Chambrone Leandro (Orcid ID: 0000-0002-2838-1015)

Why is there a lack of evidence regarding errors and complications in Periodontal and Implant therapy?

Leandro Chambrone[1] and Giovanni Zucchelli[2]

[1] Clinical Research Unit (CRU), Centro de Investigação Interdisciplinar Egas Moniz (CiiEM), Egas Moniz, CRL, Monte de Caparica, Portugal; Unit of Basic Oral Investigation (UIBO), School of Dentistry, Universidad El Bosque, Bogota, Colombia; and Department of Periodontics, School of Dentistry, The University of Pennsylvania, USA

[2] Unit of Periodontology-Dental School Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum- Bologna University, Italy

Correspondence :

Prof. Leandro Chambrone

Rua da Moóca, 2518 Cj. 13

03104-002 São Paulo, SP, Brazil

e-mail address: leandro_chambrone@hotmail.com

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ABSTRACT

The occurrence of errors, complications and adverse effects may occur as a consequence of single or multiple events related to the clinicians and / or the patient, as well. Apparently, the amount of dental literature on these undesirable outcomes has not been as prolific as those obtained for the conventional primary periodontal outcome measures. This review explores the potential reasons on the lack of studies reporting on errors and complications in Periodontal and Implant therapy, as well as other noteworthy methodological aspects, in order to enlighten their impact on the selection of the best (or most appropriate) 'gold standard' periodontal / implant-related treatment options, and on the overall decision-making process. The following points were addressed: 1) The importance of reporting errors and complications in clinical research; 2) The adequate reporting of errors and complications in Periodontology and Dental Implantology; and 3) Efficacy trials versus effectiveness studies and their impact on the assessment and report of periodontal and implant treatment-related risks and complications.

1 | INTRODUCTION

In contemporary Periodontology and Implantology, the decision-making process should take into consideration the clinical effects of several procedures and therapies. Once research findings of these treatment approaches become available, those originated of well-designed, quality assured studies are usually combined with the patient's needs / conditions and the clinician's expertise and skills to form the base of a treatment planning: that is, an evidence-based treatment approach.[1-4] As part of one of these three important components, patient-reported and -centered outcomes became an important tool in both the assessment of short-term impact of therapy of currently available treatment procedures (i.e., gold standard and alternative approaches), and on the implementation of new methods or philosophies.[3,4] Basically, the objectives of these "primary endpoints" are to quantify the patients' perceptions of treatment and answer some of the questions posed by them prior treatment delivery, for instance:

- patient preferences: "Are there other alternative options to the one considered as the best for my case?" "what are the differences between them?"
- adverse effects: "Will the treatment cause any type of discomfort, pain, tenderness, swelling or hematoma / ecchymosis?" "Does it lead to functional limitations in terms of chewing and food deglutition?" if yes, how long will they last?"
- treatment costs: "What are the costs involved with treatment options?"

As highlighted in the introductory chapter of this volume of *Periodontology 2000*, the periodontal definitions of error ("'an action or practice originated of an unintended deviation of the preestablished objectives and precision of a treatment procedure, caused by an accident, imprudence, inadequate adherence to the original surgical protocol [i.e., incorrect 'knowledge transfer' of evidence to clinical practice], or technical skills"), complications ("those unexpected intercurrences occurring during or after the execution of a treatment procedure that have potential of modifying or jeopardizing the wound healing process and the anticipated effect of treatment"), harms ("mechanical, chemical or thermal injuries or damages inflicted to the

periodontal tissues"), side effects ("those unexpected effects and events occurring following the delivery of a procedure or therapy") and adverse events ("unexpected and undesirable detrimental events occurring following the delivery of a procedure or therapy") have not been defined so far.[5]

