentistry, University of Münster, Waldeyerstrasse 30, 48149 Münster, Germany

Tel: +49 (0)251/83-47061

Fax: +49 (0)251/83-47134

Email: clovisfaggion@yahoo.com

Number of words: 3744

Running title: Appraisal of systematic reviews

Keywords: methods; dental implants; systematic review; peri-implantitis; bias

Clinical relevance

Scientific rationale for study: A methodological instrument should allow comprehensive analysis of the quality of systematic reviews to understand the quality of the available evidence and suggest clinical recommendations.

Principal findings: The overall risk of bias (ROB) in systematic reviews was high. In general, the methodological quality was higher when measured with Assessing the Methodological Quality of Systematic Reviews (AMSTAR) instrument than when measured with Risk of Bias in Systematic Reviews (ROBIS) tool. Different systematic reviews reported disagreements in the ROB of the same RCT.

Practical implications. The present findings should be used to guide researchers in the critical appraisal of systematic reviews. Complete reports on the rationale for judgments of methodological quality or ROB should be made available to readers, enabling better understanding of the variability across rating studies.

Abstract

Aim: This study aimed to (a) to evaluate and compare the performance of two methodological instruments to appraise systematic reviews, and (b) to identify potential disagreements of systematic review authors regarding risk of bias (ROB) evaluation of randomized controlled trials (RCTs) included in systematic reviews on peri-implant diseases.

Material/methods: We searched Medline, Web of Science databases, and Cochrane library for systematic reviews on peri-implant diseases published before July 11, 2017. Two authors independently evaluated the ROB and methodological quality of the systematic reviews by applying the Risk of Bias in Systematic Reviews (ROBIS) and Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tools, respectively. We assessed the ROB scores of the same RCTs published in different systematic reviews.
Results: Of the 32 systematic reviews identified, 23 reviews addressed the clinical topic of peri-implantitis. A high ROB was detected for most systematic reviews (78%) using ROBIS, whilst five systematic reviews displayed low methodological quality by AMSTAR. Almost 30% of the ROB comparisons (for the same RCTs) had different ROB ratings across systematic reviews.
Conclusions: ROBIS tool appears to provide more conservative results than AMSTAR. Considerable disagreement was found among systematic review authors rating the same RCT included in different systematic reviews.

Conflict of interest

The authors declare having no conflicts of interest.

Source of funding

No external funding, apart from the support of the authors' institution, was provided for this study.

Introduction

Systematic reviews have become an epidemic phenomena. With great variability in their quality (Ioannidis 2016), systematic reviews provide the basis for the development of clinical guidelines (Faggion 2013). Thus, systematic reviews should adhere to high quality standards to generate robust clinical recommendations, and the quality of such reviews should always be evaluated before their use.

Approaches have been developed to evaluate the different aspects of systematic reviews. For example, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) instrument is recommended to evaluate reporting standards (Moher et al. 2009). The Assessing the Methodological Quality of Systematic Reviews (AMSTAR) instrument (Shea et al. 2007) was used to assess the methodological quality of systematic reviews, despite limitations (Faggion 2015). Some AMSTAR items appear to assess reporting rather than the methodological quality (Faggion 2015).

A new approach for assessing the risk of bias (ROB) in systematic reviews has recently been proposed (Whiting et al. 2016). It involves evaluating domains that are fundamental to the development of systematic reviews (Whiting et al. 2016). The purpose of this tool is to perform an in-depth evaluation of ROB that could interfere with the reported findings. According to

Whiting et al, only a few reports have used the Risk of Bias in Systematic Reviews (ROBIS) tool within medical disciplines, but never within dentistry.

Therefore, the main objective of this study was to evaluate and compare capacity of the ROBIS and AMSTAR instruments to capture the quality of systematic reviews on the management of peri-implant diseases. A secondary objective was to evaluate whether authors of these systematic reviews agree on the rating of ROB of the same RCT included in different reviews.

Materials and Methods

Eligibility Criteria

Our inclusion criteria were systematic reviews alone or in combination with meta-analysis: (1) as clearly reported as "systematic" in the title, abstract or main text; (2) specific to the management of peri-implant disease (i.e. mucositis and peri-implantitis). We excluded reviews of a non-interventional nature, narrative reviews, and studies not available in English.

Literature Search

One author (CMF) searched Medline (via PubMed), Web of Science, The Cochrane Library, PubMed Central, and Google Scholar from inception to July 11, 2017 using defined key-words and Boolean operators (see Table 1, supplementary file). The reference lists of the retrieved systematic reviews were scanned for further systematic reviews. All searches were performed by one author (CMF); a second author (AM) verified the screening process and number of retrieved articles by conducting the same search strategy.

Data Selection

Two authors (CMF and AM) screened eligible, titles and abstracts against the predefined eligibility criteria. Full texts articles were retrieved and reviewed independently and in duplicate by two authors (CMF and AM) for final inclusion.

Assessing the methodological quality and risk of bias

Two authors (CMF and AM) assessed the methodological quality and risk of bias using the AMSTAR checklist and ROBIS tool, with differences of opinion resolved by discussion with a third author (JW). To increase the precision of data extraction, an evaluation training phase using the tools against the SR was undertaken by two reviewers (CMF and AM). Details of training phase can be found in the supplementary file.

The ROBIS tool provides a thorough way of assessing ROB in systematic reviews by using a comprehensive set of items, and grouped according to phases, on which to judge: (a) Phase 1: Assessing relevance (optional): This was not required, as the reviews had already been assessed for relevance to the research question; (b) Phase 2: Identifying concerns with the review process: this consisted of four domains against which a review was assessed (i.e. study eligibility criteria, identification and selection of studies; data collection; and study appraisal and synthesis and findings); (c) Phase 3: Judging risk of bias: this summarised the concerns identified in Phase 2 and assessed whether the conclusions of the review was supported by evidence. Each domain had five or six questions that were answered as 'Yes', 'Probably Yes', 'Probably No', 'No', and 'No Information'. We rated domains as 'Low Risk' if all questions were 'Yes' or 'Probably Yes'; 'High Risk' if they were 'No' or 'Probably No'; and judged the remainder as 'Unclear' (Whiting et al. 2016).

