UNIVERSIDADE DE BRASÍLIA

FACULDADE DE SAÚDE

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE

DISSERTAÇÃO DE MESTRADO

AMANDA OLIVEIRA LYRIO

VALIDAÇÃO DE ESTRATÉGIA DE BUSCA PARA ENSAIOS CLÍNICOS RANDOMIZADOS RELACIONADOS À PERIODONTITE

BRASÍLIA, DF

2019

UNIVERSIDADE DE BRASÍLIA
FACULDADE DE SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE

AMANDA OLIVEIRA LYRIO

VALIDAÇÃO DE ESTRATÉGIA DE BUSCA PARA ENSAIOS CLÍNICOS RANDOMIZADOS RELACIONADOS À PERIODONTITE

> Dissertação de mestrado apresentada ao Programa de Pós-Graduação em Saúde Coletiva, Universidade de Brasília, como requisito parcial para obtenção do título de Mestre em Ciências da Saúde.
>
> Área de concentração: Saúde Coletiva
> Orientador: Prof. Dr. Maurício Gomes Pereira
> Coorientadora: Ana Claudia Morais Godoy Figueiredo

BRASÍLIA, DF
2019

AMANDA OLIVEIRA LYRIO

VALIDAÇÃO DE ESTRATÉGIA DE BUSCA PARA ENSAIOS CLÍNICOS RANDOMIZADOS RELACIONADOS À PERIODONTITE

Dissertação de mestrado apresentada ao Programa de Pós-Graduação em Ciências da Saúde, Universidade de Brasília, como requisito parcial para obtenção do título de Mestre em Ciências da Saúde.

Área de concentração: Saúde Coletiva

Brasília, 25 de julho de 2019.

BANCA EXAMINADORA

Prof. Dr. Maurício Gomes Pereira – Presidente
Universidade de Brasília

Prof. Dr. Isaac Suzart Gomes Filho
Universidade Estadual de Feira de Santana

Profa. Dra Nailê Damé Teixeira
Universidade de Brasília

Prof. Dra. Simone Seixas da Cruz
Universidade Federal do Recôncavo da Bahia

BRASÍLIA, DF
2019

Dedico este trabalho a minha mãe Maria Analice, que sempre me apoiou e incentivou.

AGRADECIMENTOS

Esta fase da minha vida é muito especial e não posso deixar de agradecer a Deus pela a oportunidade e por toda força, ânimo e coragem que me ofereceu para ter alcançado minha meta. Sem Ele, nada disso seria possível.

Agradeço "in memorian" a meu pai Anilson, pelo seu amor e sua preocupação para que nada me faltasse e por sempre me ensinar a lutar pelo o que eu queria. Infelizmente ele não pode estar presente neste momento, mas não poderia deixar de agradecê-lo, pois se hoje estou aqui, devo a ele. Obrigada por tudo!! Saudade eterna!!

Agradeço também a minha mãe Maria Analice, por ser essa mulher especial, sempre presente em minha vida, me apoiando e me dando força. Sem este apoio dificilmente teria conseguido concluir essa etapa da minha vida.

Não posso deixar de agradecer a minha família e amigos, que é a minha base e foram eles que me incentivaram e me inspiraram através de gestos e palavras a superar todas as dificuldades. Em especial aos meus irmãos, Mateus e Lucas, que através da sua forma de ser, me dão força e fazem os meus dias mais especiais. Agradeço ao meu namorado Elivan, pelo seu carinho, apoio e incentivo.

Sou grata também a todos os professores que contribuíram com a minha trajetória acadêmica. Em especial a professora Simone Seixas, uma pessoa maravilhosa, além de um exemplo de profissional, a qual não tenho palavras para agradecer o cuidado, atenção e zelo em compartilhar seus conhecimentos desde a graduação. Além disso, agradeço a oportunidade de participar do NES – Núcleo de Epidemiologia e Saúde, o qual me proporcionou crescimento pessoal e profissional.

Não posso deixar de agradecer também ao meu orientador, Mauricio Pereira, um profissional de excelência, por contribuir no meu aprendizado, compartilhando seus conhecimentos. E a minha coorientadora Ana Claudia Godoy, por compartilhar sua sabedoria, o seu tempo e sua experiência, além de sempre me apoiar e incentivar.

Agradeço a Universidade de Brasília a oportunidade de realizar esse sonho e por colocar pessoas especiais em minha caminhada. Em especial a todos do Laboratório de pesquisas sobre saúde baseada em evidência pelo o apoio de forma direta ou indireta na construção dessa dissertação.

Não poderia deixar de agradecer também a equipe da Gerência de Informação e Análise de Situação em Saúde (GIASS), pelo acolhimento e aprendizado durante esse ano de mestrado.

A quem não mencionei, mas esteve presente ao meu lado eu quero lembrar que não estão esquecidos: vocês foram imensamente importantes e eu agradeço de todo meu coração.

RESUMO

Introdução: As revisões sistemáticas de ensaios clínicos randomizados, consideradas padrão-ouro para julgamento de evidência científica, podem apresentar achados conflitantes para uma mesma questão clínica e tais dissensos podem ser justificados, por exemplo, pelas distintas formas de elaboração da estratégia de busca eletrônica. Assim o objetivo do do artigo foi validar uma estratégia de busca para identificação de ensaios clínicos randomizados relacionados à periodontite. **Método**: Um estudo de validação elaborado no MedLine por meio da plataforma PubMed. Inicialmente, um filtro metodológico recomendado pela Colaboração Cochrane, para identificar ensaios clínicos randomizados foi aplicado - Etapa 1. Em seguida, dentre as referências recuperadas, aquelas relacionadas apenas à periodontite foram identificadas - Etapa 2. Posteriormente, uma frase de busca destinada à recuperação de estudos relacionados à periodontite foi elaborada por especialistas - Etapa 03. Para elevar a qualidade dessa frase de busca, o instrumento *Peer Review of Electronic Search Strategies* (PRESS) foi empregado. A Etapa 4 compreendeu a combinação da frase de busca elaborada com o filtro metodológico supracitado e posterior aplicação na plataforma PubMed para recuperação de ensaios clínicos randomizados relacionados à periodontite, sendo definida como a estratégia de busca proposta. Os dados obtidos foram analisados tomando como padrão-ouro o conjunto de referências identificado na Etapa 2 e os valores de desempenho (sensibilidade, especificidade, valor preditivo positivo e número necessário para ler) foram calculados com seus respectivos intervalos de confiança a 95%. **Resultados**: A estratégia de busca proposta quando comparada ao padrão-ouro apresentou sensibilidade de 93,2% $IC_{95\%}$ (83,8 – 97,3), especificidade 99,9% $IC_{95\%}$ (99,8 – 99,9) e valor preditivo positivo de 77,5% $IC_{95\%}$ (66,48 – 85,63). Além disso, o número necessário de documentos para ler foi 1,3, significando que ao aplicar a estratégia de busca proposta a cada 13 documentos identificados, 10 estariam relacionados à condição de interesse. **Conclusão**: De acordo com a abordagem metodológica proposta, a estratégia de busca validada apresentou bom desempenho na identificação de ensaios clínicos randomizados relacionados à periodontite.

