

## Randomized clinical trials in periodontology: focus on outcomes selection

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**Abstract:** Randomized clinical trials (RCTs) are human studies carried out to compare different treatments or interventions, and their results are used to support clinical decision-making and improve patient care. Herein, the aim of this study was to review the selection process of study outcomes in periodontology. Primary outcomes should draw the main conclusions of the study, whereas secondary outcomes should only be used to help explain the main findings and generate future research hypothesis. Outcomes are classified as clinically relevant (CROs) or surrogate outcomes. CROs – the first option for primary outcome variables - should convey not only substantial health benefits, but also be deemed important by patients. In periodontology, tooth loss/retention and oral health-related quality of life (OHRQoL) are examples of CROs. While tooth loss has main limitations as a primary outcome, emerging evidence suggest that patient-reported outcome measures (PROMs) can accurately detect OHRQoL following periodontal therapy. When CROs cannot be assessed, validated surrogate outcomes can be used as proxies. Primary outcome variables should reflect a treatment endpoint at the patient level that can be easily used to inform decision-making in daily practice. These outcomes should allow the implementation of a treat-to-target concept in which the intervention can be clearly judged against a prespecified treatment target. Recently, the presence of at most 4 sites with periodontal probing depth  $\geq 5$  mm post-treatment was suggested as an effective endpoint for periodontal trials. In perspective, a combination of validated clinical parameters and PROMs will provide a more comprehensive assessment of periodontal treatments.

**Keywords:** Clinical Trial; Treatment Outcome.

## Introduction

Randomized clinical trials (RCTs) are considered the gold standard study design for the evaluation of the efficacy and safety of interventions in health care settings.<sup>1</sup> This is accomplished by randomly assigning participants to experimental groups and then comparing groups in relation to important health outcomes, also referred to as “dependent variables” or “endpoints”. The selection of an appropriate study outcome is essential during the planning stages of a RCT. Poorly chosen outcomes may lead to findings that do not translate into true benefits for patients.



Ideally, investigators should select study outcomes that not only provide substantial health benefits, but also are deemed important by patients. Regulatory agencies, including the Food and Drug Administration, currently favor outcomes that measure “how a patient feels, functions or survives”. In this context, most trials in periodontology have focused on clinician-centered outcomes (e.g.: periodontal probing depth [PPD] reduction, clinical attachment level [CAL] gain, and radiographic bone loss) that do not capture the expectations and perceptions of the patient.

Thus, the aim of this paper was to review the selection process of study outcomes in periodontology.

## Primary and secondary outcomes

Most RCTs in dentistry explore multiple outcomes in order to assess the effects and, sometimes, safety of dental treatments and interventions. In this context, outcomes can be categorized into primary and secondary. A primary outcome is defined as the outcome that the investigator consider to be the most important among the parameters that will be assessed in the trial.<sup>2,3</sup> Primary outcomes address the main research question of the study, and consequently, determine the study design and sample size, and support the main conclusion of the study. In contrast, secondary outcomes are exploratory in nature; strictly speaking the trial is not designed to evaluate them. Findings based on secondary outcomes should not be used to draw definitive conclusions. Nevertheless, they can help to explain the primary outcomes or generate hypotheses to be explored in future trials. Preferably, the primary outcome should be a clinically relevant outcome (CRO). If it is not feasible to select a CRO as the primary outcome, a validated surrogate outcome can be used as a proxy. It is important to acknowledge that depending on the objective of the study a given outcome can be primary or secondary. For instance, pain/discomfort can be a primary outcome in a trial testing an analgesic and secondary in a trial testing a new surgical technique.

Important clinical research guidelines, including Standard Protocol Items: Recommendations for

Interventional Trials (SPIRIT),<sup>2</sup> Consolidated Standards of Reporting Trials (CONSORT)<sup>3</sup> and International Council for Harmonisation (ICH),<sup>4</sup> recommend the use of a single primary outcome in order to prevent multiplicity.<sup>5</sup> Multiplicity occurs when multiple comparisons are carried out during statistical analysis, for instance, comparison of multiple outcomes over multiple time periods (fishing expedition probability or data-fishing). Multiplicity increases the probability of type I error, which is the incorrect rejection of the null-hypothesis resulting in the mistaken conclusion that a treatment is better than the comparison intervention, when in fact it is not.<sup>6,7</sup> This may lead to the unethical reporting of the most favorable results.<sup>6,7</sup>

All outcomes, primary and secondary, must be pre-specified in the research protocol, which should be available on a public platform prior to study initiation. Several public and private clinical trial registries are currently available, including the World Health Organization International Clinical Trials Registry Platform (ICTRP), United States National Institutes of Health (Clinicaltrials.gov) and Brazilian Clinical Trials Registry (ReBec). Failure to register the protocol before the study starts can result in publication bias and selective outcome reporting (SOR). Publication bias occurs when the results of a trial influence the decision whether to publish it or not. On the other hand, SOR is a type of reporting bias that happens when the primary outcome of the study registry is modified or suppressed, or when a new outcome is added in the final publication.<sup>8,9</sup> Pre-specification of primary and secondary outcomes in a public database has been shown to reduce publication bias and SOR.

Outcomes must be completely described using the following five levels of specification in reporting outcome measures:<sup>10,11</sup> domain, measurement, metric, data aggregation method, and time point.<sup>10</sup> An example of a completely defined outcome is “mean PPD reduction after 12-months of follow-up in sites with PPD  $\geq$  5mm at baseline”. If one of these five elements is absent or unclear, the outcome is not completely defined, setting precedents for “cherry-picking”, which is the selective reporting of certain outcome measurements or time points.<sup>11</sup>

## Clinically relevant outcomes and surrogate outcomes

Researchers should select primary and secondary outcomes that are important and tangible to patients. These types of outcome are usually referred as CROs, and are also called true, direct or clinically meaningful outcomes.<sup>12</sup> Examples include death, tooth loss, number of hospitalizations, pain/discomfort and quality of life (QoL). Some CROs are reported by patients and are called patient-reported outcome measures (PROMs). Objective CROs, such as all-cause mortality or tooth loss, are rarely chosen as the primary outcome for clinical trials, because they are infrequent events and require several years of follow-up. Thus, objective CROs are frequently replaced by surrogate outcomes. Surrogate outcomes include post-treatment changes in biomarkers (e.g. gingival crevicular fluid levels of interleukin-1 $\beta$ ), in radiographic (e.g. alveolar bone loss) or clinical parameters (e.g. mean PPD) that are not themselves a direct measurement of the clinical endpoint for treatment.<sup>13</sup> Rather, they are supposed to be a proxy for the true CRO. Investigators often use surrogate outcomes in order to reduce the study sample size, follow-up and costs.

The effects of the intervention on the surrogate outcome are supposed to reliably predict a substantial effect on the CRO. Whereas some surrogates have a strong causal association with the real condition (e.g. intra-ocular pressure and glaucoma), others fail to demonstrate a correlation with the disease and its consequences (e.g. blood glucose and cardiovascular events in diabetic subjects).<sup>14</sup> Before a surrogate outcome is chosen as the primary outcome, it should be properly validated.<sup>15</sup>

### Clinically Relevant Outcomes (CROs) in periodontal trials

The choice of study outcome in periodontal clinical trials has been a great challenge for the field. In fact, the interpretation of the findings from clinical trials testing different periodontal treatments and the extrapolation of these findings to clinical practice have been hampered by the heterogeneity and subjectivity of the outcome measures used in different studies.

In periodontal clinical trials, tooth loss/retention and oral health-related quality of life (OHRQoL), assessed by PROMs, could be considered as preferred CROs. Although some authors have advocated for tooth loss,<sup>152</sup> there are several difficulties associated with the use of this parameter. First, spontaneous tooth loss after treatment is an infrequent event since extraction of teeth with very advanced disease is part of the initial therapy.<sup>163</sup> Thus, any reduction in tooth loss attributable to the experimental treatment would require several years of follow-up (e.g., 5–10 years) to be detected. Second, the relationship between oral health and tooth loss/retention depends not only on caries and periodontitis progression, but also on cultural beliefs, socio-economic characteristics, demographics, behavioral variables, and dental care philosophy. Therefore, tooth loss/retention is not frequently used as a primary outcome in RCTs testing periodontal treatments.

