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End to Crossover Designs for Studies on the Effect of Sugar Substitutes?

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Mäkinen [2009] described many points why the inclusion of the strictly controlled crossover practice in clinical trials should be separately and carefully contemplated in each instance. He presented some important aspects why the randomized clinical trial with a repeated-measures design cannot be carefully followed. In addition, a randomized experiment would violate ethical standards, or it is impossible to conduct it as a blind experiment. If reviewers have an eye for the rules of good clinical practice only, it may mean the end of crossover studies for the development of new caries-preventive methods, and of testing the efficacy of old ones in new combinations, as Mäkinen discussed.

The message can be summarized: the effect of any new drug or treatment practice must first be tested in a controlled crossover trial in which each patient is randomly assigned to a sequence of standardized treatments, including at least two treatments (of which one 'treatment' may be a standard treatment or a placebo). When the randomized clinical trial is a repeated-measures design, the subjects are randomly assigned to a sequence of treatments. But many times also natural experiments, 'observational' crossover studies and even 'field experiments' are needed to find out the real truth, not only in science but also in practice.

There is always a gap between the effect obtained in clinical trials and everyday medical practice which Niederman and Leitch [2006] summarized in their article on translational research: what is the outcome if a 100% effective drug is used in only 10% of the subjects needing that medicine? The drug is always tested by good clinical practice principles; the outcome of the treatment with the medicine can be tested only in practice-based research networks.

After evaluation of a single treatment in a controlled crossover trial, transitional research is needed to see how it works in practice. Transitional research is so important that the American Association for the Advancement of Science launched a special journal for that, *Science Translational Medicine*, in August 2009. Basic science is going 'backward', to a kind of 'case reports', this time analyzing a huge number (from thousands to millions) of patients treated in normal clinical practices.

In caries research in many countries this is easy to perform. In Finland, electronic dental records are used in all municipal health centers and in most private offices, too. The digital era has existed in many dental offices for more than 15 years.

A digital dental chart is created in the oral examination, and the treatment is coded in the progress notes longitudinally for millions of subjects/patients. My research group has developed a data-mining system which, fully automatically, picks up the necessary data and creates tooth/surface-specific survival curves of dental health, or else survival times of dental restorations, or even mean D, M or F values, as reported recently [Korhonen et al., 2009]. In 'practice-based' science, different statistical software is needed for testing the significance of the observed differences.

Because electronic dental records are commonly used in Sweden, too, the promising findings of the double-blind crossover trial by Stecksén-Blicks et al. [2009] in the same issue of *Caries Research* gives right to analyze the effect of probiotic bacteria and fluoride (separately) in milk in the course of normal dental health practices in Sweden in a crossover, double-blind and repeated-measures design with thousands of children. It would combine science and practice.

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