ABSTRACT

Background: Systematic reviews, considered the gold standard for the assessment of scientific evidence, may present conflicting findings for the same clinical issue, and such dissent may be justified, for example, by the forms of elaboration of the electronic search strategy. The aim of this paper is to validate a search strategy to identify randomized clinical trials related to periodontitis. **Method:** A validation study was developed in MEDLINE/PubMed platform. In the Stage 1, a methodological filter recommended by the Cochrane Collaboration to identify randomized clinical trials was applied. Next, among the articles retrieved, those related only to periodontitis were identified - Stage 2. Subsequently, a search statement for the retrieval of periodontitis-related articles was elaborated by experts - Stage 3. The Stage 4 defined the proposed search strategy and comprised the combination of the search statement developed with the aforementioned methodological filter and subsequent application in MEDLINE/PubMed. The obtained data were analyzed using the set of articles identified in Stage 2, as the gold-standard, and the performance values were calculated - sensitivity, specificity, precision and number needed to read - with their respective 95% confidence interval (95%CI). **Results:** The search strategy under evaluation compared to the gold-standard showed a sensitivity of 93.2% (95%CI, 83.8-97.3), specificity of 99.9% (95%CI 99.8-99.9) and a precision of 77.5% (95%CI, 66.48-85.63). In addition, the needed number of articles to read was 1.3. **Conclusion:** According to the proposed methodological approach, the search strategy under evaluation performed well in the identification of randomized clinical trials related to periodontitis.

LISTA DE ILUSTRAÇÕES

LISTA DE TABELAS

SUMÁRIO

1 APRESENTAÇÃO

O ensaio clínico randomizado é o delineamento de estudo mais recomendado para avaliar a eficácia de uma intervenção, garantindo assim uma maior qualidade da evidência (1, 2). Entretanto, dificilmente consegue-se realizar esse estudo de forma representativa, pois, geralmente é necessário um tamanho amostral significativo, alto investimento para garantir infraestrutura adequada, recursos humanos especializados, materiais para a intervenção em quantidade suficiente, na maioria das vezes (3, 4).

Devido a quantidade de artigos publicados com amostras não representativas para população ou com resultados controversos é essencial a realização de revisões sistemáticas a fim de sintetizar e avaliar se os resultados podem ser expandidos para a população ou se necessita de mais pesquisas sobre o tema (5-7), uma vez que contribuirá para tomada de decisão racional dos formuladores de políticas, prestadores de serviços de saúde e pesquisadores em todas as áreas da saúde (1, 7, 8).

A revisão sistemática necessita de uma estratégia de busca abrangente, para conseguir recuperar os artigos, publicados ou não, sobre o tema de estudo, o que lhe proporciona um resultado de qualidade, que realmente reflete o conhecimento científico existente sobre o tema(9). Mas, não raras vezes, a qualidade da estratégia de busca não é avaliada e é feita de diversas formas para o mesmo tema de estudo, tornando o resultado obtido pouco confiável (10-13). Desse modo, é de suma importância a realização de estudos que avaliem a qualidade da estratégia de busca, avaliando a sensibilidade e a precisão que a estratégia tem para recuperar as investigações sobre o tema.

Importante mencionar que a periodontite é responsável por diversos desfechos desfavoráveis para os indivíduos, além de ser fator de risco para inúmeoas agravos, como pneumonia, insuficiência renal, complicações na gestação entre outros problemas (14-16) . Desta forma, anualmente, são produzidos diversas revisões sistemáticas de ensaios clínicos randomizados relacionados com a periodontite (10-12). Mas, como mencionado anteriormente, a estratégia de busca, apesar de ser essencial para garantir a qualidade do estudo, raramente é avaliada adequadamente.

Diante disso, considerando a importância da revisão sistemática de ensaios clínicos randomizados acerca da periodontite para a tomada de decisão e a escassez de estudos que avaliem a qualidade da estratégia de busca, justifica-se o interesse em abordar o referido tema nesta dissertação de mestrado.

A presente dissertação teve como objetivo validar uma estratégia de busca para identificação de ensaios clínicos randomizados relacionados à periodontite. Para tanto, foi desenvolvido um artigo de acurácia sobre o tema estudado intitulado: Validation of a search strategy for randomized clinical trials related to periodontitis. Neste artigo foi avaliado a sensibilidade e precisão da estratégia de busca proposta. Sendo utilizada uma estratégia de busca de ensaio clínico randomizado já validada pela Cochrane unida com uma estratégia de busca de periodontite formulada por especialistas da área e avaliada por uma bibliotecária através do instrumento Peer Review of Electronic Search Strategies (PRESS) (17). O artigo produzido está disponível na sessão 3 desta dissertação.

1.1 VALIDAÇÃO DE ESTRATÉGIA DE BUSCA NA REVISÃO SISTEMÁTICA

A revisão sistemática é definida como um tipo de estudo que sintetiza a evidência científica existente (18). Sendo de grande importância, vista a quantidade exacerbada de conteúdo científico que é produzido em um curto intervalo de tempo, o que torna difícil para os profissionais de saúde, tomadores de decisão e pesquisadores conseguirem utilizar toda evidência produzida (3, 5, 19). Além disso, a revisão sistemática reduz a probabilidade de erro aleatório, aumenta a possibilidade de generalizar os resultados, avalia a qualidade metodológica dos artigos originais e, ainda, avalia se há necessidade de mais estudos sobre o tema (6, 20).