The methodological quality of included studies was evaluated using AMSTAR, a research-based instrument consisting of an 11-item checklist. It is argued that AMSTAR has good agreement, reliability, construct validity, and feasibility (Shea et al. 2009). Each AMSTAR question was scored with a 'yes', 'no', 'can't answer' or 'not applicable' response.

All evaluations were performed independently and in duplicate by two authors (CMF and AM). Disagreements were resolved by discussion until consensus was achieved. A third author (JW) was consulted in cases where consensus was not possible.

Data extraction and analysis

Two reviewers (CFM, AM) extracted data independently on a) topic (mucositis, peri-implantitis, or both), b) meta-analysis (yes or no), c) number of authors, d) country of first author, e) type of journal (with or without impact factor [IF]), f) study design, g) key study findings

We reported the findings as absolute numbers, medians, or median percentages (with respective interquartile ranges [IQRs]). Although final scores are not recommended for AMSTAR, for comparison purposes, the methodological quality of systematic reviews was classified according to the number of adequately addressed AMSTAR items, as follows: low (0–3 items), moderate (4–7 items), or high (8–11 items) (Dong et al. 2016, Gómez-García et al. 2017); "NA" answers were considered "yes" answers to facilitate comparison. Systematic reviews evaluated with ROBIS were classified as having high, low, or unclear ROB.

To address the secondary objective of this study, we used the following approach: we identified the number of systematic reviews using the Cochrane domains of bias (Higgins et al. 2008) approach and reproduced the ROB results reported in the different systematic reviews in a table of RCTs. We only reported RCTs that were included in at least two systematic reviews for the following reasons: 1) to provide information on the different ROB judgements for the same RCT included in different systematic reviews, and 2) to provide overall information on the ROB of RCTs on peri-implant diseases.

Results

Search results

We initially retrieved 1156 potential documents from the electronic databases. Thirty-two systematic reviews on the management of peri-implant diseases were included. Figure 1 shows the flowchart of the detailed search process. Lists of included and excluded systematic reviews (with reasons for exclusion) are provided in the supplementary file.

General study characteristics

A total of 23 systematic reviews addressed therapies for peri-implantitis, whilst four addressed mucositis, and five addressed both peri-implantitis and mucositis. Meta-analyses were performed in 13 systematic reviews. The median number of authors was 3 (IQR:3–5). Authors from European countries published the greatest number of systematic reviews (n = 17). The reviews were published in 17 different scientific journals, predominantly dental journals (n = 14). The median IF of the journals was 2.84 (IQR:1.86–3.92). The median number of primary studies included in the systematic reviews was 11 (IQR:7-18). Most primary studies were performed on humans only (n = 25). The general study characteristics of the included studies are summarized in Table 1. More details on the methodology, results and conclusions of systematic reviews are reported in Table 2, supplementary file.

Results from the ROBIS Tool

A total of 128 domains were evaluated with the ROBIS tool. Twenty-seven domains were rated as having a low ROB, 66 as having a high ROB, and 35 as having an unclear ROB (Table 2). Domains 2 (study identification and selection) and 4 (synthesis and findings) had the greatest number of concerns regarding a high ROB (n = 22 and 20, respectively). Domains 1 (study eligibility criteria) and 4 (synthesis and findings) had the greatest number of concerns regarding

a low ROB (n = 10 and 9, respectively). The greatest number of concerns of an unclear ROB (n = 13) were found in domain 1. Results from the complete ROBIS assessment are reported in Tables 2 and 3. Table 3 (supplementary file) reports the potential concerns regarding bias in the different ROBIS domains.

Results from the AMSTAR Instrument

A total of 352 answers to the AMSTAR items were evaluated; 193, "yes"; 145, "no" or "CA"; and 14 "NA." The greatest number of "yes" answers were given for items 1 (Was an *a priori* design provided? n=30) and 6 (Were the characteristics of the included studies provided? n = 30). The greatest number of "no" answers were given for item 11 (Was the conflict of interest included? n = 32). Item 2 (Was there duplicate study selection and data extraction?) received the greatest number of "CA" answers (n = 16). The complete AMSTAR assessment is provided in Tables 4 and 5.

Comparison Between the results from the ROBIS and AMSTAR Tools

Overall, with the ROBIS tool, 25 systematic reviews were rated as having a high ROB, 4 as having a low ROB, and 3 as having an unclear ROB. In our AMSTAR classification, 5, 13, and 14 systematic reviews were rated as having a low, moderate, and high methodological quality, respectively. Systematic reviews analyzed with AMSTAR had a median of 62% (IQR:40%-80%) items answered positively ("yes" answers). The four systematic reviews rated as having an overall low ROB had the highest percentage of AMSTAR items answered with "yes" (median, 86.5% [IQR:81%–91%]). Using the proposed classification, systematic reviews with high methodological quality had a low ROB.

ROB of RCTs Included in the Systematic Reviews

Fourteen systematic reviews used the Cochrane domain-based approach for assessing RCTs, enabling comparison across systematic reviews. The ROB of 35 RCTs included in the systematic reviews are presented in Table 4 (supplementary file). In all RCTs, at least one domain was found to have high or unclear ROB. Of the 194 potential ROB domain comparisons (within the same RCTs across different systematic reviews), 57 (29%) comparisons were found to have different ROB ratings (domains highlighted in Table 3, supplementary file). The median number of the same RCTs included in different systematic reviews was 3 (IQR = 2-5).

Discussion

The main objective of this study was to evaluate the performance of two tools to evaluate methodological aspects of systematic reviews on the management of peri-implant diseases. Based on the ROBIS tool, most systematic reviews had a high ROB. However, based on the AMSTAR instrument, most systematic reviews had a high methodological quality. The systematic reviews with a low ROB had the greatest number of positively-answered AMSTAR items. A secondary objective was to evaluate the agreement on the rating of ROB of the same RCT included in different reviews. The results showed that ROB ratings, for the same RCT included in different systematic reviews, varied considerably. Finally, our results suggest that RCTs on peri-implant diseases have high or unclear ROB.

