

In response to the FDA's draft guidance document governing the conduct of clinical study design for trials examining the anti-gingivitis effects of oral care products, I am gravely concerned with the delegation of the clinical endpoint of bleeding to secondary endpoint status. The guidelines as written would preclude the use of indices based solely on bleeding (PBI, SBI, etc.) and dichotomous derived bleeding scores from combined indices such as LS GI from being employed as the primary clinical endpoint for the measurement of gingivitis. In my investigation and talking to the periodontists that do clinical research for me as well as to my colleagues at Tufts University who treat patients bleeding indices relate most closely to disease and identify the patients at greatest risk.

In contrast, a pure visual clinical scale such as MGI could be used as a primary outcome in the absence of measuring a bleeding effect. I do not believe that there is a rational biologic basis for this point of view. I also believe that the guidelines as written will substantially affect the development of anti-gingivitis products. I would like you to consider the technical argument outlined below in support of gingival bleeding as a primary outcome for the testing of anti-gingivitis products.

It has been accepted in the dental community that plaque-associated gingivitis is identified clinically by gingival bleeding, redness, edema causing loss of tissue form, and gingival tenderness since the early work of Loe in 1965, and later by Suzuki in 1988. Gingival bleeding upon stimulation is internationally accepted as a clinical sign of gingival inflammation. Since Muhleman paper in 1971 gingival bleeding has been reported in clinical and histological studies to be an earlier and more sensitive sign of gingival inflammation relative to visual alterations, such as redness and edema. ((Loe 1965, Kornman 1987, Muhleman 1971, Greenstein 1981.) Other authors have reported both bleeding and redness to be early signs of gingivitis. In some indices, such as SBI bleeding precedes color changes (with 1 = bleeding with no color change and 2 = bleeding with reddening), while other combined indices such as LS GI color change proceeds bleeding (with 1 = redness and no bleeding and 2 = bleeding). The SBI and PBI indices have both been shown to statistically significantly positively correlate to number of inflammatory cells in gingival connective tissue upon histomorphometric analysis. (Engelberger 1983)

Additionally Oliver (1969) found that the percentage of inflamed area of total connective tissue is weakly correlated to LS GI scores, although minimal difference in area of inflamed tissue was observed between biopsies with GI = 1 and GI = 2 scores. The studies demonstrate that gingival bleeding is an early sign of gingivitis and may occur prior to or at the same time as color change and edema. To my knowledge there is little data to supporting that color changes are an earlier event than bleeding or that ordinal combined gingival indices like LS GI accurately represent the underlying biology.

Gingival bleeding is a more relevant and visible endpoint for patients. It is a clinically relevant measure of gingivitis to both the clinician for both dentists and patients. Examination of gingival bleeding points is a routine part of standard oral exams and a common question that dentists ask their patients as part of a medical/dental history. When I am screening for periodontal studies, asking about bleeding is frequently the best way to

determine eligibility over the phone, since patients are aware of bleeding and it is the frequently the reason they seek care. Importantly, reduction in the number of bleeding sites is a more interpretable result than a reduction observed in an index score based on color. It is both objective and ordinal in nature. It has been shown to be predictive of future disease risk

Presence or absence of gingival bleeding remains one of the most useful clinical predictors for future disease risk as measured by periodontal attachment loss. Absence of gingival bleeding over a 4 year maintenance period ensured periodontal health in 98.5% of sites. In contrast, sites that repetitively bled following probing had significant attachment loss in 30% of the instances.(Lang 1986)

Bleeding indices are more objective and easier to calibrate/standardize than visual combined indices. In general, the use of bleeding instead of other visual signs of inflammation as the indicator of gingival change has the clinical advantage in that it is a more objective sign. (Polson 1985) Bleeding is either present or absent, while color changes require subjective estimation by the examiner. (Meitner, 1979). With combined indices like LS GI, as many as four distinct examiner styles have been documented reinforcing the conclusion that combined indices are quite subjective. In calibration exercises, we and others have found it very difficult to calibrate to (McClanahan 2001) This examiner subjectivity presents significant obstacles in effectively calibrating examiners for multicenter studies. Bleeding indices are easier to control through the standardization of probing force, angulation and time to bleeding following soft tissue stimulation. Thus we have placed more value in this index though we have collected both.