Editorial

What still remains missing from participants' selection criteria in clinical trials and systematic reviews?

Craig S. Miller, DMD, MS; Alonso Carrasco-Labra, DDS, MSc; Arwa M. Farag, BDS, DMSc; Anura Ariyawardana, BDS, MS, MRACDS (OralMed); Rui Albuquerque, DMD, MS, PhD, FHEA, FDS RCS (OM); Milda Chmieliauskaite, DMD, MPH; Michael Glick, DMD

Systematic reviews are one of the most powerful tools for translating research into clinical practice. When appropriately conducted, they serve one of the main principles of science: the idea that science is a cumulative and reproducible process.[1,2] Another principle is that science should be evidence based with a contemporary goal that health claims should be based on systematic reviews that summarize the best available evidence.[3,4] This is why systematic reviews are essential for determining the current state of the evidence, informing clinical practice guidelines and policies, and facilitating the identification of gaps in knowledge and are described among the most cited type of research in the literature.[5,6] However, systematic reviews range in quality, and adherence to guidelines for systematic reviews and proper evolution of these guidelines are essential for reproducible and evidentiary findings.

When clinicians critically appraise a systematic review to inform practice, 1 key aspect is to determine the extent to which the review explicitly addresses a focused or relevant clinical question.[7,8] By focused or relevant, we mean a review question that gathers evidence from primary studies in a way that, when pooled or summarized together, would present an estimate of a treatment effect that makes sense from a clinical perspective. In other words, clinicians need to evaluate whether "across the range of patients, interventions or exposures, and outcomes, it is plausible that the intervention will have a similar effect."[8] In many cases, important differences in any of these components of the review question are responsible for the presence of heterogeneity (that is, included studies that provide different results) in meta-analysis. Unexplained heterogeneity reduces our confidence in the certainty of the evidence.[9] In addition, when assessing applicability (that is, generalizability or external validity) of systematic review findings to patient care, users of systematic reviews need to determine the extent to which the characteristics of the participants or population in the review and, by extension, those in the primary studies were similar to the patients they see in their practice.[6]

In an effort to ensure transparency and to guarantee that key information is provided to readers to evaluate the aspects described in the paragraph above, the scientific community has developed reporting standards. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for systematic reviews in its item 6, "types of participants,"[10] and the Consolidated Standards of Reporting Trials (CONSORT) statement for randomized controlled trials in its item 4a, "eligibility criteria for participants," and item 21, "generalisability (external validity, applicability) of the trial findings,"[11] request that researchers explicitly present participants' selection criteria and discuss their implications. However, little attention has been given to the impact of inaccurate or incomplete inclusion and exclusion criteria, particularly, diagnostic criteria and potential prognostic factors, as well as a consistent case definition and outcome criteria.

We gain insight into this problem when evaluating even common oral diseases, such as periodontitis. For example, Manau and colleagues[12] and Bueno and colleagues[13] suggest that using different case definitions for periodontitis can result in substantial differences in the reported prevalence and outcomes. Moreover, the application of different oral assessment measures and the absence of a standard case definition for periodontal disease have complicated the interpretation of

Editorials represent the opinions of the authors and not necessarily those of the American Dental Association or the American Academy of Oral Medicine.

results of systematic reviews that have investigated the association between periodontal disease and comorbid conditions.[14] As noted by Preshaw,[15] the multiplicity of case definitions used to assign a diagnosis (of periodontitis) "greatly compromises our ability to draw meaningful conclusions from a body of published research."[15]

The problem is again observed when systematic reviews that have investigated implant failure are analyzed. Systematic reviews that studied the association of smoking and dental implant failure have poorly described or omitted a consistent definition of smoking with respect to type, quantity, and duration of use, as well as requiring consistent criteria for implant failure.[16-19] In these reviews, criteria used to adjudicate implant failure ranged from complete loss of the implant, to loss of the implant with radiographic evidence of bone loss, to having persistent pain associated with the implant. These varying criteria contribute to diverse reasons for implant failure, including factors related to anatomic placement, previous pain or inflammation at the implant site, referred pain, or an underlying medical condition, which are factors completely unrelated to smoking, usually not accounted for or simply disregarded in the analysis.