An overview of published systematic reviews enables the evaluation of the available scientific evidence at different levels (Smith et al. 2011) by analyzing both primary and secondary studies. We aimed to provide a comprehensive overview of the features of systematic reviews by applying two tools; the first tool (ROBIS) was developed to evaluate the ROB, and the second tool (AMSTAR) was used to evaluate methodological quality (i.e., both represented a different concept). The ROB is related to internal validity; this concept has already been applied to other study designs (Higgins et al. 2016, Sterne et al. 2016). The methodological quality is a broader and more comprehensive concept that involves aspects such as external validity (de Vet et al. 2001).

Assessing the methodological quality and risk of bias

According to our knowledge, this is the first dentistry-based study to apply the ROBIS tool to evaluate the ROB in systematic reviews. A strength of the ROBIS tool is that it entails descriptive reporting of the rationale used to address (low, unclear, or high) concerns in the four bias domains. Therefore, this information can be compared across systematic reviews exploring the same research question. Furthermore, reporting the rationale in detail enables the readers to understand why decisions were made (based on both specific domains and overall ROB; Table 2, supplementary file). However, performing evaluations with the ROBIS tool is sometimes challenging. A sound knowledge of methodological principles, issues to be addressed, and statistical analyses may be required to adequately evaluate the domains. The tool uses multiple-choice answers; thus, it is sometimes difficult to reach a consensus. Some domains are more

difficult to evaluate; for example, in the current study, domain 4 (Synthesis and findings) was particularly complex, particularly when no meta-analyses were present. However, the main difficulty identified in this study was related to establishing consensus across researchers (Perry et al. 2017), particularly with regard to domain 4. This difficulty was reported in a previous methodological study that compared the ROBIS and AMSTAR tools; ROBIS was found to demonstrate fair reliability and good construct validity, but was complex compared with the AMSTAR instrument (Bühn et al. 2017).

Furthermore, domain 4 received high ROB ratings in some cases because of the inappropriateness of meta-analyses. In our sample, only 13 systematic reviews presented meta-analytic estimates of therapies. The authors claimed that because of the large heterogeneity among the included clinical trials, it was not possible to conduct meta-analyses. However, some systematic reviews, which included meta-analyses, received high ROB ratings because they included studies with different designs. Such an approach is not recommended as it may lead to higher estimates (Parker et al. 2013). Hence, meta-analyses should be conducted properly, only when sufficient clinical and statistical homogeneity is present among trials (Deeks et al. 2008).

Domain 2 (Identification and selection of studies) was another challenging ROBIS domain. It had the greatest number of unclear or high ROB scores. Only one systematic review rated this domain as having a low ROB. In most systematic reviews, a lack of comprehensive search strategies (i.e., inclusion of unpublished material and language restriction) was the most important reason for poor ROB ratings. Some evidence suggests a controversial influence excluding grey literature or imposing language limitations to estimates of treatment effect sizes (Hopewell et al. 2007, Driessen et al. 2015, Schmucker et al. 2017). This ambiguity could influence bias ratings; thus, we tended to apply a high concern in cases of more search limitations.

The AMSTAR instrument has been used as a standard approach for evaluating systematic reviews. However, methodological limitations have recently been emphasized (Faggion 2015, Burda et al. 2016, Wegewitz et al. 2016). One important limitation of AMSTAR is the difficulty of differentiate methodological quality from quality of reporting. AMSTAS has, however, the advantage of being more user friendly than ROBIS. An updated version of AMSTAR has been published to overcome its methodological limitations (Shea et al. 2017). The authors of the AMSTAR-2 checklist retained 10 of the 11 original items and added a few additional items.

There also made some changes to the original rating system. However, the updated checklist does not appear to facilitate descriptive reporting on the rationale used to score the items. The authors of this revised tool asked researchers to provide feedback on its applicability to different settings, to facilitate its improvement (Shea et al. 2017).

Comparison with other studies

Currently, only a few available studies have simultaneously incorporated the ROBIS and AMSTAR tools. When a search using the keywords *AMSTAR and ROBIS* was conducted in MEDLINE (via PubMed, on July 22, 2017), only three studies (Andersen et al. 2017, Perry et al. 2017, Bühn et al. 2017) were found to have used both tools to evaluate systematic reviews. This is likely because ROBIS was only recently made available; furthermore, the complexity of ROBIS might hinder its use. In one study (Perry et al. 2017), AMSTAR provided fewer positive results than did ROBIS (five systematic reviews with scores of >6, versus seven with a low ROB). In the second study (Andersen et al. 2017), the mean AMSTAR score of 12 systematic reviews was 3.3, reflecting the overall ROB measured by ROBIS (which revealed that most systematic reviews had high ROB; two systematic reviews were considered to have an unclear ROB). The third study (Bühn et al. 2017) found a strong correlation between positive ROBIS and AMSTAR scores based on 16 systematic reviews in the field of occupational health. However, our results suggest more conservative results with ROBIS analysis. These heterogeneous findings support the need for a clear rationale for ROB ratings to understand the reasons for variability in judgment.

Assessment of RCTs included in the systematic reviews

Evaluation of the RCTs, included in the systematic reviews on peri-implant diseases, demonstrated that all had at least one domain with high or unclear ROB. These results are disappointing from a methodological perspective. It is arguable whether systematic reviews of high quality but based on clinical studies with high or unclear ROB, are useful for clinical decision-making. Another point of interest was the disagreement between assessors rating ROB for the same RCT but for different systematic reviews. Almost 30% of the comparisons were contradictory, with different ratings of domain-specific ROB in the same RCT (Table 3, supplementary file). Some RCTs in this sample received completely opposing ROB ratings (high versus low) in different systematic reviews. This inconsistency could be related to the level of information available. If examiners of a systematic review have more comprehensive

information after contacting the researcher (who conducted the RCT), they may rate the ROB with more confidence. In contrast, examiners who do not contact the researcher may have only partial information and, thus, rate the review as having an unclear ROB. Other explanations for these inconsistencies include the heterogeneity of methodological knowledge among examiners or different criteria for determining the ROB. Hence, it is important that systematic reviewers report the rationale used to rate the ROB (Faggion 2016) in both RCTs and systematic reviews to enable readers to understand the differences between ratings for the same evaluated study.