The occurrence of errors, complications and adverse effects may occur as a consequence of single or multiple events related to the clinicians (most of the time) and / or the patient, as well. Moreover, with the development of internet and the possibility of making new publications available in online platforms, the number of Periodontal and Implant Dentistry research papers has been increasing considerably. However, has the number of publications reporting on errors, complications and adverse effects / events increased in a similar fashion? No, it hasn't…Apparently, the amount of dental literature on these undesirable outcomes has not been as prolific as those obtained for the conventional primary periodontal outcome measures. Accordingly, this reduced amount of information gives room for the formulation of two other additional questions: *Why is there a lack of evidence regarding errors and complications and adverse effects in periodontology and dental implantology*? And *what is the value of reporting undesirable treatment outcomes (if there is any)*? This chapter aims to explore these and other noteworthy methodological aspects, in order to enlighten their impact on the selection of the best (or most appropriate) 'gold standard' periodontal / implant-related treatment options, and on the overall decision-making process.

2 | THE IMPORTANCE OF REPORTING ERRORS AND COMPLICATIONS IN CLINICAL RESEARCH

The quantification of adverse events may vary according to the disease or patient`s condition, the complexity of the procedures and the binomial professional knowledge-skills. A recent survey conducted in two US dental schools and one multispecialty large group practice listed the

most common adverse events (and respective procedures) occurring in dentistry:[6] a) inability to swallow (dental anesthesia);[6] b) severe tachycardia and light-headedness and chronic trauma to tongue from margin of dental restoration (dental filling);[6] c) persistent bleeding and involuntary trauma to soft tissue remote from surgical site (dental extraction);[6] d) persistent traumatic ulcer (use of lower partial denture);[6] e) wounds development after traumatic dental procedure and bone damage (dental implant surgery);[6] and f) oral soft tissue laceration from loose wires (orthodontic procedure).[6] However, the question whether it is important or not the reporting of adverse effects, although straightforward and somehow obvious, deserves some additional insights. According the *World Health Organization* (WHO),[7] the primary purpose of reporting errors is to improve patient safety (i.e., "freedom of accidental injuries"), in order to: a) offering valuable evidence achieved by detailing and examining similar cases that shall be used by others (i.e., researchers, clinicians, academic institutions and industry) to clarify common underlying reasons linked to the occurrence of adverse events;[7] and b) to advance future decision-making process by implementing alternative or new treatment strategies that may be used to prevent or reduce the risk of detrimental events.[7] The occurrence or reporting of an adverse event, *per se*, does not improve safety, but this may be considered the first step to promote the above-mentioned modifications to treatment planning.[7,8]

Moreover, it should be noted that the reporting of adverse events needs to be accompanied by a critical analysis (statistical or not) of the potential reasons linked with the occurrence of the condition and its potential impact on the treatment outcomes. The use of classification systems or even scales (e.g., the visual analog scale) may allow the standardization and quantification (extension and severity) of adverse events, and this information may be applied to advance in the knowledge of the profession.[7,9] However, the use of classification systems may be challenging because some types of adverse events may not fit in only one category, thus clinical research should be as much doummented as possible to include all adverse effects occuring during the course of the applied treatment approach.[9] Consequently, it is extremely important that "the lessons learned" with the occurrence of errors would not remain stuck into the patient's files[7] (i.e., they should be shared with dental community).

3 | ADEQUATE REPORTING OF ERRORS AND COMPLICATIONS IN PERIODONTOLOGY AND DENTAL IMPLANTOLOGY: THE MISSING LINK

The request of adequately reporting the occurrence of adverse events (i.e., adverse effects, errors and complications) is extremely necessary and important for clinical practice, and different areas of medicine have struggled with it for a long time.[10-19] For instance, numerous publications have stressed the need of a comprehensive report on treatment errors and complications,[10-19] but why are they "missing" in the literature compared to the data on the treatment`s primary outcomes of interest? And why is it important?