Another example is found in the ongoing work by Group V of the World Workshop on Oral Medicine VII. This group is conducting a systematic review that is focused on the definition and diagnostic criteria used in randomized controlled trials on burning mouth syndrome. Among the 36 studies in their analyses, most failed to report using appropriate selection criteria and tests to rule out hyposalivation, anemia, diabetes, candidiasis, medications, parafunctional habits, and oral mucosal disease.[20-55] Many of these primary studies also failed to state the number of patients screened who were excluded for these specific conditions. Accordingly, the possibility of inclusion of participants in these primary studies who do not or may not have the disease of interest cannot be discarded, which threatens the credibility of the reported outcomes.

Researchers need to not only describe in detail the selection criteria applied and participants' characteristics but also need to provide an accurate description of the diagnostic means to determine patients' conditions and explicit case definitions.

This issue has contrasting implications. If study researchers use strict criteria to define or diagnose a condition, this could result in a highly homogeneous sample of patients, but it may result in excluding relevant data. In contrast, use of less strict or inexact diagnostic criteria may include patients who potentially do not have the disease, are misclassified, or are heterogeneous. In these circumstances, evidence that seems relevant may not be. This issue becomes even more problematic when reviewers combine populations from studies with both strict and loose criteria into 1 meta-analysis. In this situation, clinicians would need to be presented with sensitivity analysis to test the robustness of the results that compares studies that applied more and less strict inclusion criteria.[56] Accordingly, we summarize several key questions to be considered when critically appraising the type of participants in primary studies and systematic reviews (Box).

A 2-fold solution is required for this problem. First, from a primary study perspective, researchers need to not only describe in detail the selection criteria applied and participants' characteristics but also need to provide an accurate description of the diagnostic means to determine patients' conditions and explicit case definitions. Here, requiring an ontology (a structured vocabulary created by experts) could provide for better consistency in using primary data.[57] Second, in an effort to minimize the possibility of introducing undesirable heterogeneity, systematic reviewers should carefully collect information from studies about the conditions, case definitions, and diagnostic strategies used at the moment of enrollment and consider these elements when attempting to conduct meta-analyses.

The same rigor expected from the diagnostic process in clinical practice should be seen in primary studies. Users of systematic reviews and primary studies should have all the necessary information to determine to what extent the patients in those study designs are similar enough to the patients they regularly see in practice. Reporting findings when there is limited, contrasting, or no

Box. Key factors when appraising participants' selection criteria in primary and secondary research

- What are the key and demographic characteristics of the participants or population in the study?
- Did the researchers exclude potential participants or populations and were acceptable methods or tests used as a basis for the exclusion?
- If the participants or population is affected by a condition or disease, how is the condition or disease defined by the researchers (case definition)?
- What are the diagnostic criteria presented by the researchers to establish the condition or the disease in the participants or population at the time of enrollment?
- Who was responsible for making the diagnosis and were acceptable methodical assessments used to make the diagnosis?
- What is the setting in which the participant or population enrollment occurred?
- How likely is it that a diagnostic misclassification of participants or population could have occurred, given the diagnostic process used by the researcher?

information on case definitions, conditions, and diagnostic strategies seriously affects the ability to evaluate the generalizability of the evidence and affects the credibility of the research findings.

We hope that this communication leads to efforts to properly address the stringency of these criteria (Box) so less evidence from primary studies, systematic reviews, and meta-analysis would be unnecessarily disregarded because of uncertain selection criteria and case definitions, thus reducing waste in research and increasing its clinical value. ■

https://doi.org/10.1016/j.adaj.2018.08.027

Dr. Miller is a professor and the chief, Division of Oral Diagnosis, Oral Medicine, Oral Radiology MN324, Department of Oral Health Practice, College of Dentistry, University of Kentucky, Lexington, KY 40536, e-mail cmiller@uky.edu. Address correspondence to Dr. Miller.

Dr. Carrasco-Labra is the director, Center for Evidence-Based Dentistry, American Dental Association, Chicago, IL; and an instructor, Evidence-Based Dentistry Unit and Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, University of Chile, Santiago, Chile.

Dr. Farag is an assistant professor, Division of Oral Medicine, Department of Diagnostic Sciences, School of Dental Medicine, Tufts University, Boston, MA.

Dr. Ariyawardana is an adjunct senior lecturer, College of Medicine and Dentistry, James Cook University, Queensland, Australia; and the priniciple dentist, Metro South Oral Health, Brisbane, Queensland, Australia.

Dr. Albuquerque is a consultant in Oral Medicine and honorary clinical senior lecturer, Dental Institute, King's College London at Guy's & St Thomas' hospitals, London, UK.

Dr. Chmieliauskaite is an assistant professor, Department of Oral and Maxillofacial Medicine, School of Dental Medicine, Case Western Reserve University, Cleveland, OH.

Dr. Glick is a professor, Department of Oral Diagnostic Sciences, School of Dental Medicine, University at Buffalo, The State University of New York, Buffalo, NY, and the editor, The Journal of the American Dental Association.

Disclosure. None of the authors reported any disclosures.

ORCID Number. Michael Glick: http://orcid.org/0000-0003-4236-5385.

For information regarding ORCID numbers, go to http://orcid.org.

1. Chalmers I. The lethal consequences of failing to make use of all relevant evidence about the effects of medical treatments: the need for systematic reviews. In: Rothwell P, ed. *Treating Individuals: From Randomised Trials to Personalised Medicine*. London: The Lancet; 2007: 37-58.

2. Gurevitch J, Koricheva J, Nakagawa S, Stewart G. Meta-analysis and the science of research synthesis. *Nature*. 2018;555(7695):175-182.

3. Chalmers I. Addressing uncertainties about the effects of treatments offered to NHS patients: whose responsibility? *J R Soc Med*. 2007;100(10):440-441.

4. Djulbegovic B, Guyatt GH. Progress in evidence-based medicine: a quarter century on. *Lancet*. 2017; 390(10092):415-423.

5. Patsopoulos NA, Analatos AA, Ioannidis JP. Relative citation impact of various study designs in the health sciences. *JAMA*. 2005;293(19):2362-2366.

6. Carrasco-Labra A, Brignardello-Petersen R, Glick M, Guyatt GH, Azarpazhooh A. A practical approach to evidence-based dentistry, VI: how to use a systematic review. *JADA*. 2015;146(4):255-265.e1.

7. Evaniew N, Carrasco-Labra A, Devereaux PJ, et al. How to use a randomized clinical trial addressing a surgical procedure: users' guide to the medical literature. *JAMA Surg*. 2016;151(7):657-662.

8. Murad MH, Montori VM, Ioannidis JP, et al. How to read a systematic review and meta-analysis and apply the results to patient care: users' guides to the medical literature. *JAMA*. 2014;312(2):171-179.

9. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 7—rating the quality of evidence, inconsistency. *J Clin Epidemiol*. 2011;64(12):1294-1302.

10. Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for a Systematic Review And Meta-analysis of Individual Participant Data: the PRISMA-IPD statement. *JAMA*. 2015;313(16):1657-1665.

11. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol*. 2010;63(8):834-840.

12. Manau C, Echeverria A, Agueda A, Guerrero A, Echeverria JJ. Periodontal disease definition may determine the association between periodontitis and pregnancy outcomes. *J Clin Periodontol*. 2008;35(5):385-397.

13. Bueno AC, Ferreira RC, Cota LO, Silva GC, Maghalhaes CS, Moreira AN. Comparison of different criteria for periodontitis case definition in head and neck cancer individuals. *Support Care Cancer*. 2015;23(9):2599-2604.

14. Scannapieco FA, Bush RB, Paju S. Associations between periodontal disease and risk for atherosclerosis, cardiovascular disease, and stroke: a systematic review. *Ann Periodontol*. 2003;8(1):38-53.

15. Preshaw PM. Definitions of periodontal disease in research. *J Clin Periodontol*. 2009;36(1):1-2.

16. Chen H, Liu N, Xu X, Qu X, Lu E. Smoking, radiotherapy, diabetes and osteoporosis as risk factors for dental implant failure: a meta-analysis. *PLoS One*. 2013; 8(8):e71955.

17. Chrcanovic BR, Albrektsson T, Wennerberg A. Smoking and dental implants: a systematic review and meta-analysis. *J Dent*. 2015;43(5):487-498.

18. Hinode D, Tanabe S, Yokoyama M, Fujisawa K, Yamauchi E, Miyamoto Y. Influence of smoking on osseointegrated implant failure: a meta-analysis. *Clin Oral Implants Res*. 2006;17(4):473-478.

19. Strietzel FP, Reichart PA, Kale A, Kulkarni M, Wegner B, Kuchler I. Smoking interferes with the prognosis of dental implant treatment: a systematic review and meta-analysis. *J Clin Periodontol*. 2007;34(6):523-544.

20. Lopez-Jornet P, Camacho-Alonso F, Leon-Espinosa S. Efficacy of alpha lipoic acid in burning mouth syndrome: a randomized, placebo-treatment study. *J Oral Rehabil*. 2009; 36(1):52-57.

21. Lopez-Jornet P, Camacho-Alonso F, Molino-Pagan D. Prospective, randomized, double-blind, clinical evaluation of *Aloe vera Barbadensis*, applied in combination with a tongue protector to treat burning mouth syndrome. *J Oral Pathol Med*. 2013;42(4):295-301.

22. Marino R, Torretta S, Capaccio P, Pignataro L, Spadari F. Different therapeutic strategies for burning mouth syndrome: preliminary data. *J Oral Pathol Med*. 2010;39(8):611-616.

23. Palacios-Sanchez B, Moreno-Lopez LA, Cerero-Lapiedra R, Llamas-Martinez S, Esparza-Gomez G. Alpha lipoic acid efficacy in burning mouth syndrome: a controlled clinical trial. *Med Oral Patol Oral Cir Bucal*. 2015;20(4):e435-e440.

24. Petruzzi M, Lauritano D, De Benedittis M, Baldoni M, Serpico R. Systemic capsaicin for burning mouth syndrome: short-term results of a pilot study. *J Oral Pathol Med*. 2004; 33(2):111-114.

25. Rodriguez de Rivera Campillo E, Lopez-Lopez J, Chimenos-Kustner E. Response to topical clonazepam in patients with burning mouth syndrome: a clinical study. *Bull Group Int Rech Sci Stomatol Odontol*. 2010;49(1):19-29.

26. Sardella A, Lodi G, Demarosi F, Tarozzi M, Canegallo L, Carrassi A. *Hypericum perforatum* extract in burning mouth syndrome: a randomized placebo-controlled study. *J Oral Pathol Med*. 2008;37(7):395-401.

27. Sardella A, Uglietti D, Demarosi F, Lodi G, Bez C, Carrassi A. Benzydamine hydrochloride oral rinses in management of burning mouth syndrome: a clinical trial. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1999; 88(6):683-686.

28. Silva LA, Siqueira JT, Teixeira MJ, Siqueira SR. The role of xerostomia in burning mouth syndrome: a case-control study. *Arq Neuropsiquiatr*. 2014;72(2): 91-98.

29. Silvestre FJ, Silvestre-Rangil J, Tamarit-Santafe C, Bautista D. Application of a capsaicin rinse in the treatment of burning mouth syndrome. *Med Oral Patol Oral Cir Bucal*. 2012;17(1):e1-e4.

30. Spanemberg JC, Cherubini K, de Figueiredo MA, Gomes AP, Campos MM, Salum FG. Effect of an herbal compound for treatment of burning mouth syndrome: randomized, controlled, double-blind clinical trial. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2012;113(3): 373-377.

31. Spanemberg JC, López López J, de Figueiredo MA, Cherubini K, Salum FG. Efficacy of low-level laser therapy for the treatment of burning mouth syndrome: a randomized, controlled trial. *J Biomed Opt*. 2015;20(9):098001.

32. Sugaya NN, Silva EF, Kato IT, Prates R, Gallo CB, Pellegrini VD. Low intensity laser therapy in patients with burning mouth syndrome: a randomized, placebo-controlled study. *Braz Oral Res*. 2016;30(1):e108.

33. Tammiala-Salonen T, Forssell H. Trazodone in burning mouth pain: a placebo-controlled, double-blind study. *J Orofac Pain*. 1999;13(2):83-88.

34. Toida M, Kato K, Makita H, et al. Palliative effect of lafutidine on oral burning sensation. *J Oral Pathol Med*. 2009;38(3):262-268.

35. Treldal C, Jacobsen CB, Mogensen S, et al. Effect of a local anesthetic lozenge in relief of symptoms in burning mouth syndrome. *Oral Dis*. 2016;22(2):123-131.

36. Umezaki Y, Badran BW, DeVries WH, Moss J, Gonzales T, George MS. The efficacy of daily prefrontal repetitive transcranial magnetic stimulation (rTMS) for burning mouth syndrome (BMS): a randomized controlled single-blind study. *Brain Stimul*. 2016;9(2):234-242.

37. Valenzuela S, Lopez-Jornet P. Effects of low-level laser therapy on burning mouth syndrome. *J Oral Rehabil*. 2017;44(2):125-132.

38. Valenzuela S, Pons-Fuster A, Lopez-Jornet P. Effect of a 2% topical chamomile application for treating burning mouth syndrome: a controlled clinical trial. *J Oral Pathol Med*. 2016;45(7):528-533.

39. Arduino PG, Cafaro A, Garrone M, et al. A randomized pilot study to assess the safety and the value of low-level laser therapy versus clonazepam in patients with burning mouth syndrome. *Lasers Med Sci*. 2016; 31(4):811-816.

40. Bergdahl J, Anneroth G, Perris H. Cognitive therapy in the treatment of patients with resistant burning mouth syndrome: a controlled study. *J Oral Pathol Med*. 1995; 24(5):213-215.

41. Bessho K, Okubo Y, Hori S, Murakami K, Iizuka T. Effectiveness of kampo medicine (sai-boku-to) in treatment of patients with glossodynia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1998;86(6):682-686.

42. Cano-Carrillo P, Pons-Fuster A, Lopez-Jornet P. Efficacy of lycopene-enriched virgin olive oil for treating burning mouth syndrome: a double-blind randomised. *J Oral Rehabil*. 2014;41(4):296-305.

43. Carbone M, Pentenero M, Carrozzo M, Ippolito A, Gandolfo S. Lack of efficacy of alpha-lipoic acid in burning mouth syndrome: a double-blind, randomized, placebo-controlled study. *Eur J Pain*. 2009;13(5):492-496.

44. Cavalcanti DR, da Silveira FR. Alpha lipoic acid in burning mouth syndrome: a randomized double-blind placebo-controlled trial. *J Oral Pathol Med*. 2009;38(3): 254-261.

45. Femiano F. Burning mouth syndrome (BMS): an open trial of comparative efficacy of alpha-lipoic acid (thioctic acid) with other therapies. *Minerva Stomatol*. 2002;51(9):405-409.

46. Femiano F, Gombos F, Scully C. Burning mouth syndrome: open trial of psychotherapy alone, medication with alpha-lipoic acid (thioctic acid), and combination therapy. *Med Oral*. 2004;9(1):8-13.

47. Femiano F, Gombos F, Scully C, Busciolano M, De Luca P. Burning mouth syndrome (BMS): controlled open trial of the efficacy of alpha-lipoic acid (thioctic acid) on symptomatology. *Oral Dis*. 2000;6(5):274-277.

48. Femiano F, Scully C. Burning mouth syndrome (BMS): double blind controlled study of alpha-lipoic acid (thioctic acid) therapy. *J Oral Pathol Med*. 2002;31(5):267-269.

49. Gremeau-Richard C, Dubray C, Aublet-Cuvelier B, Ughetto S, Woda A. Effect of lingual nerve block on burning mouth syndrome (stomatodynia): a randomized crossover trial. *Pain*. 2010;149(1):27-32.

50. Gremeau-Richard C, Woda A, Navez ML, et al. Topical clonazepam in stomatodynia: a randomised placebo-controlled study. *Pain*. 2004;108(1-2):51-57.

51. Heckmann SM, Kirchner E, Grushka M, Wichmann MG, Hummel T. A double-blind study on clonazepam in patients with burning mouth syndrome. *Laryngoscope*. 2012;122(4): 813-816.

52. Jorgensen MR, Pedersen AM. Analgesic effect of topical oral capsaicin gel in burning mouth syndrome. *Acta Odontol Scand*. 2017;75(2):130-136.

53. Jurisic Kvesic A, Zavoreo I, Basic Kes V, et al. The effectiveness of acupuncture versus clonazepam in patients with burning mouth syndrome. *Acupunct Med*. 2015; 33(4):289-292.

54. Lopez-D'alessandro E, Escovich L. Combination of alpha lipoic acid and gabapentin, its efficacy in the treatment of burning mouth syndrome: a randomized, double-blind, placebo controlled trial. *Med Oral Patol Oral Cir Bucal*. 2011;16(5):e635-e640.

55. Lopez-Jornet P, Camacho-Alonso F, Andujar-Mateos P. A prospective, randomized study on the efficacy of tongue protector in patients with burning mouth syndrome. *Oral Dis*. 2011;17(3):277-282.

56. O'Connor D, Green S, Higgins JPT. Defining the review question and developing criteria for including studies. In: Higgins JPT, Green S, eds. *Cochrane Handbook of Systematic Reviews of Intervention*. Version 5.1.0 (updated March 2011). London, UK: The Cochrane Collaboration; 2011. Available at: www.handbook.cochrane.org. Accessed August 18, 2018.

57. Smith B, Goldberg LJ, Ruttenberg A, Glick M. Ontology and the future of dental research informatics. *JADA*. 2010;141(10):1173-1175.