Devido a relevância da revisão sistemática, muitos estudos com este delineamento estão sendo publicados nos últimos anos na área da odontologia (21-24). Mas, para garantir a qualidade dos resultados desses estudos, é necessário cautela em alguns detalhes na execução do trabalho, como por exemplo, utilizar mais de duas bases de dados e buscar estudos na literatura cinzenta (9). Sendo essencial também uma estratégia de busca bem elaborada, para conseguir recuperar a maioria dos estudos sobre o tema, caso contrário não é possível ter

certeza que o resultado da revisão sistemática reflete as evidências científicas existentes (9, 17, 25).

Apesar da importância da estratégia de busca, não há um consenso para a elaboração desta, sendo comum que os estudos utilizem estratégias diferentes para temas semelhantes (13). Além disso, geralmente, não é avaliado acurácia da estratégia para recuperar os estudos do tema de interesse, o que impossibilita garantir que a estratégia de busca utilizada possui sensibilidade e precisão adequada (25, 26).

Diante da relevância da validação da estratégia de busca, diversos estudos estão avaliando a acurácia destas em alguns temas específicos, o que possivelmente irá refletir na qualidade de futuras revisões sistemáticas (25, 27, 28). Sendo importante ressaltar que não foi encontrada nenhuma publicação acerca de estratégia de busca validada na área da odontologia e, consequentemente, não há nenhuma de periodontite.

1.2 PERIODONTITE

A periodontite é uma condição inflamatória crônica multifatorial definida como uma perda patológica do ligamento periodontal e do osso alveolar (29, 30). Importante mencionar que esta doença possui alta prevalência na população mundial e está associada a diversas condições desfavoráveis nos portadores, como desfechos adversos na gravidez, por exemplo, parto prematuro e a outras doenças inflamatórias sistêmicas como a artrite reumatoide e insuficiência renal (14, 15, 31).

Desta forma, a periodontite tem sido alvo de diversos estudos a fim de avaliar a eficácia dos tratamentos (32). E como dificilmente o estudo de ensaio clínico randomizado consegue ser representativo para a população, estão sendo produzidos diversos estudos de revisão sistemática sobre o tema (10, 31, 33, 34).

1.3 REFERÊNCIAS

1. Group GW. Grading quality of evidence and strength of recommendations. BMJ: British Medical Journal. 2004;328(7454):1490.

2. Ruberg SJ, Akacha M. Considerations for Evaluating Treatment Effects From Randomized Clinical Trials. Clin Pharmacol Ther. 2017;102(6):917-23.

3. Brasil. Ministério da Saúde. Secretaria de Ciência TeIEDdCeT. Diretrizes metodológicas: elaboração de revisão sistemática e metanálise de ensaios clínicos randomizados. A Normas e Manuais Técnicos. 2012:92-.

4. DE OLIVEIRA MAP, Parente RCM. Entendendo ensaios clínicos randomizados. Brazilian Journal of Videoendoscopic Surgery. 2010;3(4):176-80.

5. Mulrow CD. Rationale for systematic reviews. BMJ. 1994;309(6954):597-9.

6. Delgado-Rodríguez M, Sillero-Arenas M. Systematic review and meta-analysis. Med Intensiva. 2018;42(7):444-53.

7. Sampaio R, Mancini M. Estudos de revisão sistemática: um guia para síntese criteriosa da evidência científica. Brazilian Journal of Physical Therapy. 2007;11:83-9.

8. Akobeng AK. Understanding randomised controlled trials. Arch Dis Child. 2005;90(8):840-4.

9. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.

10. Ikram S, Hassan N, Raffat MA, Mirza S, Akram Z. Systematic review and meta-analysis of double-blind, placebo-controlled, randomized clinical trials using probiotics in chronic periodontitis. J Investig Clin Dent. 2018;9(3):e12338.

11. Gartenmann SJ, Weydlich YV, Steppacher SL, Heumann C, Attin T, Schmidlin PR. The effect of green tea as an adjunct to scaling and root planing in non-surgical periodontitis therapy: a systematic review. Clin Oral Investig. 2019;23(1):1-20.

12. Mokeem S. Efficacy of adjunctive low-level laser therapy in the treatment of aggressive periodontitis: A systematic review. J Investig Clin Dent. 2018;9(4):e12361.

13. Jenkins M. Evaluation of methodological search filters--a review. Health Info Libr J. 2004;21(3):148-63.

14.	Deschamps-Lenhardt S, Martin-Cabezas R, Hannedouche T, Huck O. Association between periodontitis and chronic kidney disease: Systematic review and meta-analysis. Oral Diseases. 2019;25(2):385-402.

15.	Pattanashetti JI, Nagathan VM, Rao SM. Evaluation of Periodontitis as a Risk for Preterm Birth among Preeclamptic and Non-Preeclamptic Pregnant Women - A Case Control Study. J Clin Diagn Res. 2013;7(8):1776-8.

16.	Gomes-Filho IS, de Oliveira TF, da Cruz SS, Passos-Soares JeS, Trindade SC, Oliveira MT, et al. Influence of periodontitis in the development of nosocomial pneumonia: a case control study. J Periodontol. 2014;85(5):e82-90.

17.	McGowan J, Sampson M, Salzwedel DM, Cogo, E., Foerster, et al. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. Journal of Clinical Epidemiology. 2016;75:40-6.

18.	Wang X, Hawkins BS, Dickersin K. Cochrane systematic reviews and co-publication: dissemination of evidence on interventions for ophthalmic conditions. Syst Rev. 2015;4:118.

19.	Linde K, Willich SN. How objective are systematic reviews? Differences between reviews on complementary medicine. J R Soc Med. 2003;96(1):17-22.

20.	Boren SA, Moxley D. Systematically reviewing the literature: building the evidence for health care quality. Mo Med. 2015;112(1):58-62.

21.	Salhi L, Rompen E, Sakalihasan N, Laleman I, Teughels W, Michel JB, et al. Can Periodontitis Influence the Progression of Abdominal Aortic Aneurysm? A Systematic Review. Angiology. 2019;70(6):479-91.

22.	Cafferata EA, Jerez A, Vernal R, Monasterio G, Pandis N, Faggion CM. The therapeutic potential of regulatory T lymphocytes in periodontitis: A systematic review. J Periodontal Res. 2019;54(3):207-17.

