INTRODUCTION
When data from periodontal clinical trials are reported, clinicians should not be left to wonder about the clinical relevance of statistically significant results. As new procedures are developed, they need to be evaluated to determine if they provide statistically and clinically significant benefits. If both are furnished, the therapeutic modality can be considered for incorporation into treatment regimes. Currently, there is too great reliance on using statistical significance testing, or hypothesis testing, to detect a statistically significant difference between therapies, which then often is used to infer that a therapy supplied a clinically meaningful result. This is problematic because it is possible for a procedure to provide a statistically significant improvement, while the result may not be clinically significant. These two related subjects are important because they can influence how clinicians interpret the results of clinical trials and how patients subsequently are treated.1

Accordingly, there is a need to define a set of criteria related to clinical parameters that would reflect important therapeutic changes that have clinical relevance to the practitioner. This review addresses the limitations of statistical significance testing and the advantages of identifying criteria related to periodontal clinical parameters used to define clinical significance and also various levels of clinical significance.

DEFINING CLINICAL SIGNIFICANCE:
The definition of clinical significance varies depending on the specific clinical field being addressed, the size of the effect, the measurement used to evaluate a therapy and the clinical importance of the findings. Hujoel and colleagues (2000) suggested a working definition for clinical significance as “statistically significant difference in a clinically important outcome identified in a definitive or phase III clinical trial.”2

Gary Greenstein (2003) defined clinical significance as a change that may alter how a clinician will treat a patient, and this value judgment varies depending on the situation.1

A dilemma concerning the interpretation of data from periodontal clinical trials exists because the profession has been reluctant to establish standards to quantify clinical significance. This has resulted in using arbitrary statistical standards to define the merits of therapeutic techniques. Feinstein stated that “there is an entrenched reluctance to judge the familiar” (use of routine clinical parameters) “and docile conformity in accepting the unfamiliar” (hypothesis testing).3 This problem could be resolved if changes representing meaningful results were defined for clinical parameters in diverse situations, thereby facilitating hypothesis testing regarding relevant clinical findings. Periodontal diseases are site specific, and various types of defects and diseases may require different definitions of clinical significance for their responses to therapy. In this regard, it would be advantageous to define important clinical improvements that previously have been referred to with different terms such as “clinically significant,” “clinically meaningful,” “clinically relevant,” “quantitatively significant,” “of biological distinction” or “substantively important.”4 Identifying important criteria related to particular periodontal parameters would help clinicians select the most appropriate therapy for specific problems. No one criterion applies to all situations. Nevertheless, the need to quantitate clinical significance becomes very apparent when hypothesis testing’s shortcomings are delineated.

PERSPECTIVES ON THE DEFINITION OF CLINICAL SIGNIFICANCE:
Clinicians play a critical role in defining a clinically meaningful result and needs to relate various monitored clinical parameters to the goals of therapy.
The clinician also may be interested in the size of the effects, time needed for therapy, ease of implementation, cost, side effects, duration of results, consumer acceptability and so forth. While with regard to clinical significance, patients are interested in reduction of specific symptoms with their resolution and quality-of-life issues such as retention of their teeth, comfort, good function of their teeth, and lack of side effects. The researcher may consider small statistically significant changes to be clinically important because they demonstrate a benefit that did not occur by chance. These small improvements could be considered windows of opportunity that may provide avenues for additional research. On the other hand, one researcher has said that “to determine clinical significance, the overall purpose of the study, its design and size of the effect that may matter to a patient first must be determined.”

Federal regulatory agencies, such as the U.S. Food and Drug Administration, or FDA, are concerned about both safety and effectiveness of treatment methods. In general, once a product is considered safe, federal regulatory agencies focus on results that are statistically significant, thereby providing mathematical certainty that the results attained did not occur by chance. This helps bring products to market that are superior to standard controls or are equivalent to available products. Whereas, the aim of a health care system is to provide adequate access to quality care at a reasonable cost.

