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Improvement in Selection of Study Participants: Discussion of Dr. Downer's Presentation

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Introduction.

The reduction in caries experience in the developed countries and the introduction of standard active controls have highlighted our need to increase the efficiency of caries prophylactic trials. The comparison of a standard active control with a new formulation, although not new in medical research, is a relatively new approach in caries prophylactic trials.

Downer and Mitropoulos have proposed that we follow the example of medical researchers and refine the nature of the test hypothesis with the expectation of gains in the efficiency of the trial. They base their assumption on the work of Schwartz *et al.*[1], who partitioned trials into explanatory and pragmatic trials. The adoption of this explanatory approach would enable research workers to perform more efficient trials, although with some lack of generality of application. This change in clinical trial design is long overdue.

Pre-clinical examination selection.

On the basis of a literature survey and analysis of additional data sets[2-4], it is possible to confirm most of the conclusions of Downer and Mitropoulos regarding preselection by age and sex. Age and, by implication, dental age are probably the most important factors in the selection of subjects. Lind *et al.*[5] showed that, when an identical caries prophylactic agent was tested in two different age groups – namely, 8- and 11-year-old subjects – a significant result was achieved one year earlier with the older age group.

Prior to the advent of standard active controls, it was possible to argue that the selection of girls would provide a more efficient experiment when dentifrices were tested, while boys would provide a more efficient test of a mouthrinse or professional applications of APF gel[2,6]. However, some recent trials indicate that there is no advantage in single-sex studies.[4,7]

Post-clinical examination selection.

Downer has been the leading advocate of post-clinical examination selection to reduce group sizes in caries prophylactic trials. In Copenhagen[6], he proposed that the selection of subjects with six specific key surfaces at risk would improve clinical trial efficiency. Independent statistical analysis of other data sets in the U.K.[8] and Boston[9] have failed to confirm the effectiveness of these pre-selection criteria, and in their current report the authors now acknowledge that pre-selection of specific key surfaces is data-set-dependent.

Prior to discussing the new selection criteria of Downer and Mitropoulos, we ought to remind ourselves of the formula that governs sample size. Schwartz *et al.*[1] have shown that the minimum number of subjects needed in each group is:

$$n = (\epsilon_\alpha + \epsilon_\beta)^2 \cdot \frac{2\sigma^2}{\Delta^2}$$

where:

(a) ϵ_α and ϵ_β corresponded to the error rates α and β, respectively;
(b) σ^2 is the variance of the variable under study (it is assumed that the variance is the same for both groups); and
(c) Δ (delta) is the difference between the true group means.

The authors have already established that the delta component is being eroded by the use of standard active controls and the decline in prevalence. However, recent data from the southeast of England[10] have shown that,

with the decline in mean caries prevalence, there is, in fact, a relative rise in variance, with the coefficient of variation changing from the former 60% to now reaching 100%.

With respect to the alpha and beta levels, this sub-equation can be regarded as a weighting factor. Downer and Mitropoulos have ignored the beta level in this presentation and concentrated only on the alpha component. Kingman[11], in an elegant paper, re-stated the importance of beta levels, and it should be acknowledged that an increase from a 50% chance of detecting a true difference to a 95% chance would increase the number required *per* group by greater than a factor of three.

With respect to the alpha level, one assumes that the authors have based their calculations on the conservative two-tailed mode. However, the textbook by Schwartz *et al.* (1980) – who originally proposed the explanatory trial – is unusual inasmuch as it devotes equal space to both one-tailed and two-tailed experiments. Although the one-tailed mode is usually frowned upon by medical statisticians[12], it may be worth considering in a human anti-caries trial when there is ample *a priori* evidence from animal and laboratory studies.

Downer and Mitropoulos have introduced us to the concept of minimum cost in terms of reduction in group sizes. However, there is a more fundamental cost reduction that they have overlooked – namely, the reduction in the duration of the trial. The traditional three-year study may be unnecessarily lengthy to demonstrate a difference.

Replicated analysis of three other clinical trials[2-4] based on DMFS (e) >3 confirmed the conclusion by Downer and Mitropoulos that worthwhile reductions in group size can be achieved by pre-selection on these criteria, since group size could be at least halved, compared with traditional clinical trial design[13]. However, although certain trials[2,3] showed that a sample size of 50 per group was sufficient to demonstrate a difference, there was a lack of homogeneity of variance, and the resulting transformations did tend to increase this minimum figure.

In three clinical trials[2-4], significant differences between groups were achieved by radiographic findings alone by the end of the second year of the study. These findings were confirmed by the combined clinical and radiographic data on the subsequent examinations. These findings are indirectly substantiated by the classic British toothpaste studies[14-19], which showed higher test statistics between groups with respect to radiographic findings than clinical examinations.

Considerable gains in efficiency were achieved when the data[2-4] were retrospectively analyzed using two-year results and by selecting subjects with a DMFS (e) >3. These gains in efficiency were improved further by restricting the analysis to the radiographic increments on the posterior approximal surfaces.

These findings confirm the potential value of excluding subjects who are likely to experience small caries increments during the course of a trial.

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