23.	Du M, Bo T, Kapellas K, Peres MA. Prediction models for the incidence and progression of periodontitis: A systematic review. J Clin Periodontol. 2018;45(12):1408-20.

24.	Alakhali MS, Al-Maweri SA, Al-Shamiri HM, Al-Haddad K, Halboub E. The potential association between periodontitis and non-alcoholic fatty liver disease: a systematic review. Clin Oral Investig. 2018;22(9):2965-74.

25.	Beynon R, Leeflang MM, McDonald S, Eisinga A, Mitchell RL, Whiting P, et al. Search strategies to identify diagnostic accuracy studies in MEDLINE and EMBASE. Cochrane Database Syst Rev. 2013(9):MR000022.

26.   Li L, Smith HE, Atun R, Tudor Car L. Search strategies to identify observational studies in MEDLINE and Embase. Cochrane Database Syst Rev. 2019;3:MR000041.

27.   Golder S, Wright K, Loke YK. The development of search filters for adverse effects of surgical interventions in medline and Embase. Health Info Libr J. 2018;35(2):121-9.

28.   Durão S, Kredo T, Volmink J. Validation of a search strategy to identify nutrition trials in PubMed using the relative recall method. J Clin Epidemiol. 2015;68(6):610-6.

29.   Slots J. Periodontitis: facts, fallacies and the future. Periodontol 2000. 2017;75(1):7-23.

30.   Wilder RS, Moretti AJ. Gingivitis and periodontitis in adults: Classification and dental treatment. UpToDate Retrieved from http://www uptodate comlpatients/content/topic do. 2010.

31.   Silvestre FJ, Silvestre-Rangil J, Bagán L, Bagán JV. Effect of nonsurgical periodontal treatment in patients with periodontitis and rheumatoid arthritis: A systematic review. Med Oral Patol Oral Cir Bucal. 2016;21(3):e349-54.

32.   Aljudaibi S, Duane B. Do adjunctive statins improve periodontal treatment outcomes in patients with chronic periodontitis? Evid Based Dent. 2019;20(1):18-9.

33.   Chen J, Chen Q, Hu B, Wang Y, Song J. Effectiveness of alendronate as an adjunct to scaling and root planing in the treatment of periodontitis: a meta-analysis of randomized controlled clinical trials. J Periodontal Implant Sci. 2016;46(6):382-95.

34.   Zhang Z, Zheng Y, Bian X. Clinical effect of azithromycin as an adjunct to non-surgical treatment of chronic periodontitis: a meta-analysis of randomized controlled clinical trials. J Periodontal Res. 2016;51(3):275-83.

2 OBJETIVO

- Validar uma estratégia de busca para identificação de ensaios clínicos randomizados relacionados à periodontite

3 ARTIGO: VALIDATION OF A SEARCH STRATEGY FOR RANDOMIZED CLINICAL TRIALS RELATED TO PERIODONTITIS

ABSTRACT

Background: Systematic reviews, considered the gold standard for the assessment of scientific evidence, may present conflicting findings for the same clinical issue, and such dissent may be justified, for example, by the forms of elaboration of the electronic search strategy. The aim of this paper is to validate a search strategy to identify randomized clinical trials related to periodontitis. **Method:** A validation study was developed in MEDLINE/PubMed platform. In the Stage 1, a methodological filter recommended by the Cochrane Collaboration to identify randomized clinical trials was applied. Next, among the articles retrieved, those related only to periodontitis were identified - Stage 2. Subsequently, a search statement for the retrieval of periodontitis-related articles was elaborated by experts - Stage 3. The Stage 4 defined the proposed search strategy and comprised the combination of the search statement developed with the aforementioned methodological filter and subsequent application in MEDLINE/PubMed. The obtained data were analyzed using the set of articles identified in Stage 2, as the gold-standard, and the performance values were calculated - sensitivity, specificity, precision and number needed to read - with their respective 95% confidence interval (95%CI). **Results:** The search strategy under evaluation compared to the gold-standard showed a sensitivity of 93.2% (95%CI, 83.8-97.3), specificity of 99.9% (95%CI 99.8-99.9) and a precision of 77.5% (95%CI, 66.48-85.63). In addition, the needed number of articles to read was 1.3. **Conclusion:** According to the proposed methodological approach, the search strategy under evaluation performed well in the identification of randomized clinical trials related to periodontitis.

Keywords: Methodological Studies; Research Design; Systematic Review; Periodontitis; Sensitivity.

3.1 INTRODUCTION

In the last decades, the systematic review, defined as a type of study that synthesizes the scientific evidence existing in the literature, has provided ample space in the field of health, including dentistry. It is estimated that in 2010, 11 systematic reviews were published per day[1]. Most likely, this number should be even higher today. Regarding dentistry, it is estimated that approximately 1,000 (thousand) systematic reviews were published in 2017, according to the MEDLINE using PubMed platform (MEDLINE /PubMed) *.

Although it is considered the gold standard for the assessment of scientific evidence, systematic reviews of randomized clinical trials often present conflicting findings for the same issue[2]. Considering the reproducibility of this design, the aforementioned conflict between the findings does not seem justifiable, *a priori.*

However, a closer inspection of the stages of the systematic review protocol may explain this phenomenon. One of them concerns the elaboration of the electronic search strategy, which can be simplified as a "specific algorithm". The construction of this syntax occurs through index terms/synonyms and symbols to retrieve articles that report evidence about a particular research question in an electronic bibliographic database[3,4].

However, it is highlighted that an electronic search strategy holds strong subjectivity in itself, to the point that scholars argue that different researchers invariably tend to build different strategies on the same object of interest[5,6]. For example, a quick search in the periodontal literature on strategies aiming to identify periodontitis-related studies can identify different ways of elaborating strategies with different sets of references retrieved with varying accuracy. It can impact directly in the quality of the systematic search and its results as well as the time required for its execution[7-10].

Therefore, strengthening the means to validate search strategies, estimating quantitative indicators of their performance, such as the strategy sensitivity and specificity, is a reasonable way to increase the quality of the identification of studies and, consequently, of the findings of systematic reviews. This article aims to validate a search strategy for the identification of randomized clinical trials related to periodontitis.

* The filter prepared by PubMed for the identification of systematic reviews.

3.2 METHODS

3.2.1 Study design

This is a methodological study for the validation of a search strategy to identify randomized clinical trials related to periodontitis on MEDLINE /PubMed.

3.2.2 Procedures for identification of the gold-standard set and the retrieved articles using the search strategy under evaluation

Stage 1 – Application of the Cochrane Collaboration's methodological filter

Initially, the methodological filter was applied to identify randomized clinical trials, which was validated by the Cochrane Collaboration (Cochrane Highly Sensitive Search Strategy - HSSS) and has high sensitivity and precision for MEDLINE /PubMed [11]. A chronological filter was also used from January 01 to March 31, 2018.

Stage 2 – Application of the eligibility criteria

Among the articles retrieved concerning to randomized clinical trials, those related only to periodontitis were identified. In addition, exclusion criteria comprised of studies involving animal models and reviews of randomized clinical trials. This stage of reading titles and abstracts was performed by two authors (SSC and AOL) and confirmed by a more experienced periodontist (ISGF), in case of disagreement. When necessary, full-text versions were evaluated.

Thus, after performing the above stages, a set of references that composed the gold-standard articles was selected: randomized clinical trials, related to periodontitis.

Stage 3 – Definition of the search statement related to periodontitis

The search statement for identifying the condition of interest (periodontitis) was developed using the tool "advanced search" in MEDLINE/PubMed, as follows: 1) controlled vocabulary terms related to periodontitis were identified; 2) a periodontist and general dentist (ISGF and SSC) identified the main keywords and their derivations; 3) the retrieved articles were carefully analyzed, and the terms that were associated with studies not related to periodontitis were discarded, for example the term "gingivitis"; and 4) the procedure was repeated until the strategy was considered adequate, using the *Peer Review of Electronic Search Strategies* (PRESS)[4] checklist with the assistance of an experienced librarian (VSSS).

Stage 4 – Application of the search strategy under evaluation

Stage 4 comprised the combination of the search statement developed (Stage 3) with the abovementioned methodological filter (Stage 1) and subsequent application in MEDLINE/PubMed for the retrieval of randomized clinical trials related to periodontitis, defined as the search strategy under evaluation.

3.2.3 Data analysis procedures

The proposed search strategy was evaluated by analyzing the extent to which it retrieved the studies in the gold-standard articles set, and the sensitivity, specificity, and precision of this strategy were calculated according to the following formulas:

$$I - Sensitivity = \frac{True\ positive}{True\ positive + False\ negative}$$

$$II - Specificity = \frac{True\ negative}{True\ negative + False\ positive}$$

$$III - Precision = \frac{True\ positive}{True\ positive + False\ positive}$$

$$IV - Number\ needed\ to\ read = \frac{1}{Precision}$$

The 95% confidence intervals ($_{95\%}$CI) of the strategy performance values were calculated for each estimated measurement.

3.3 RESULTS

At the end of Stage 1, a total of 18,056 articles were retrieved according to the Cochrane Highly Sensitive Search Strategy (HSSS) methodological filter combined with the chronological filter. Of these, 178 were conducted using an animal model, 18 were letters to the editor, seven were scoping reviews, 11 were reviews of reviews, and 715 were systematic reviews of clinical trials (Figure 1). As for the other studies, 17,127 clinical trials were conducted on humans, of which only 59 were related to periodontitis, comprising of gold-standard articles set obtained in Stage 2.

After the evaluation of the search strategy with PRESS, a search statement was obtained, employing controlled vocabulary terms, title and abstract filters, connected by Boolean operators, combined with a chronological filter. Thus, according to figure 1, at the end of the Stage 3, 3.843 articles were obtained. By using the final strategy under evaluation, 72 randomized clinical trials related to periodontitis were retrieved at the Stage 4. It is noteworthy, however, that from the total of retrieved articles, one study (1.4%) did not belong to the set of randomized clinical trials identified with the Cochrane Collaboration methodological filter, although this was of interest of the bibliographical search. Therefore, the study was excluded from the analysis, being classified as an outlier.

Thereby, among the 71 retrieved articles, 65 were related to periodontitis. However, when only randomized clinical trials were selected, 55 articles were included in the performance analysis of the search strategy under evaluation. The findings of the performance analysis showed that the final search strategy had a sensitivity of 93.2% ($_{95\%}$CI 83.8 - 97.3), specificity of 99.9% ($_{95\%}$CI 99.8 - 99.9) , precision of 77.5% ($_{95\%}$CI 66.5-85.7) and number needed to read of 1.3 studies (Table 1).

Figure 1 - Flowchart of the procedures of identification of the gold-standard set and the articles retrieved using the search strategy under evaluation.
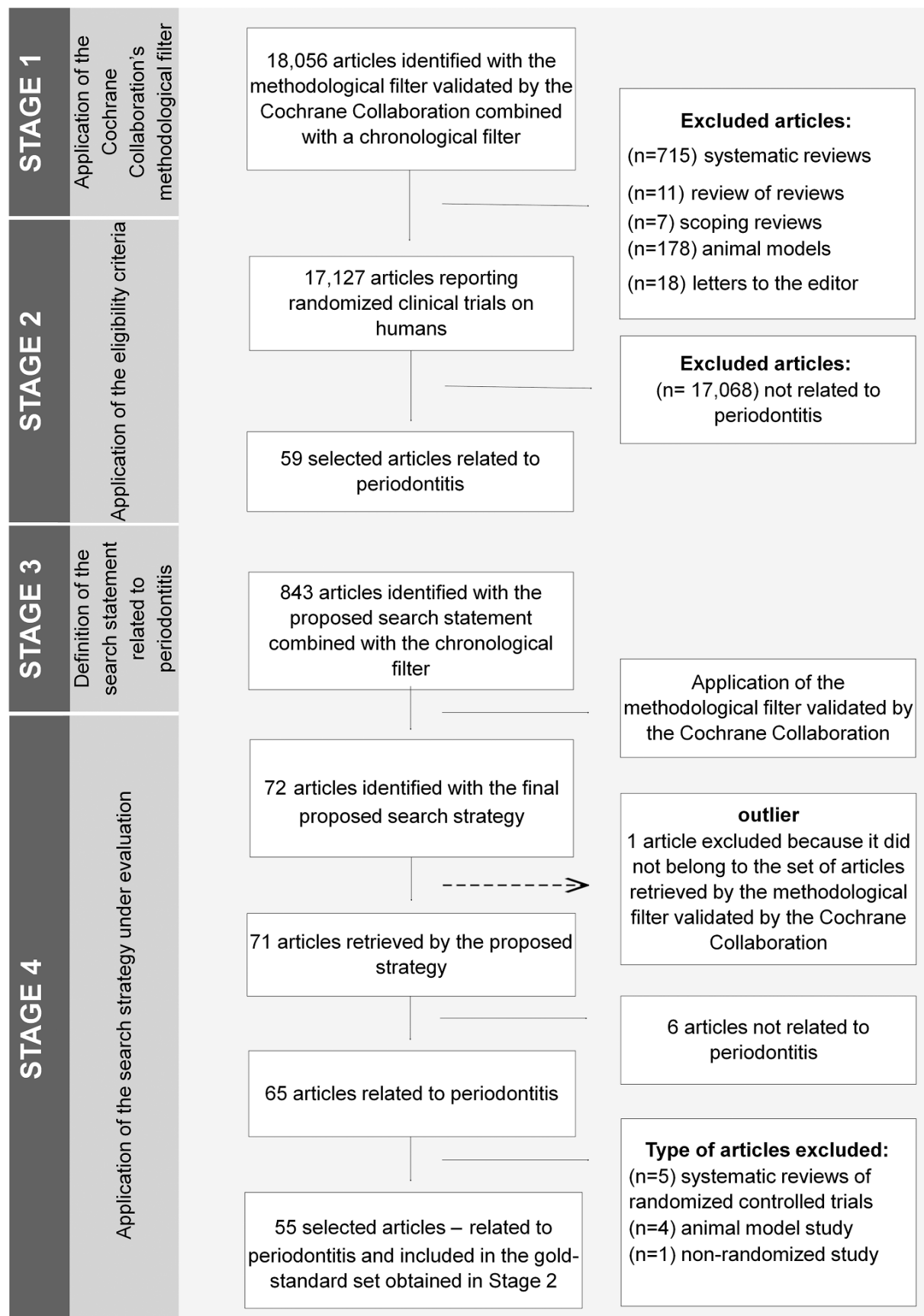
Table 1 - Sensitivity, specificity, and precision, their respective 95% confidence intervals (95%CI), and number needed to read for the comparison between the search strategy under evaluation and the set of gold-standard articles.

Indicator	Value	95%IC
Sensitivity (%)	93.2	83.8-97.3
Specificity (%)	99.9	99.8-99.9
Precision (%)	77.5	66.5-85.6
NNR * (absolute value)	1.3	-

* Number needed to read (NNR) = 1/ precision

3.4 DISCUSSION

3.4.1 Main results

The main findings of the present study suggest that the search strategy under evaluation, used to identify randomized clinical trials related to periodontitis in MEDLINE/PubMed, presented a good performance when compared to the gold-standard strategy, based on validity indicators - sensitivity, specificity, precision and number needed to read.

3.4.2 Comparison with other types of study about the topic

Studies that carried out validation of a strategy to identify randomized clinical trials specifically related to periodontitis were not found. However, there are investigations that validated strategies to identify studies related to other areas. In addition, some studies[11,12] carried out validation of search strategies employing a method similar to the one presented here, with a gold-standard based also on the HSSS filter of the Cochrane Collaboration.

With a similar goal, a strategy to obtain a sensitive search about randomized clinical trials on diet and nutrition was developed[12]. The gold-standard of the aforementioned study was based on the HSSS, and 298 systematic reviews of the Cochrane Collaboration were employed, rather than original articles as in the present study. Also, it was observed that the best strategy of the study on diet and nutrition showed sensitivity of 88.6%, close to the indicator estimated in this study 93.2%.

Similarly, another investigation, in an attempt to recognize articles related to adverse effects to surgery[13], the sensitivity of two search strategies was estimated. In their best strategy, sensitivity measurements of 93% for MEDLINE and 95% for Embase were obtained. Thus, indicators similar to those estimated in this investigation were also observed.

3.4.3 Strengths

The search strategy proposed in this study can be well applied to the elaboration of systematic reviews of randomized clinical trials related to periodontitis, since it will promote a reduction in the operational time of an important stage of this type of secondary study - the identification of publications to be included[14-17].

According to one of the performance indicators evaluated, the number needed to read[18,19], for every 13 articles identified, 10 would likely be of interest to the researchers, conferring a higher operational speed for this stage. Therefore, the elaborated strategy can be useful for reducing time and human resources for the elaboration of bibliographic researches.

Consequently, there can be a considerable cost reduction for the performance of systematic reviews related to periodontitis, which are commonly useful for the synthesis of evidence[5,7,20]. In addition, there is an increase in the validity of the review since the strategy developed showed high sensitivity in the identification of studies on the topic of interest.

It should be noted that the adoption of the gold-standard search strategy was based on two pillars. The first one, which has recognized validity, since a filter developed by the Cochrane Collaboration (HSSS)[11] was used to identify all randomized clinical trials in the period determined in this investigation. The second pillar concerns to the construction of a search statement, specific for periodontitis, developed independently by two researchers with experience and qualification in the field of knowledge, improving the reliability of the identification of relevant studies.

It is also noteworthy that this search statement was evaluated by a professional with a background in Librarianship, according to the recommendations of PRESS, aiming to improve the quality of the research in the database[21,22].

3.4.4 Limitations

In this study, the consultation only to the platform MEDLINE/PubMed can represent a limitation since it restricts the extrapolation of the good performance of the strategy developed to other databases[17]. However, the adaptation of MEDLINE/PubMed search syntax to the main electronic databases, such as Embase or Web of Science, is a usual procedure, it does not require great effort by the researchers[5].

Another limitation refers to the chronological filter applied to the Cochrane strategy for the identification of randomized clinical trials, which included the three initial months of the year 2018. This decision provided a convenience sample of the studies published that year, instead of a

probabilistic sample that would be more desirable to increase the representativeness of the included studies in the referred year.

In this sense, the next steps for this investigation include the use of all randomized clinical trials over a year to minimize the potential problem of generalized restriction. Another improvement would be an evaluation of the quality of the investigations retrieved using the evaluated strategy, since this step was not performed in this study.

3.5 CONCLUSION

The developed search strategy exhibited good performance for the adequate retrieval of randomized clinical trials related to periodontitis. Additionally, it can be a useful tool in reducing time and cost for researchers.

3.6 CONFLICT OF INTEREST

The authors also declare no conflicts of interest related to the study.

3.7 REFERENCES

1.   Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? PLoS Med. 2010;7(9):e1000326.

2.   Ioannidis JP. Meta-research: The art of getting it wrong. Res Synth Methods. 2010;1(3-4):169-184.

3.   Sampson M, McGowan J, Cogo E, Grimshaw J, Moher D, Lefebvre C. An evidence-based practice guideline for the peer review of electronic search strategies. J Clin Epidemiol. 2009;62(9):944-952.

4.   McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol. 2016;75:40-46.

5.   Jenkins M. Evaluation of methodological search filters--a review. Health Info Libr J. 2004;21(3):148-163.

6.   Franco JVA, Garrote VL, Escobar Liquitay CM, Vietto V. Identification of problems in search strategies in Cochrane Reviews. Res Synth Methods. 2018;9(3):408-416.

7.   Faggion CM, Atieh MA, Park S. Search strategies in systematic reviews in periodontology and implant dentistry. J Clin Periodontol. 2013;40(9):883-888.

8.   Natto ZS, Abu Ahmad RH, Alsharif LT, et al. Chronic Periodontitis Case Definitions and Confounders in Periodontal Research: A Systematic Assessment. Biomed Res Int. 2018;2018:4578782.

9.   Manrique-Corredor EJ, Orozco-Beltran D, Lopez-Pineda A, Quesada JA, Gil-Guillen VF, Carratala-Munuera C. Maternal periodontitis and preterm birth: Systematic review and meta-analysis. Community Dent Oral Epidemiol. 2019.

10.   Peddis N, Musu D, Ideo F, Rossi-Fedele G, Cotti E. Interaction of biologic therapy with apical periodontitis and periodontitis: A systematic review. Aust Dent J. 2019.

11.   Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. J Med Libr Assoc. 2006;94(2):130-136.

12.   Durão S, Kredo T, Volmink J. Validation of a search strategy to identify nutrition trials in PubMed using the relative recall method. J Clin Epidemiol. 2015;68(6):610-616.

13.   Golder S, Wright K, Loke YK. The development of search filters for adverse effects of surgical interventions in medline and Embase. Health Info Libr J. 2018;35(2):121-129.

14.   Budhram D, Navarro-Ruan T, Haynes RB. The efficiency of database searches for creating systematic reviews was improved by search filters. J Clin Epidemiol. 2018;95:1-6.

15.   Lefebvre C, Glanville J, Beale S, et al. Assessing the performance of methodological search filters to improve the efficiency of evidence information retrieval: five literature reviews and a qualitative study. Health Technol Assess. 2017;21(69):1-148.

16.   Shariff SZ, Sontrop JM, Haynes RB, et al. Impact of PubMed search filters on the retrieval of evidence by physicians. CMAJ. 2012;184(3):E184-190.

17.   Pillastrini P, Vanti C, Curti S, et al. Using PubMed search strings for efficient retrieval of manual therapy research literature. J Manipulative Physiol Ther. 2015;38(2):159-166.

18.   Bachmann LM, Coray R, Estermann P, Ter Riet G. Identifying diagnostic studies in MEDLINE: reducing the number needed to read. J Am Med Inform Assoc. 2002;9(6):653-658.

19.   Olaussen A, Semple W, Oteir A, Todd P, Williams B. Paramedic literature search filters: optimised for clinicians and academics. BMC Med Inform Decis Mak. 2017;17(1):146.

20.   Rollin L, Darmoni S, Caillard JF, Gehanno JF. Searching for high-quality articles about intervention studies in occupational health--what is really missed when using only the Medline database? Scand J Work Environ Health. 2010;36(6):484-487.

21.   Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.

22.   Spry C, Mierzwinski-Urban M. The impact of the peer review of literature search strategies in support of rapid review reports. Res Synth Methods. 2018;9(4):521-526.

APPENDIX A - SEARCH PHRASES FROM THE STRATEGY EVALUATED

- Cochrane Collaboration methodological filter (Cochrane Highly Sensitive Search Strategy - HSSS):

#1	randomized controlled trial[Publication Type]
#2	controlled clinical trial[Publication Type]
#3	randomized [Title/Abstract]
#4	placebo[Title/Abstract]
#5	clinical trials as topic[MeSH Terms]
#6	randomly[Title/Abstract]
#7	trial[Title]
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	animals [mh] NOT humans [mh]
#10	#8 NOT #9

- Search phrases to recover periodontitis-related studies:

#1	"Periodontitis" [Title/Abstract]
#2	"Periodontitis" [MeSH Terms]
#3	"Disease, Periodontal" [Title/Abstract]
#4	"Disease, Periodontal" [MeSH Terms]
#5	"Diseases, Periodontal" [Title/Abstract]
#6	"Diseases, Periodontal" [MeSH Terms]
#7	"Periodontal Disease" [Title/Abstract]
#8	"Periodontal Disease" [MeSH Terms]
#9	"Parodontosis" [Title/Abstract]
#10	"Parodontosis" [MeSH Terms]
#11	"Parodontoses" [Title/Abstract]
#12	"Parodontoses" [MeSH Terms]
#13	"Pyorrhea Alveolaris" [Title/Abstract]
#14	"Pyorrhea Alveolaris" [MeSH Terms]
#15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR

	#11 OR #12 OR #13 OR #14

APPENDIX B – PEER REVIEW OF ELECTRONIC SEARCH STRATEGIES (PRESS)

PRESS Guideline **— Search Submission & Peer Review Assessment**
SEARCH SUBMISSION: THIS SECTION TO BE FILLED IN BY THE SEARCHER

Searcher:	Amanda Oliveira Lyrio	**Email:**	amandalyryo@hotmail.com
Date submitted:	11/07/2018	**Date requested by:**	11/14/2018

Systematic Review Title:

Search strategy for randomized clinical trials related to periodontitis

This search strategy is:

X	My PRIMARY (core) database strategy — First time submitting a strategy for search question and database
	My PRIMARY (core) strategy — Follow-up review NOT the first time submitting a strategy for search question and database. If this is a response to peer review, itemize the changes made to the review suggestions
	SECONDARY search strategy— First time submitting a strategy for search question and database
	SECONDARY search strategy — NOT the first time submitting a strategy for search question and database. If this is a response to peer review, itemize the changes made to the review suggestions

Database
(i.e., MEDLINE,CINAHL…):

Pubmed

Interface
(i.e., Ovid, EBSCO, PUBMED…):

Pubmed

Research Question
(Describe the purpose of the search)

What is the best search strategy for randomized clinical trials related to periodontitis?