It has been argued that the restricted number of information on adverse effects and complications in randomized clinical trials might be associated to different reasons, such as: a) negligence due to ignorance, when the design of a study ignored or underestimated the collection of these effects;[20] b) 'willful' negligence, as a result of a neglected or deficient collection of information;[20] c) potential data restriction due the occurrence of zero events or a very restricted number of adverse effects;[20] d) distortion due to a partial / biased report of research findings and misinterpretation of the available literature;[20] and even e) silence (i.e., when the authors purposely opted to offer a "selective reporting" and do not talk about them).[20] Although negligence due to ignorance might hamper the overall quality of a study, it is certainly less critical than the deliberate option of not collecting, for any particular reason, some important outcomes of treatment (i.e., selective data collection) during follow-up. It is well-known that most papers published in dental journals are originally part of masters' or PhD`s theses and due to publication restrictions (i.e., number of words contained in the print version) not all the available information can be presented in the final printed document.[20,21] For instance, a recent case study on the use of Orlistat (i.e., a drug indicated for obesity management marketed with the trade name of Xenical) found that unpublished clinical study reports (i.e., those reports that reviews the methodology and outcomes of clinical studies requiring selling approval in the USA [FDA – Food and Drug Administration] and Europe [EMA – European Medicines Agency]) provided by Roche (Genentech; South San Francisco, CA, USA) displayed ampler and more detailed data of adverse events / harms than

to those available in the papers published in scientific / academic journals.[21] Thus, some important parts of the research, such as the complete report of wound healing adverse events, can be collected and made available as 'online supplemental materials / appendixes' that be consulted anytime.[20] With respect to data distortion, this causes a more problematic impact than data restriction[20] or data interpretation of expert opinion-based literature (i.e., commentaries, editorials, guidelines and consensus statements),[20] as it may involve data manipulation (i.e., alteration of results in order to reach or not 'statistical significance' about the potential harms of a certain therapy). Finally, silence on the safety or indications of a treatment approach or a drug, due to marketing reasons, has been reported in literature as well.[20,22,23]

Moreover, it should be noted that interpretation of the clinical impact of adverse effects and complications on the primary outcomes of interest (i.e., those clinically relevant for the condition of interest) is extremely problematic when the information available in a randomized clinical trial or systematic review (i.e., the most appropriate and powerful designs of study for the evaluation of treatment interventions) was not reported in detail. The extension of some of these issues has not been investigated in Periodontology or Dental Implantology so far, but a clear example can be found in a publication that evaluated the reporting of adverse events in surgical trials published in the *Annals of Surgery*, *JAMA Surgery*, and the *British Journal of Surgery*.[24] The authors of this review found that the lack of definitions and rare report on trans-surgical complications can compromise the judgement and interpretation of studies dealing with these and other postsurgical adverse events.[24] Although the importance of reporting harms / adverse effects has been recognized by the most important intervention's research methodological statements (the Consolidated Standards of Reporting Trials [CONSORT][25] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA]),[26] detailed information of their severity and impact on treatment results may not be adequately reported in a published paper.[10,19] However, rendering clear definitions of the conditions of interest and quantifying severity (e.g., amount of post-treatment bleeding or extension of suture dehiscence) into some categories (e.g., mild, moderate or severe) may not be an easy task. Despite that, it should be considered that

partial data reporting does not allow precise evaluations on both the positive and negative effects of procedures, a condition that may inflate or underestimate the treatment benefit / harm estimation (i.e., whether the clinical benefits promoted by therapy outweigh or not potential for harm),[27,28] Correspondingly, incomplete wound healing adverse events reports can imprudently have a direct influence on the interpretation of the efficacy of clinical trials or even the calculation of pooled estimates (i.e., meta-analyses), leading clinicians to consider less adequate treatment options, during the decision-making process, as the most effective ones for the condition the patient has.[29] Consequently, the definition of treatment success should be based on a delicate balance between reporting treatment success (i.e., findings of the clinical outcomes of interest) and the impact of patient-reported outcomes, such as adverse effects, aesthetics and function. This combination will provide the net benefit rating of a procedure.[27,28,30,31]

The importance of collecting data on patient-reported outcomes in Periodontology and Dental Implantology has been thoroughly recognized in the literature.[27,28,30-40] Patient-reported outcomes can be defined as the information obtained from the patient`s self-report about his / hers own health conditions, that have not been collected or interpreted by other personnel involved with the study (i.e., clinician, nurses, staff, etc).[41] The use of patient-reported outcomes provide a qualitative evaluation of 'subjective outcomes', such as chewing discomfort, edema and pain, that could be sized by patients and converted into measurable scales.[31,34,39,40] The visual analog scale is probably the most used tool for assessing the levels of discomfort and pain following to different modalities of non-surgical and surgical periodontal treatment.[30,31,34,39,40] However, McGuire et al.[30] in a commentary published in the *Journal of Periodontology* stated that the use of patient-reported outcomes may be limited when designing a randomized clinical trial because "patient responses may be influenced by knowing the nature of their treatments and by subtle cues from investigators". Based on that, these authors highlighted the importance of cautiously taking into consideration the selection and design of the patient-reported outcomes scales of interest for the study, as well as the way these qualitative scales are administrated to prevent unwanted introductions or error or biases.[30]

As reported above, the adherence of a study protocol to the standard CONSORT or PRISMA statements, *per se*, does not indicate the need and importance of reporting wound healing adverse events details (these statements simply identify the need of reporting "all important adverse events or side effects in each intervention group).[25,26] However, extensions of these statements have been developed to include a better appraisal of harms[42,43] (Table 1). These aim to improve data presentation and overcome the use of the most "common poor reporting practices for harms-related data" (as stated in the CONSORT Extension for Harms),[42] such as "using generic or vague statements, such as 'the drug was generally well tolerated' or 'the comparator drug was relatively poorly tolerated'"[42]… "failing to provide separate data for each study arm"[42]… "providing summed numbers for all adverse events for each study arm, without separate data for each type of adverse event"[42]… "providing summed numbers for a specific type of adverse event, regardless of severity or seriousness"[42]… "reporting only the adverse events observed at a certain frequency or rate threshold (for example, > 3% or > 10% of participants)"[42]… "reporting only the adverse events that reach a P value threshold in the comparison of the randomized arms (for example, $P < 0.05$)"[42]… "reporting measures of central tendency (for example, means or medians) for continuous variables without any information on extreme values"[42]… "improperly handling or disregarding the relative timing of the events, when timing is an important determinant of the adverse event in question"[42]… "not distinguishing between patients with one adverse event and participants with multiple adverse events"[42]… "providing statements about whether data were statistically significant without giving the exact counts of events"[42]… or "providing statements about whether data were statistically significant without giving the exact counts of events".[42]

Although it should be clear that any unexpected outcome, even slight, should be explained in detail, authors should also noticeably state in the results when no wound healing adverse events / complications happened.[42] In addition, it is important to expand the reliability and clearness of papers reporting the occurrence of errors and complications / wound healing adverse events, specially within those who are industry sponsored.[44,45] There is evidence in the medical

[46-51]and dental[52,53] literature that studies reporting conflict of interest seems to be more likely to report better results when compared to studies not reporting conflict. These findings also reinforce the need of improving the report of wound healing adverse events.

4 | EFFICACY TRIALS VERSUS EFFECTIVENESS STUDIES AND THEIR IMPACT ON THE ASSESSMENT AND REPORT OF PERIODONTAL AND IMPLANT TREATMENT-RELATED RISKS AND COMPLICATIONS

Efficacy trials versus effectiveness studies: how different are they? Irrespective of the type of study design (i.e., randomized clinical trial, controlled clinical trial, case series or case report) clinicians take into consideration to support their treatment plan during the decision-making process, without a doubt these terms ('efficacy' and 'effectiveness') share one thing in common: they all reflect the results (or efficiency) of what a treatment approach can deliver for the patient.[3] The final goal of any periodontal and implant-related procedure is the achievement of the foreseen / expected outcomes of therapy (i.e., predictability of treatment), in order to provide the patient a healthy state "as close as possible" to a 'pristine' periodontal / peri-implant tissues condition.[3,29]