It is also important to discuss the ROB domain on masking, which can be grouped into two domains: the masking of personnel and patients and that of examiners (Higgins et al. 2008). The former is related to the masking of operators, patients, and all participants directly involved in the procedure. It is, therefore, challenging to mask heterogeneous procedures and this domain can, therefore, have a high ROB because of methodological limitations in masking therapies. This was true for many RCTs on the management of peri-implant diseases. The second domain is related to the masking of assessors (those evaluating the results of therapies); this can be easily achieved by isolating the examiner from previous information. In the present study, some systematic reviews did not make this crucial differentiation and reported the masking domain alone, thus impairing our understanding of the effect of the ROB on the results.

There was also an overlap in the RCTs included in several systematic reviews published and evaluated herein. In some cases, the same study appeared in seven systematic reviews. This overlap may be explained by the large number of studies published on this subject in the past few years because of the alarming frequency of peri-implant diseases (Atieh et al. 2013, Derks and Tomasi 2015, Monje et al. 2016) (Figure 1, supplementary file). Moreover, there was perhaps insufficient time for the publication of new primary studies because many systematic reviews were published in the same year.

The Cochrane Collaboration recently launched an updated version of the ROB tool for RCTs (Higgins et al. 2016). This tool aims to overcome some limitations of the previous version (Higgins et al. 2011), used in many systematic reviews included in the present critical assessment. However, this new version requires further testing among a representative sample of RCTs, across different medical disciplines, to evaluate its performance against the previous version.

Limitations of this study

Our study has some limitations. First, we only included systematic reviews published in English; thus, some relevant information may have been excluded from our assessment. This limitation was necessary to ensure that the study was realistic and achievable within a constrained time frame. However, many systematic reviews in this sample were published in highly-ranked dental or medical journals that may reflect the best available material. Hence, the results may have been more negative if a sample of systematic reviews, published in lower-ranked journals, had been included. Second, we included systematic reviews (n = 5) that included both animal experiments and clinical trials. Although there is no clear recommendation in the ROBIS guidelines regarding the type of studies included in systematic reviews, the ROB is higher in studies with inferior designs than in RCTs. Thus, there may have been no need for formal evaluation. However, to be as inclusive as possible, we included a representative sample of the systematic reviews on peri-implant diseases.

Recommendations for Future Research and Future Directions

Based on the present findings, our recommendations are as follows:

- The authors of systematic reviews and RCTs should, in addition to performing ROB evaluation, report the rationale used to rate ROB (Faggion 2016). This will provide readers with an understanding of why specific domains were rated with specific ROB scores. Variability among ROB evaluations, as shown in the present study, demonstrates that the authors of systematic reviews may have different opinions on ROB. Similarly, users of checklists such as AMSTAR should also report their rationale for evaluating the methodological quality. This comprehensive reporting of the assessment will allow readers to understand potential disagreements between different tools.
- It is important for the authors of systematic reviews to directly contact the authors of RCTs to obtain more comprehensive information and reduce the large number of "unclear" answers to questions related to different ROB domains.
- When reporting information on masking, the authors of systematic reviews should make clear distinction between the masking of personnel (operators), patients, and examiners.
- The level of information in systematic reviews and RCTs is directly related to the need to rate the ROB or methodological quality. The more detailed the information, the less

interpretation will be required for a reader to understand the quality and extent to which a specific study is free of bias. Therefore, the authors of systematic reviews and RCTs should strictly follow the appropriate guidelines for reporting such studies (Altman and Simera 2016).

Concluding remarks

Our findings demonstrate that the ROBIS tool provided a more detailed assessment with more conservative results; however, it seems more challenging to use than AMSTAR. Furthermore, there was variability in the ROB ratings between systematic reviews evaluating the same RCTs. The findings in the present study are important information to guide further primary and secondary research in this topic.

References

Altman, D.G. & Simera, I. (2016) A history of the evolution of guidelines for reporting medical research: the long road to the EQUATOR Network. *Journal of the Royal Society of Medicine*, **109**:67-77.

Andersen, R.D., Langius-Eklöf, A., Nakstad, B., Bernklev, T. & Jylli, L. (2017) The measurement properties of pediatric observational pain scales: a systematic review of reviews. *International Journal of Nursing Studies*, **73**:93-101.

Atieh, M.A., Alsabeeha, N.H., Faggion, C.M. Jr. & Duncan, W.J. (2013) The frequency of peri-implant diseases: a systematic review and meta-analysis. *Journal of Periodontology*, **84**:1586-98.

Burda, B.U., Holmer, H.K. & Norris, S.L. (2016) Limitations of a measurement tool to assess systematic reviews (AMSTAR) and suggestions for improvement. *Systematic Reviews*, **5**:58.

Bühn, S., Mathes, T., Prengel, P., Wegewitz, U., Ostermann, T., Robens, S. & Pieper, D. (2017) The risk of bias in systematic reviews (ROBIS) tool showed fair reliability and good construct validity. *Journal of Clinical Epidemiology*, pii: S0895-4356(16)30672-2. doi: 10.1016/j.jclinepi.2017.06.019. [Epub ahead of print]

de Vet, H.C., van der Weijden, T., Muris, J.W., Heyrman, J., Buntinx, F. & Knottnerus, J.A. (2011) Systematic reviews of diagnostic research. Considerations about assessment and incorporation of methodological quality. *European Journal of Epidemiology*, **17**:301-6.

Deeks, J.J., Higgins, J.P.T. & Altman, D.G. (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins, J.P.T. & Green, S. (editors). Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons, 2008.

Derks, J. & Tomasi, C. (2015) Peri-implant health and disease. A systematic review of current epidemiology. *Journal of Clinical Periodontology*, **42**:S158-71.

Dong, J., Teng, G., Wei, T., Gao, W. & Wang H. (2016) Methodological quality assessment of meta-analyses and systematic reviews of probiotics in inflammatory bowel disease and pouchitis. *PLoS One*, **11**:e0168785.

Driessen, E., Hollon, S.D., Bockting, C.L., Cuijpers, P. & Turner, E.H. (2015) Does publication bias inflate the apparent efficacy of psychological treatment for major depressive disorder? A systematic review and meta-analysis of US National Institutes of Health-funded trials. *PLoS One*, **10**:e0137864.

Faggion, C.M. Jr. (2013) The development of evidence-based guidelines in dentistry. *Journal of Dental Education*, **77**:124-36.

Faggion, C.M. Jr. (2015) Critical appraisal of AMSTAR: challenges, limitations, and potential solutions from the perspective of an assessor. *BMC Medical Research Methodology*, **15**:63.
Faggion, C.M. Jr. (2016) The rationale for rating risk of bias should be fully reported. *Journal of Clinical Epidemiology*, **76**:238.

Gómez-García, F., Ruano, J., Aguilar-Luque, M., Gay-Mimbrera, J., Maestre-Lopez, B., Sanz-Cabanillas, J.L., Carmona-Fernández, P.J., González-Padilla, M., Vélez García-Nieto, A. & Isla-Tejera, B. (2017) Systematic reviews and meta-analyses on psoriasis: role of funding sources, conflict of interest and bibliometric indices as predictors of methodological quality. *British Journal of Dermatology*, **176**:1633-44.

Higgins, J. P. & Altman, D. G. (2008) Assessing risk of bias in included studies. In: Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series (eds J. P. Higgins and S. Green), John Wiley & Sons, Ltd, Chichester, UK. doi: 10.1002/9780470712184.ch8

Higgins, J.P., Altman, D.G., Gøtzsche, P.C., Jüni, P., Moher, D., Oxman, A.D., Savovic, J., Schulz, K.F., Weeks, L., Sterne JA & Cochrane Bias Methods Group; Cochrane Statistical

Methods Group (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *British Medical Journal*, **343**:d5928.

Higgins, J.P.T., Sterne, J.A.C., Savović, J., Page, M.J., Hróbjartsson, A., Boutron, I., Reeves, B. & Eldridge, S. A revised tool for assessing risk of bias in randomized trials. In: Chandler, J., McKenzie, J., Boutron, I., Welch, V. (editors). Cochrane Methods. Cochrane Database of Systematic Reviews 2016, Issue 10 (Suppl 1). dx.doi.org/10.1002/14651858.CD201601.

Hopewell, S., McDonald, S., Clarke, M. & Egger, M. (2007) Grey literature in meta-analyses of randomized trials of health care interventions. *Cochrane Database of Systematic Reviews*, (2):MR000010.

Ioannidis, J.P. (2016) The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses. *Milbank Q*, **94**:485-514.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G. & PRISMA Group. (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology*, **62**:1006-12.

Monje, A., Aranda, L., Diaz, K.T., Alarcón, M.A., Bagramian, R.A., Wang, H.L. & Catena, A. (2016) Impact of maintenance therapy for the prevention of peri-implant diseases: a systematic review and meta-analysis. *Journal of Dental Research*, **95**:372-9.

Parker, L.A., Saez, N.G., Porta, M., Hernández-Aguado, I. & Lumbreras, B. (2013) The impact of including different study designs in meta-analyses of diagnostic accuracy studies. *European Journal of Epidemiology*, **28**:713-20.

Perry, R., Leach, V., Davies, P., Penfold, C., Ness, A. & Churchill, R. (2017) An overview of systematic reviews of complementary and alternative therapies for fibromyalgia using both AMSTAR and ROBIS as quality assessment tools. *Systematic Reviews*, **6**:97.

Schmucker, C.M., Blümle, A., Schell, L.K., Schwarzer, G., Oeller, P., Cabrera, L., von Elm, E., Briel, M., Meerpohl, J.J. & OPEN consortium. (2017) Systematic review finds that study data not published in full text articles have unclear impact on meta-analyses results in medical research. *PLoS One*, **12**:e0176210.

Shea, B.J., Grimshaw, J.M., Wells, G.A., Boers, M., Andersson, N., Hamel, C., Porter, A.C., Tugwell, P., Moher, D. & Bouter, L.M. (2007) Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology*, **7**:10.

Shea, B.J., Hamel, C., Wells, G.A., Bouter, L.M., Kristjansson, E., Grimshaw, J., Henry, D.A. & Boers, M. (2009) AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *Journal of Clinical Epidemiology*, **62**:1013-20.

Shea, B.J., Reeves, B.C., Wells, G., Thuku, M., Hamel, C., Moran, J., Moher, D., Tugwell, P., Welch, V., Kristjansson, E. & Henry, D.A. (2017) AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *British Medical Journal*, **358**:j4008.

Smith, V., Devane, D., Begley, C.M. and Clarke, M. (2011) Methodology in conducting a systematic review of systematic reviews of healthcare interventions. *BMC Medical Research Methodology*, **11**:15.

Sterne, J.A., Hernán, M.A., Reeves, B.C., Savović, J., Berkman, N.D., Viswanathan, M., Henry, D., Altman, D.G., Ansari, M.T., Boutron, I., Carpenter, J.R., Chan, A.W., Churchill, R., Deeks, J.J., Hróbjartsson, A., Kirkham, J., Jüni, P., Loke, Y.K., Pigott, T.D., Ramsay, C.R., Regidor, D., Rothstein, H.R., Sandhu, L., Santaguida, P.L., Schünemann, H.J., Shea, B., Shrier, I., Tugwell, P., Turner, L., Valentine, J.C., Waddington, H., Waters, E., Wells, G.A., Whiting, P.F. & Higgins, J.P. (2016) ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *British Medical Journal*, **355**:i4919.

Wegewitz, U., Weikert, B., Fishta, A., Jacobs, A. & Pieper, D. (2016) Resuming the discussion of AMSTAR: What can (should) be made better? *BMC Medical Research Methodology*, **16**:111.

Whiting, P., Savović, J., Higgins, J.P., Caldwell, D.M., Reeves, B.C., Shea, B., Davies, P., Kleijnen, J., Churchill, R. & ROBIS group. (2016) ROBIS: A new tool to assess risk of bias in systematic reviews was developed. *Journal of Clinical Epidemiology*, **69**:225-34.

Figure legends

Figure 1. Flowchart of the study selection

Table 1. Characteristics of the included systematic reviews

Systematic review	Condition	Meta-analysis performed	Number of authors	Country	Journal	Impact factor (2015)	Number of studies included in the systematic review	Subjects	Type of study designs included in the systematic review
Ata-Ali et al. 2015	Mucositis	No	3	Spain	Implant Dentistry	1.023	7	Humans	RCT
Chan et al. 2014	Peri-implantitis	Yes	5	USA	Journal of Periodontology	2.844	21	Humans	CS, Cohort, QEs, RCT
Kotsakis et al. 2014	Peri-implantitis	Yes	5	USA	Journal of Periodontology	2.844	6	Humans	CCT, RCT
Kotsovilis et al. 2008	Peri-implantitis	No	4	Greece	Journal of Clinical Periodontology	3.915	5	Humans	RCT
Klinge et al. 2002	Peri-implantitis	No	3	Sweden	Journal of Clinical Periodontology	3.915	21	Humans and animals	CCT, CS, CR
Natto et al. 2015	Peri-implantitis	No	4	USA	International Journal of Oral and Maxillofacial Implants	1.859	13	Humans	PCR, CS, CR, CCT, RCT
Wilson 2013	Peri-implantitis	No	1	Not stated	Primary Dental Journal	WIF	23	Unclear	Unclear

Esposito et al. 2012	Peri-implantitis	Yes	3	England	Cochrane Library	6.035	9	Humans	RCT
Faggion et al. 2013	Peri-implantitis	Yes	4	Germany	Clinical Implant Dentistry and Related Research	4.152	11	Humans	RCT, CCT
Faggion et al. 2014	Peri-implantitis	Yes	5	Germany	Journal of Clinical Periodontology	3.915	11	Humans	RCT
Heitz-Mayfield and Mombelli 2014	Peri-implantitis	No	2	Australia	International Journal of Oral and Maxillofacial Implants	1.859	43	Humans	CS, RCT
Javed et al. 2013	Peri-implantitis	No	6	Saudi Arabia	International Dental Journal	0.967	10	Humans	CS, prospective and RCT
Khoshkam et al. 2013	Peri-implantitis	Yes	8	USA	Journal of Dental Research	4.602	12	Humans	CS, QEs, RCT
Mailoa et al. 2014	Peri-implantitis	Yes	5	USA	Journal of Periodontology	2.844	9	Humans and animals	CS, QEs, RCT
Muthukuru et al. 2012	Peri-implantitis	No	4	USA	Clinical Oral Implants Research	3.464	11	Humans	RCT
Romeo et al. 2004	Mucositis and peri-	No	3	Italy	Minerva Stomatologica	WIF	Unclear	Humans and animals	Unclear

	implantitis								
Sahrmann et al. 2011	Peri-implantitis	No	3	Switzerland	Clinical Implant Dentistry and Related Research	4.152	17	Humans	CCT, Cohort, CS, CR
Salvi and Ramseier et al. 2015	Mucositis	No	2	Switzerland	Journal of Clinical Periodontology	3.915	11	Humans	RCT
Schwarz et al. 2015a	Mucositis and peri-implantitis	Yes	3	Germany	Journal of Clinical Periodontology	3.915	6	Humans	RCT, CCT
Schwarz et al. 2015b	Mucositis	Yes	3	Germany	Journal of Clinical Periodontology	3.915	7	Humans	RCT
Schwarz et al. 2015c	Mucositis and peri-implantitis	Yes	3	Germany	International Journal of Implant Dentistry	WIF	32	Humans	RCT, CCT
Taschieri et al. 2015	Peri-implantitis	No	4	Italy	The Scientific World Journal	WIF	5	Humans	Unclear (general definitions)
Vohra et al. 2014	Mucositis and peri-implantitis	No	5	Saudi Arabia	Photochemical & Photobiological Sciences	2.235	12	Humans, animals, in-vitro	Unclear
Yan et al. 2015	Peri-implantitis	Yes	5	China	Lasers in Medical	2.461	4	Humans	RCT

					Science				
Ramanauskaite et al. 2016a	Peri-impantitis	No	4	Switzerland	Journal of Oral & Maxillofacial Research	WIF	6	Humans	RCT, Cohort, retrospective
Ramanauskaite et al. 2016b	Peri-implantitis	Yes	3	Lithuania	Quintessence International	0.821	29	Humans	Prospective and retrospective
Suarez-Lopez del Amo et al. 2016	Mucositis and peri-implantitis	No	3	USA	Journal of Oral & Maxillofacial Research	WIF	14	Humans	RCT, Cohort, CS, CCT
Daugela et al. 2016	Peri-implantitis	Yes	3	Lithuania	Journal of Oral & Maxillofacial Research	WIF	18	Humans	PCS, CS, RCT
Ghanem et al. 2016	Peri-implantitis	No	7	USA	Photodiagnosis and Photodynamic Therapy	2.412	9	Humans and animals	RCT
Mahato et al. 2016	Peri-implantitis	No	3	China	Springer Plus	0.982	20	Humans	Unclear
de Almeida et al. 2017	Peri-implantitis	No	6	Brazil	Implant Dentistry	1.023	10	Humans	Unclear
Zeza & Piloni 2012	Mucositis	No	2	Italy	Annali di Stomatologia	WIF	5	Humans	RCT and observational studies

RCT: randomized controlled study; CS: case series; QEs: quasi-experiments; CCT: clinical controlled trial; CR: case report; PCR: prospective clinical report; PCS: prospective clinical study; WIF: without impact factor - not found in the database.

Table 2. Results after analysis with the risk of bias in systematic reviews (ROBIS) tool.