Companies developing dental products search for statistically significant differences between therapies since it is easier to attain this threshold than it is to try to achieve a level of clinical significance that has not been accepted universally by clinicians. Third-party payers usually are focused on reimbursement and accountability. They may want to see a large change in an important clinical parameter and its ability to prevent or reduce the potential of disease relapse by the patient.

LEVELS OF CLINICAL SIGNIFICANCE:
The term clinically significant could be made more relevant by recognizing (1) the nature of the benefits (tangible/intangible) and (2) the size of the treatment effect (large/small). These two criteria for classifying clinical significance are now defined.

TANGIBLE VS INTANGIBLE BENEFITS:
Tangible benefits are those treatment outcomes that reflect how a patient feels, functions, survives. The word tangible is defined as “capable of being precisely identified or realized by the mind.” Examples of tangible benefits could include improved oral health related quality of life, a decrease in self-reported symptoms (e.g., bleeding) after brushing, prevention of tooth loss, or elimination of a painful periodontal abscess. Tangible benefits can also be referred to as "clinically relevant" benefits or "clinically meaningful" benefits.

Intangible benefits cannot be realized by the patient's mind. Changes in probing attachment level as a result of scaling, changes in enamel mineralization level as a result of fluorides, and changes in the size of periapical radiolucency as a result of a root canal treatment are examples of changes the mind cannot identify or realize; thus they are intangible treatment benefits. Intangible treatment benefits can often be measured objectively by the clinician or by laboratory methods.

A first step in assessing the clinical significance of a treatment is to determine whether the documented treatment benefits are tangible or intangible. This distinction is important because intangible benefits do not necessarily translate into tangible benefits. A medication that lowers elevated blood lipid levels (an intangible benefit) may shorten life span (a tangible patient harm). A treatment that increases bone density (an intangible benefit) can increase fracture risk (a tangible patient harm). A treatment that provides extensive periodontal bone regeneration (an intangible benefit) can lead to tooth loss (a tangible harm).

SIZE OF THE TREATMENT EFFECT:
A second important criterion for assessing clinical significance is the size of the treatment effect. The size of the treatment effect is a comparison of the success rates of the experimental treatment and the control treatment. The larger the likelihood of obtaining an expected benefit of a treatment (relative to control treatment), the more clinically significant the treatment. It is suggested that if the odds ratio associated with the treatment comparison is 0.25 or smaller (when compared to the control), the size of the treatment effect may be considered large.
The likelihood of obtaining a treatment benefit is a determinant of clinical significance; the larger the likelihood, the more confident a patient can feel that a treatment will be successful. Although it is possible to have a clear, unequivocal definition of what constitutes a tangible benefit associated with treatment, it is not possible to have similar rigorous definition of what can be considered a large likelihood.9

DEFINING FOUR LEVELS OF CLINICAL SIGNIFICANCE:
Based on the nature of the benefit (tangible/intangible) and the size of the treatment effect (large/small), four levels of clinical significance can be defined

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Dr. Phillip Hujoel at 1st International Conference on EBD — November 8—9, 2003 — Atlanta, Georgia, USA introduced a four-level scale to assess clinical significance.10

Clinical Significance Level 1:
Treatments of clinical significance level 1 are the "magical bullets," the "miracle cures" in which the treatment provides a tangible benefit and the size of the treatment effect is large. Examples of such treatments include the use of vitamin C to treat scurvy, bone marrow transplantation to treat leukemia, and dental implants to improve the oral-health-related quality of life of edentulous individuals. In all three examples, the benefits of the treatment are tangible, and the size of the treatment effect is large. An understanding of biologic mechanisms of treatment actions is not required to establish that a treatment has clinical significance level 1. For example; lemon juice was identified as an effective method to prevent scurvy in 1601, but it was not until the beginning of the twentieth century that vitamin C was isolated. In contrast, HRT, for which the biologic mechanisms explaining how the drug provided benefits were supposedly so well understood, resulted in more harm than good.9

Clinical Significance Level 2:
The term clinical significance level 2 is used to describe treatments that have been demonstrated to provide a tangible benefit, but for which the likelihood of obtaining the benefit from treatment is small. Because the size of the benefit of one therapy over another is small, randomized controlled trials (RCTs), often large in size and rigorous in execution and analysis, are required to provide unequivocal evidence that the treatment provides tangible patient benefits. Examples of such treatments include the advantage of tissue plasminogen activator (t-PA) over streptokinase and the benefits of penciclovir in the treatment of herpetic lesions.