PROMs are a promising option for assessing CROs in periodontal trials. These parameters can be broadly understood as “measurements of any aspect of a patient’s health status that come directly from the patient”<sup>17</sup> and that facilitates a comprehensive approach to patient assessment frequently identifying problems that are overlooked in routine practice. PROMs are powerful tools to inform patients and clinicians about morbidity and ‘patient suffering’, especially in chronic diseases. PROMs provide information on the patient experience and can be the target of therapeutic intervention and improve the quality of patient care by creating a holistic approach to clinical decision-making.<sup>17</sup> PROMs are currently used in regulatory decisions, including submissions to the Food and Drug Administration and European Medicines Agency, as a measure of the patient’s perspective on the performance of medical devices and treatments. PROMs can assess subjective CROs that are used as primary outcomes depending on the disease/condition being studied.

Collecting PROM data is an effective way to standardize practice and improve patient management. Whether PROMs can improve the quality of patient care remains under debate.<sup>17</sup> Over the past two decades, several studies have measured the impact of oral health on QoL.<sup>18</sup> These QoL measures, which

were initially designated as socio-dental indicators or subjective indicators of oral health, are now more commonly referred to as self-reported QoL measures related to oral health.<sup>17</sup> Particularly, studies have shown a significant association between periodontitis and OHRQoL.<sup>19,20,21</sup> Periodontitis clinical consequences may negatively impact QoL regarding emotional, social and functional aspects as well as symptoms in acute processes and the severity of the disease.<sup>22,23</sup>

Few RCTs have investigated the effect of periodontal treatment on OHRQoL.<sup>21,24–29</sup> Although limited in their number and scope, the overall findings indicate a positive impact of periodontal interventions on OHRQoL (Table 1). Several RCTs have evaluated the effect of implant dentistry on

PROMs showing a positive effect of removable and fixed implant-supported prostheses on patient satisfaction and QoL.<sup>30</sup> Similarly, RCTs comparing different treatment options for gingival recession have shown that certain surgical techniques had a significant impact on patient's aesthetic satisfaction and post-operative morbidity.<sup>31</sup>

RCTs that use PROM endpoints follow similar study design and methodology than those focusing on clinical endpoints. However, important issues of particular relevance to PROM assessments, such as missing values, multiple outcomes, and the statistical analysis, require careful attention.<sup>32</sup> Proper instrument selection is essential for RCTs using PROM outcomes. The application of validated and widely

**Table 1.** Summary of randomized clinical trials that evaluated PROMs.

| Author (year)                       | Intervention and sample   | Time evaluation                            | PROM evaluation  | Main results  |
|-------------------------------------|---|--|------------------|---|
| Santuchi et al., 2016 <sup>21</sup> | Scaling and root planning (n = 45) and full-mouth debridement (n = 45)  | Baseline, 1 and 6 months                   | OIDP             | Both groups showed significant improvement on clinical parameters and OIDP; no significant differences between groups.  |
| Åslund et al., 2008 <sup>24</sup>   | Non-surgical therapy using a piezo-ceramic device (n = 30) or cures (n = 29) in individuals with mild to moderate periodontitis   | Baseline, treatment, and 1, 4, and 8 weeks | OHQoL-UK         | Both groups showed improvements in clinical parameters, pain scores and QoL measures  |
| Agado et al., 2012 <sup>25</sup>    | Ultrasonic debridement (n = 10), hand instrumentation (n = 10), and a control group (n = 10) in chronic obstructive pulmonary disease patients  | Baseline and 4 weeks post-treatment        | SGRQ             | Total SGRQ-A scores decreased slightly for all groups with no significant difference among groups and no significant interaction  |
| Santuchi et al., 2015 <sup>26</sup> | Scaling and root planning per quadrant (n = 37) and one-stage full-mouth disinfection (n = 41)  | Baseline and 6 months                      | DFS, DAS and VAS | Patients with higher PROs showed worse clinical parameters before and after treatment. After both treatments, fear and anxiety decreased with no significant differences between groups. No significant differences in pain scores between groups |
| Cortelli et al., 2018 <sup>27</sup> | Ultrasonic debridement in combination with essential-oils in diabetic (n = 30) and non-diabetic individuals (n = 30), or placebo mouthwash in diabetic (n = 30) and non-diabetic individuals (n = 30) | Baseline and 3 months                      | OHQoL-UK         | Combined treatment with EO provided OHQoL improvements in both systemic conditions, but not in placebo groups   |
| Musskopf et al., 2018 <sup>28</sup> | Pregnant women receiving scaling and root planning/maintenance (n = 96), or supragingival scaling and polishing (n = 114)   | Before and after treatment                 | OHIP-14          | Both groups showed significant reduction in OHIP-14 scores; control group had significantly higher odds of worsening their OHIP-14 scores and their perception of oral conditions than test group   |
| Zhou et al., 2019 <sup>29</sup>     | 60 CPOD individuals: (n = 20) scaling and root planning treatment, (n = 20) supragingival scaling treatment and (n = 20) oral hygiene instructions only with no periodontal treatment                 | Baseline, 1 and 2 years                    | SGRQ             | The impacts scores of two treatment groups were significantly lower than control group at 2-year follow-up  |

OHQoL-UK: United Kingdom OHQoL questionnaire; SGRQ: St. George's Respiratory Questionnaire; DFS: Dental Fear Survey; DAS: Dental Anxiety Scale VAS: Visual Analogue Scale; OIDP: Oral Impacts on Daily Performance; OHIP-14: Oral Health Impact Profile-14.

used questionnaires following an interview format is regarded as best practice. In perspective, a combination of PROMs as primary outcome and established periodontal parameters as secondary outcomes may provide a more comprehensive assessment of current and innovative new treatments.

### Surrogate outcomes in periodontal trials

Although a few clinical studies have used CROs such as tooth loss and OHRQoL such as patient satisfaction, post-treatment discomfort/pain and aesthetic perception as primary outcomes,<sup>33</sup> most RCTs in periodontology have used surrogate parameters as primary outcomes. The most commonly used parameters are mean PPD reduction or CAL gain at initially deeper periodontal sites.<sup>34</sup> Mean gingival recession and percent root coverage are also frequently used in RCTs focused on esthetics<sup>5</sup>. Unfortunately, there are several drawbacks associated with the use of such parameters, such as: (i) limited evidence that they reflect long-term benefits for patients, (ii) challenging interpretation of the results since clinicians do not use averages to evaluate the result of their treatments in daily clinical practice, and (iii) changes in mean clinical values do not reflect an endpoint for treatment (i.e., disease remission/control) at the patient level.

A possible solution for this conundrum is the use of a surrogate outcome that reflects an endpoint for treatment at the patient level for which there is strong evidence of substantial effect on CROs. This approach would allow the implementation of the “treat-to-target” concept largely used in medicine, but still relatively unknown in dentistry. The idea is to treat a disease until a prespecified clinical or laboratorial target is achieved. A classic example in medicine is the use of a threshold for blood pressure (e.g., 120/80 mm Hg) as a surrogate outcome in trials testing medications to prevent myocardial infarction or heart failure. The main challenge of a treatment approach based on the treat-to-target concept is to identify targets that reflect disease remission/control and that may predict meaningful long-term benefits to patient

Researchers and clinicians have been exploring other primary outcome variables to address the above-

mentioned shortcomings for surrogate outcomes in periodontology.<sup>35-38</sup> Presence of residual pockets after therapy has been associated with lack of long-term periodontal stability and disease recurrence.<sup>16,39-44</sup> Deep pockets are colonized by a more dysbiotic subgingival biofilm containing higher levels of periodontal pathogens than shallow pockets,<sup>45</sup> which favors the persistence of periodontal inflammation. In periodontology, two surrogate outcomes based on the number of residual sites at the patient level after active periodontal therapy have been suggested as potential endpoints for treatment in RCTs: Mombelli and co-workers suggested “number of sites with PPD  $\geq 5$ mm and bleeding on probing (BOP)”<sup>35,46</sup> and Feres and co-workers “presence of at most 4 sites with PPD  $\geq 5$ mm” after treatment<sup>8</sup>. The later criterion was initially suggested as a secondary outcome,<sup>36</sup> then reported in several RCTs in the literature,<sup>38,47-56</sup> and finally presented as a primary outcome variable for treatment.<sup>37</sup> Recently, this outcome was validated in a study that included a comprehensive analysis of 724 patients from the United States, Germany and Brazil.<sup>34</sup> The validation process was able to demonstrate that the proposed outcome was effective in distinguishing between patients showing signs of periodontal disease remission/control from those showing signs of uncontrolled disease up to 2 years post-treatment. In addition, these patients had a microbial profile more compatible with health up to 2 years post-treatment.<sup>53,57</sup> Another interesting finding in that study was that full mouth BOP seemed to worsen the results of treatment. Regression models showed that the presence of  $> 10\%$  and  $> 20\%$  sites with BOP in the mouth post-treatment increases the risk of a patient leaving the endpoint between 1 and 2 years of follow-up, with an OR = 3.5 and 8.7, respectively.

Robust risk assessment studies should be planned in order to establish if these new surrogate endpoints correlate with long-term periodontal stability, tooth survival, OHRQoL, and other patient-centered outcomes. The selection of surrogate outcomes in clinical trials should take into consideration the study objectives since periodontal disease treatment and periodontal reconstruction may require different criteria for success. Table 2 summarizes the main concepts described in this article, with examples.



**Table 2.** Summary of concepts and examples.

| Type of outcome                           | Definition   | Examples   |
|---|--|--|
| Clinically relevant outcomes (CROs)       | Outcomes that directly measure how a patient feels, functions or survives  | Death, number of hospitalizations, tooth loss, oral health-related quality of life   |
| Patient-reported outcome measures (PROMs) | Measurements of any aspect of a patient's health status that come directly from the patient. PROMs are considered to be CROs.                              | Pain/discomfort, self-assessment of function and esthetics, oral health-related quality of life  |
| Surrogate outcomes                        | Outcomes that are not themselves a direct measurement of the clinical endpoint. Rather, they are supposed to be a proxy for the true CRO                   | Gingival crevicular fluid levels of interleukin-1 $\beta$ , radiographic alveolar bone loss, clinical attachment gain  |
| Primary outcome                           | The pre-specified outcome considered to be of greatest importance to the study; study design and sample size calculations are based on the primary outcome | Depending on the objective of the study a given outcome can be primary or secondary.   |
| Secondary outcomes                        | All other outcomes in the study. The trial is not designed to evaluate them, so they are exploratory in nature   | E.g.: pain assessed using a visual analog scale can be a primary outcome in an RCT testing an analgesic and secondary in a RCT comparing two root coverage surgical techniques |

## CONCLUSION

The proper selection of study outcomes is an essential step during the protocol development of RCTs. Investigators should select CROs that not only provide substantial health benefits, but also are deemed important by patients.

OHRQoL are emerging as preferred primary outcomes in clinical research. Data derived from RCTs support the concept that PROMs are able to accurately assess improvements in patient OHRQoL following periodontal treatment, such as satisfaction, discomfort/pain and aesthetics. Future RCTs using validated PROMs and samples with broader characteristics are necessary to expand the use of PROMs in periodontology.

Surrogate outcomes can be used as proxies when the use of CROs is not feasible. Surrogate outcomes

traditionally used in periodontal clinical research do not reflect a treatment endpoint at the patient level that can be easily used to inform decision-making in daily practice. Instead of outcomes based on group averages, we suggest the use of partially validated surrogate outcomes based on the presence of residual “pockets” following treatment, such as the presence of  $\leq 4$  sites with PPD  $\geq 5$  mm. This surrogate outcome has been shown to correlate with disease remission/control following non-surgical periodontal treatment for up to 2 years. Thus, it allows the implementation of a treat-to-target concept in periodontal trials clearly outlining if the intervention has achieved a prespecified treatment target.

A combination of outcomes assessing OHRQoL and clinical parameters reflecting an endpoint for periodontal treatment may provide a more comprehensive assessment of new treatments and interventions.

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