In this modern era of "evidence-based decision-making" where systematic reviews of randomized clinical trials became one of the primary types of study used for the selection of the best available treatment options for intervention procedures, the question remains: *Are systematic reviews of interventions clinically efficient in gathering information of treatment complications / adverse effects*? The instantaneous answer to this simple question for sure should be YES because it is expected that `high quality systematic reviews` should report on complications and adverse effects, as well. However, the preferable type of study used as the source of information (i.e. randomized clinical trial) may not provide the definitive information (or in other words, the real-word clinical scenario) on this issue.[3] As an experimental example, it would not be feasible for this *Periodontology 2000* chapter to search the literature for all relevant randomized clinical

trials, on the diverse non-surgical and surgical periodontal and implant-related treatment approaches, just to provide a report on the real prevalence of adverse effects / complications. Consequently, a selection of recent systematic reviews including at least five randomized clinical trials were used to exemplify the prevalence of adverse events caused by some periodontal and implant-based therapies (Table 2). [28,39,40,54-62] On one hand, it could be identified that the majority of randomized clinical trials included in most of these systematic reviews[28,39,40,54-58,60,62] did not describe the occurrence of wound healing adverse events. On the other hand, two systematic reviews included a high number of randomized clinical trials reporting on adverse events (at least 50% of included trials).[59,61] Interestingly, in both reviews,[59,61] the occurrence of adverse events, apparently, seems associated to the extension and complexity of the treatment procedures (i.e., lateral and vertical ridge augmentation). Thus, another question arises: Why?

It can be argued that efficacy trials have been associated "to the probability of benefit to individuals in a defined population from an intervention administered under ideal conditions," while effectiveness studies involve "the impact in real-world situations by assessing the benefit of an intervention provided to typical individuals by the average practitioner under ordinary conditions."[3,63] Efficacy trials are undeniably relevant for the establishment of the best treatment options (cost-benefit ratio). However, the use of randomized clinical trials may not be that advantageous to answer main enquiries regarding unusual adverse events because: a) well-designed randomized clinical trials are usually conducted under very stringent methods, in terms of patients selection (inclusion criteria), interventions (standardized procedures) and personnel (calibrated and well-trained clinicians), in order to improve the homogeneity of procedures and reduce the number of unexpected adverse events; and b) sample size calculation for periodontal and implant-related randomized clinical trials usually requires the inclusion of a very "restricted number of patients" (i.e., usually between 10-40 participants distributed across each treatment arm, with few trials including more than 50 patients) [28,39,40,54-62,64] compared to medical drug-testing randomized clinical trials that may involve hundreds of patients.[65-67] Thus, obtaining a sample of periodontal patients experiencing "the adverse effects of interest" may not be easily

available for analysis. Consequently, outcomes gathered from private practice retrospective studies (i.e., case series and case-control studies) may assist in answering these questions and fill the gap of knowledge on the factors influencing the occurrence of adverse events. Despite their methodological limitations (i.e., lack of standardized analysis, treatment methods and data compilation), these may offer a larger amount of information due their retrospective nature and potential inclusion of bigger samples of patients (> 100).[68-71]

These conditions, *per se*, are extremely relevant for the clinical practice (in the end this is what really matters to the clinician and the patient) as they can allow a better understanding of the behavior and management of the most common and unusual wound healing adverse events.

5 | CONCLUDING REMARKS

To address the problem of lack of evidence regarding errors and complications in Periodontology and Dental Implantology, the appraisal of adverse events should be described in detail in any published paper (i.e., in the same way authors use to do for the primary treatment outcomes of interest). The adverse events (i.e., errors, complications, harms and adverse effects) of interest should be clearly defined, as well as their severity and extension. When deemed feasible, the influence of the results of patients / sites experiencing wound healing adverse events should be explored during the calculation of the statistical analyses. For studies reporting few events and where it might not be possible to run such estimates, subgroup reports (i.e. results of patients with and without wound healing adverse events) should be presented separately (i.e., mean values with confidence intervals or percentage). This will improve the consistence and robustness of reports, allow a better interpretation of the clinical impact of wound healing adverse events on the results of therapy, and assist clinicians during the decision-making process (in other words, this will allow an individualized selection of the most appropriate treatment approaches for each patient and disease or condition of interest).

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Table 1: Items included in the CONSORT[42] and PRISMA[43] Statements Harm Extensions

	CONSORT[42]	PRISMA[43]
Title and abstract	"If the study collected data on harms and benefits, the title or abstract should so state"	"Specifically mention 'harms' or other related terms, or the harm of interest in the review"
Introduction	"If the trial addresses both harms and benefits, the introduction should so state"	
Material and Methods	"List addressed adverse events with definitions for each (with attention, when relevant, to grading, expected vs. unexpected events, reference to standardized and validated definitions, and description of new definitions)" "Clarify how harms-related information was collected (mode of data collection, timing, attribution methods, intensity of ascertainment, and harms-related monitoring and stopping rules, if pertinent)" "Describe plans for presenting and analyzing information on harms (including coding, handling of recurrent events, specification of timing issues, handling of continuous measures, and any statistical analyses)"	"Specify how zero events were handled, if relevant"
Results	"Describe for each arm the participant withdrawals that are due to harms and their experiences with the allocated treatment" "Provide the denominators for analyses on harms" "Present the absolute risk per arm per adverse event type, grade, and seriousness, and present appropriate metrics for recurrent events, continuous variables, and scale variables, whenever pertinent" "Describe any subgroup analyses and exploratory analyses for harms"	"Define each harm addressed, how it was ascertained (e.g., patient report, active search), and over what time period" "Describe any assessment of possible causality"
Discussion	"Provide a balanced discussion of benefits and harms with emphasis on study limitations, generalizability, and other sources of information on harms"	

Table 2 – Percentage of RCTs included into SR that reported the occurrence of wound healing adverse events

Study	Treatment Approach	RCTs reporting WHAE	Types of WHAE reported (treated sites)*
Chambrone et al.[28]	Infrared lasers for the treatment of periodontitis	14.28% (04/28 RCTs)	Pain, bleeding, or swelling (nonsurgical treatment); Swelling (surgical treatment)
Chambrone et al.[54]	aPDT for the treatment of periodontitis and peri-implantitis	3.84 % (01/26 RCTs)	Pain (nonsurgical treatment of resisual sites)
Clementini et al.[55]	Minimally invasive periodontal surgeries (versus other techniques or associated to biomaterials)	40.00% (04/10 RCTs)[#]	Discomfort/ pain (usually up to 1 week)
Matarasso et al.[56]	Periodontal regeneration of intrabony defects (use of enamel matrix derivative and bone grafts)	0% (0/12 RCTs)	The included RCTs did not report the occurrence of WHAE
Chambrone et al.[39,40]	Root coverage	31.25 % (15/48 RCTs)	Occurrence of an early discomfort (up to 2 weeks after treatment) with or without pain /swelling, flap dehiscence, biomaterial exposure
Cairo et al.[57]	Soft tissue augmentation at implant sites	14.28% (02/14 RCTs)	Mucositis and provisional restoration detachment
Avila-Ortiz et al.[58]	Alveolar ridge preservation	18.18% (04/22 RCTs)	Discomfort, edema, inflammation, soft tissue graft necrosis, alveolar osteitis,
Naenni et al.[59]	Lateral ridge augmentation prior to implant placement	50% (08/16 RCTs)[#]	Discomfort, edema, pain, ecchymosis, soft tissue dehiscence, membrane exposure, acute infection with loss of the majority of graft material and bone block exposure
Thoma et al.[60]	Lateral ridge augmentation performed simultaneously with implant placement	The number of trials not reported (?/16 RCTs)[#]	Soft tissue dehiscence, membrane exposure and implant exposure,
Urban et al.[61]	Vertical ridge augmentation	100% (06/06 RCTs)[#]	Flap dehiscence, wound dehiscence, membrane exposure, perforation of soft tissue expander, titanium mesh exposure, abscess, infection and fistula,
Chan et al.[62]	Surgical approaches to treat peri-implantitis	Not available (05 RCTs)[#]	Information on WHAE was not reported / recorded

*outcomes of procedures involving donor sites were not included in the table; [#]the review included different types of studies , but only the data from randomized clinical trial were included in this table; aPDT - antimicrobial photodynamic therapy; RCT – randomized clinical trial; WHAE – wound healing adverse events