PI(E)COS Format

(Outline the PICOs for your question — i.e., Patient, Index test, Reference standard, Outcome, and Study Design — as applicable)

P	Human
O	Periodontitis
S	Randomized clinical trials

Inclusion Criteria
(List criteria such as age groups, study designs, etc., to be included)

1	Randomized clinical trials
2	Studies accompanying the diagnosis of confirmed periodontitis

Exclusion Criteria
(List criteria such as study designs, date limits, etc., to be excluded)

1	Animal studies

Was a search filter applied?
Yes (X)   No ( )

If YES, which one(s) (e.g., Cochrane RCT filter, PubMed Clinical Queries filter)? Provide the source if this is a published filter. *[mandatory if YES to previous question]*

(((((((((((randomized controlled trial[Publication Type]) OR controlled clinical trial[Publication Type]) OR controlled clinical trial[Title/Abstract]) OR placebo[Title/Abstract]) OR clinical trials as topic[MeSH Terms]) OR randomly[Title/Abstract]) OR trial[Title])) NOT ((animals [mh]) NOT humans [mh]))))

Other notes or comments you feel would be useful for the peer reviewer?

Please copy and paste your search strategy here, exactly as run, including the number of hits per line. *[mandatory]*

((((((((((((((((Periodontitis[Title/Abstract]) OR Periodontitis[MeSH Terms]) OR Gingivitis[Title/Abstract]) OR Gingivitis[MeSH Terms]) OR Periodontal Diseases[Title/Abstract]) OR Periodontal Diseases[MeSH Terms]) OR Disease, Periodontal[Title/Abstract]) OR Diseases, Periodontal[Title/Abstract]) OR Periodontal Disease[Title/Abstract]) OR Parodontosis[Title/Abstract]) OR Parodontoses[Title/Abstract]) OR Pyorrhea Alveolaris[Title/Abstract]) OR Gingivitides[Title/Abstract])))) AND (((((((((Cross-Sectional Studies[Mesh:noexp] OR cross-sectional[TIAB] OR Prevalence[mesh:noexp] OR prevalence[tiab] OR transversal study[tiab]))) OR (("Case-Control Studies"[Mesh:noexp] OR "retrospective studies"[mesh:noexp] OR "Control Groups"[Mesh:noexp] OR (case[TIAB] AND control[TIAB]) OR (cases[TIAB] AND controls[TIAB]) OR (cases[TIAB] AND controlled[TIAB]) OR (case[TIAB] AND comparison*[TIAB]) OR (cases[TIAB] AND comparison*[TIAB]) OR "control group"[TIAB] OR "control groups"[TIAB]))) OR ((cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR retrospective studies[mesh:noexp] OR cohort[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB]))) OR "Epidemiologic Studies"[Mesh:noexp])) OR ((Incidence[mesh:noexp] OR incidence[tiab])))	25828
#1	(((((((((((((Periodontitis[Title/Abstract]) OR Periodontitis[MeSH Terms]) OR Gingivitis[Title/Abstract]) OR Gingivitis[MeSH Terms]) OR Periodontal Diseases[Title/Abstract]) OR Periodontal Diseases[MeSH Terms]) OR Disease, Periodontal[Title/Abstract]) OR Diseases, Periodontal[Title/Abstract]) OR Periodontal Disease[Title/Abstract]) OR Parodontosis[Title/Abstract]) OR Parodontoses[Title/Abstract]) OR Pyorrhea Alveolaris[Title/Abstract]) OR Gingivitides[Title/Abstract])))	96107
#2	(((((((((((randomized controlled trial[Publication Type]) OR controlled clinical trial[Publication Type]) OR controlled clinical trial[Title/Abstract]) OR placebo[Title/Abstract]) OR clinical trials as topic[MeSH Terms]) OR randomly[Title/Abstract]) OR trial[Title])) NOT ((animals [mh]) NOT humans [mh]))))	1052178

PEER REVIEW ASSESSMENT: THIS SECTION TO BE FILLED IN BY THE REVIEWER

Reviewer: Viviane Seixas Silva Silveira	**Email:** viviane.silveira@gmail.com
Date completed: 11/13/2018	

1. TRANSLATION

A --No revisions	X
B -- Revision(s) suggested	
C -- Revision(s) required	

If "B" or "C," please provide an explanation or example:

2. BOOLEAN AND PROXIMITY OPERATORS

A --No revisions	X
B -- Revision(s) suggested	
C -- Revision(s) required	

If "B" or "C," please provide an explanation or example:

3. SUBJECT HEADINGS

A --No revisions	
B -- Revision(s) suggested	
C -- Revision(s) required	X

If "B" or "C," please provide an explanation or example:

The terms "gingivitis" e "gingivitides" does not accurately translate the ending item of the acronym PICO, which is to evaluate the frequency of periodontitis, so I recommend removing them. In addition I recommend adding some synonyms of the term "periodontitis" in the title and abstract, for example: "periodontitides", "pericementitis", "pericementitides".

4. TEXT WORD SEARCHING

A --No revisions	
B -- Revision(s) suggested	x
C -- Revision(s) required	

If "B" or "C," please provide an explanation or example:

I recommend using the quotation marks, since the terms used are representative of PICO.

5. SPELLING, SYNTAX, AND LINE NUMBERS

A --No revisions	**x**
B -- Revision(s) suggested	
C -- Revision(s) required	

If "B" or "C," please provide an explanation or example:

6. LIMITS AND FILTERS

A --No revisions	**x**
B -- Revision(s) suggested	
C -- Revision(s) required	

If "B" or "C," please provide an explanation or example:

OVERALL EVALUATION
(Note: If one or more "revision required" is noted above, the response below must be "revisions required".)

A --No revisions	
B -- Revision(s) suggested	
C -- Revision(s) required	**x**

Additional comments:

There are revisions that need to be performed, as described in the previous items.