	Phase 2				Phase 3
Systematic review	**Study eligibility criteria**	**Identification and selection of studies**	**Data collection and study appraisal**	**Synthesis and findings**	**Risk of bias in the review**
Ata-Ali et al. 2015	LOW	HIGH	HIGH	LOW	HIGH
Chan et al. 2014	LOW	HIGH	HIGH	HIGH	HIGH
Daugela et al. 2016	LOW	UNCLEAR	HIGH	HIGH	HIGH
de Almeida et al. 2017	UNCLEAR	HIGH	HIGH	HIGH	HIGH
Esposito et. al 2012	LOW	LOW	LOW	LOW	**LOW**
Faggion et al. 2013	LOW	LOW	LOW	HIGH	HIGH
Faggion et al. 2014	LOW	UNCLEAR	LOW	LOW	**LOW**
Ghanem et al. 2016	LOW	HIGH	UNCLEAR	HIGH	HIGH
Heitz-Mayfield & Mombelli 2014	LOW	HIGH	LOW	LOW	**LOW**
Javed et al. 2013	HIGH	HIGH	HIGH	HIGH	HIGH
Khoshkam et al. 2013	LOW	UNCLEAR	UNCLEAR	HIGH	HIGH
Klinge et al. 2012	HIGH	HIGH	HIGH	HIGH	HIGH
Kotsakis et al. 2014	UNCLEAR	HIGH	LOW	HIGH	HIGH
Kotsovilis et al. 2008	UNCLEAR	UNCLEAR	UNCLEAR	LOW	HIGH
Mahato et al. 2016	HIGH	HIGH	UNCLEAR	LOW	HIGH
Mailoa et al. 2014	UNCLEAR	HIGH	HIGH	HIGH	HIGH
Muthukuru et al. 2012	UNCLEAR	HIGH	HIGH	HIGH	HIGH
Natto et al. 2015	HIGH	HIGH	HIGH	HIGH	HIGH
Ramanauskaite et al. 2016a	UNCLEAR	UNCLEAR	UNCLEAR	LOW	HIGH
Ramanauskaite et al. 2016b	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	HIGH
Romeo et al. 2004	HIGH	HIGH	HIGH	HIGH	HIGH
Sahrmann et al. 2011	HIGH	HIGH	HIGH	HIGH	HIGH
Salvi & Ramseier 2015	UNCLEAR	HIGH	UNCLEAR	LOW	UNCLEAR
Schwarz et al. 2015a	UNCLEAR	HIGH	UNCLEAR	HIGH	UNCLEAR

Schwarz et al. 2015b	UNCLEAR	HIGH	UNCLEAR	UNCLEAR	HIGH
Schwarz et al. 2015c	UNCLEAR	HIGH	UNCLEAR	UNCLEAR	UNCLEAR
Suarez-Lopez del Amo et al. 2016	UNCLEAR	UNCLEAR	HIGH	LOW	HIGH
Taschieri et al. 2015	UNCLEAR	HIGH	HIGH	HIGH	HIGH
Vohra et al. 2014	HIGH	HIGH	HIGH	HIGH	HIGH
Wilson 2013	HIGH	HIGH	HIGH	HIGH	HIGH
Yan et al. 2015	LOW	UNCLEAR	LOW	UNCLEAR	**LOW**
Zeza and Piloni 2012	HIGH	HIGH	UNCLEAR	HIGH	HIGH

Table 3. Concern-of-bias results across the four risk of bias domains in the risk of bias in systematic reviews (ROBIS) tool.

	Phase 2				Phase 3
Concern of bias	**Study eligibility criteria**	**Identification and selection of studies**	**Data collection and study appraisal**	**Synthesis and findings**	**Risk of bias in the review**
LOW	10 (31)	2 (6)	6 (19)	9 (28)	4 (13)
HIGH	9 (28)	22 (69)	15 (47)	20 (63)	25 (78)
UNCLEAR	13 (41)	8 (25)	11 (34)	3 (9)	3 (9)

Values are given as number (percentage).

Table 4. Results after the analysis of the assessing the methodological quality of systematic reviews (AMSTAR) instrument.

Systematic review	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Total n (percentage) *
Ata-Ali et al. 2015	Y	CA	N	N	Y	Y	Y	Y	Y	NA	N	6 (60)
Chan et al. 2014	Y	Y	Y	N	Y	Y	Y	Y	Y	CA	N	8 (73)
Daugela et al. 2016	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	8 (73)
de Almeida et al. 2017	Y	CA	N	N	N	Y	N	N	CA	NA	N	2 (20)
Esposito et al. 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10 (91)
Faggion et al. 2013	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9 (82)
Faggion et al. 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10 (91)
Ghanem et al. 2016	Y	CA	Y	N	N	Y	Y	Y	CA	N	N	5 (45)
Heitz-Mayfield & Mombelli 2014	Y	Y	Y	N	Y	Y	Y	Y	Y	NA	N	8 (80)
Javed et al. 2013	Y	CA	Y	N	Y	Y	N	N	N	NA	N	4 (40)
Khoshkam et al. 2013	Y	CA	Y	N	N	Y	N	N	Y	Y	N	5 (45)
Klinge et al. 2012	Y	CA	N	N	N	Y	N	N	CA	CA	N	2 (18)
Kotsakis et al. 2014	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	9 (82)
Kotsovilis et al. 2008	Y	Y	Y	N	Y	Y	Y	Y	Y	NA	N	8 (80)
Mahato et al. 2016	Y	Y	N	N	N	Y	N	N	Y	NA	N	4 (40)
Mailoa et al. 2014	Y	CA	Y	N	Y	Y	Y	Y	Y	Y	N	8 (73)
Muthukuru et al. 2012	Y	Y	N	N	Y	Y	N	N	Y	NA	N	5 (50)
Natto et al. 2015	Y	CA	Y	N	N	Y	CA	N	CA	CA	N	3 (27)
Ramanauskaite et al. 2016a	Y	CA	Y	N	N	Y	Y	Y	CA	NA	N	5 (50)
Ramanauskaite et al. 2016b	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	7 (64)

Romeo et al. 2004	N	CA	N	N	N	N	N	N	N	NA	N	0 (0)
Sahrmann et al. 2011	Y	CA	Y	N	Y	Y	N	N	Y	NA	N	5 (50)
Salvi and Ramseier 2015	Y	CA	Y	N	Y	Y	Y	Y	Y	NA	N	7 (70)
Schwarz et al. 2015a	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	9 (82)
Schwarz et al. 2015b	Y	CA	Y	N	Y	Y	Y	Y	Y	Y	N	8 (73)
Schwarz et al. 2015c	Y	CA	Y	N	Y	Y	Y	Y	Y	Y	N	8 (73)
Suarez-Lopez del Amo et al. 2016	Y	Y	Y	N	Y	Y	Y	Y	Y	NA	N	8 (80)
Taschieri et al. 2015	Y	CA	Y	N	N	Y	N	N	Y	NA	N	4 (40)
Vohra et al. 2014	Y	CA	Y	N	Y	Y	N	N	N	CA	N	4 (40)
Wilson 2013	N	N	CA	CA	N	N	N	N	CA	CA	N	0 (0)
Yan et al. 2015	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	9 (82)
Zeza and Piloni 2012	Y	N	N	N	N	Y	Y	Y	Y	NA	N	5 (50)

CA: can´t answer; N: no; NA: not applicable; Y: yes

*To calculate the percentage of items answered with “Y,” ratings of NA were not considered.

Item 1. Was an 'a priori' design provided?

Item 2. Was there duplicate study selection and data extraction?

Item 3. Was a comprehensive literature search performed?

Item 4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?

Item 5. Was a list of studies (included and excluded) provided?

Item 6. Were the characteristics of the included studies provided?

Item 7. Was the scientific quality of the included studies assessed and documented?

Item 8. Was the scientific quality of the included studies used appropriately in formulating conclusions?

Item 9. Were the methods used to combine the findings of studies appropriate?

Item 10. Was the likelihood of publication bias assessed?

Item 11. Was the conflict of interest included?

Table 5. Results for each of the 11 items in the assessing the methodological quality of systematic reviews (AMSTAR).

Score	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11
Yes	30 (94)	14 (44)	24 (75)	3 (9)	19 (59)	30 (94)	20 (63)	20 (63)	23 (72)	10 (31)	0 (0)
No	2 (6)	2 (6)	7 (22)	28 (88)	13 (41)	2 (6)	11 (34)	12 (37)	3 (9)	3 (9)	32 (100)
Cannot answer	0 (0)	16 (50)	1 (3)	1 (3)	0 (0)	0 (0)	1 (3)	0 (0)	6 (19)	5 (16)	0 (0)
Not applicable	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	14 (44)	0 (0)

Values are given as number (percentage).

Item 1. Was an 'a priori' design provided?

Item 2. Was there duplicate study selection and data extraction?

Item 3. Was a comprehensive literature search performed?

Item 4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?

Item 5. Was a list of studies (included and excluded) provided?

Item 6. Were the characteristics of the included studies provided?

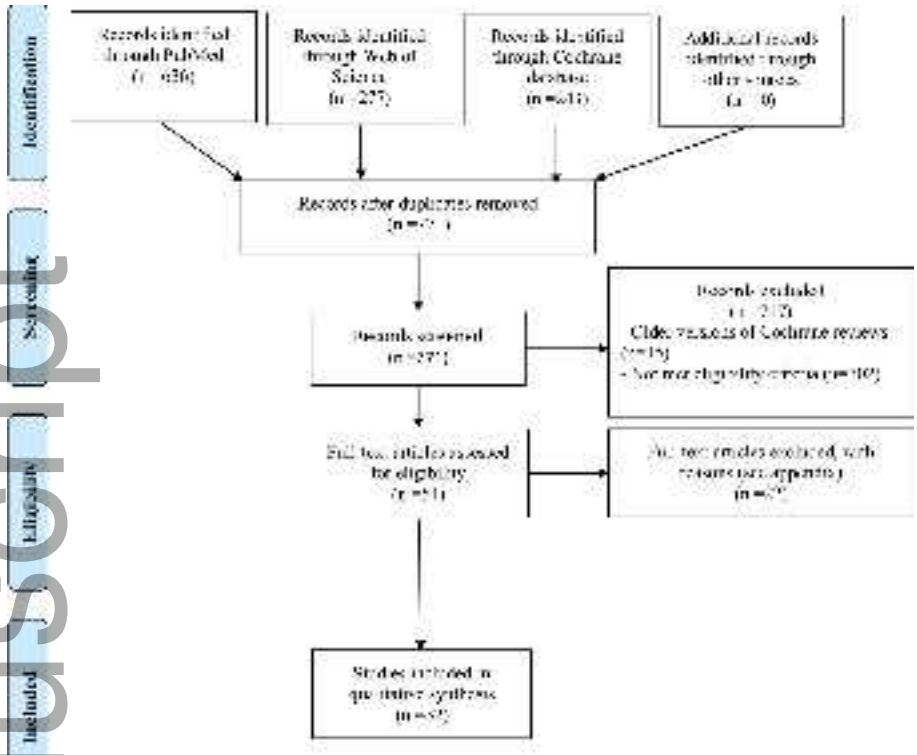
Item 7. Was the scientific quality of the included studies assessed and documented?

Item 8. Was the scientific quality of the included studies used appropriately in formulating conclusions?

Item 9. Were the methods used to combine the findings of studies appropriate?

Item 10. Was the likelihood of publication bias assessed?

Item 11. Was the conflict of interest included?



jcpe_12893_f1.tif

Author/s:
Faggion, CM;Monje, A;Wasiak, J

Title:
Appraisal of systematic reviews on the management of peri-implant diseases with two methodological tools

Date:
2018-06-01

Citation:
Faggion, C. M., Monje, A. & Wasiak, J. (2018). Appraisal of systematic reviews on the management of peri-implant diseases with two methodological tools. JOURNAL OF CLINICAL PERIODONTOLOGY, 45 (6), pp.754-766. https://doi.org/10.1111/jcpe.12893.

Persistent Link:
http://hdl.handle.net/11343/284029