Determining the clinical relevance of treatments of clinical significance level 2 is an individual choice in which issues such as cost and side effects often play a more important role. For example, the mortality rate with t-PA is 6.3%, whereas the mortality rate with streptokinase 7.3%. In other words, there is a 1% increased chance for survival associated with t-PA. In the 1990s, when this treatment was introduced, the increased cost for t-PA was $2000. Is a 1% increased survival probability worth $2000? Different individuals, different governments, and different health insurance companies may decide differently on this important question. Indeed, some individuals may believe that if large RCTs are required to determine treatment effectiveness, the clinical significance of the treatment is questionable. By using the terminology "clinical significance level 2," the concept of small, tangible patient benefit can quickly be communicated without becoming trapped in meaningless discussions regarding the clinical relevance of small benefits.9

Clinical Significance Level 3:
Treatments of clinical significance level 3 are the magical bullets, the miracle cures in the surrogate world where the beneficial but intangible effects of treatment are so convincing that the need for RCTs may appear remote. Examples of such treatments include the use of chlorhexidine varnish in the prevention of caries. With a treatment that has the label of "clinical significance level 3," there is always the uncertainty of whether the intangible benefits translate into real, tangible patient benefits. It has been a common observation that the larger the effect size observed on the surrogate, the more likely the surrogate benefit translates into a real, tangible patient benefit. However, assuming that large, intangible treatment benefits invariably translate into tangible treatment benefits remains a dangerous assumption, no matter how large the effect on the surrogate endpoint. A 40% chlorhexidine varnish used for the prevention of caries was reported to result in a 99.9% mutans streptococci reduction in all the 20 subjects treated.
and the streptococci stayed below detectable levels for at least 4 weeks in nine subjects. In contrast, the placebo varnish-sealant led to only a 32% mutans streptococci reduction, and none of the 20 subjects had mutans streptococci below detectable levels for 4 weeks. Based on these data, it was reported that, "Chlorzoin will wipe out dental decay much like smallpox." A subsequent RCT in 1240 children at high risk for caries did not translate into a reduction of large cavities in the teeth. The Chlorzoin group had more carious lesions as compared to placebo group. This example shows that even large, intangible treatment benefits do not always translate into tangible treatment benefits.9

Clinical Significance Level 4:
Treatments of clinical significance level 4 are those treatments which have reliable evidence from large randomized controlled trials of small, intangible treatment benefits. Because the treatment effects are small, epidemiological studies are almost always incapable of identifying treatment of clinical significance level 4. Examples of treatments of clinical significance level 4 include those that cause a small decrease in lipid level, a small drop in blood pressure, or a small decrease in pocket depth. Large leaps of faith are often required to jump from the observations that small changes in surrogate endpoints translate into real, tangible benefits. Treatment of clinical significance level 4 may cause more harm than good, and there is debate whether the drug-approval process should be changed. If such a change were to occur, it could have significant consequences for periodontal therapies because most approved periodontal therapies are of clinical significance level 4, and minimal information on their long-term safety is available.9

CONCLUSION:
Treatment that provide a tangible patient benefit (Level 1 or 2) are of greater value and should correspond to a higher level of clinical significance than treatment with evidence of only intangible benefits (Level 3 and 4). Similarly, treatments with a large likelihood for clinical improvement (Level 1 and 3) are clinically more significant than treatments with a small likelihood for clinical improvement (Level 2 and 4). Providing four hierarchical levels of clinical significance may help clinicians and patients communicate more effectively regarding the clinical significance of a treatment.

REFERENCES: