Discovery!

Irwin D. Mandel, *Editor*

Chilton, Fertig, Fleiss, and the Task Force on Design and Analysis in Dental and Oral Research

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In 1996, the Task Force on Design and Analysis celebrated its 25th birthday. During the 25 years of its existence, the Task Force has served as a "think tank" of biostatisticians and clinical epidemiologists with extensive experience in dental data and with strong backgrounds in clinical trials. Its members have been drawn from universities, private research centers, and government, and they have made numerous contributions to dental research, with specific attention to the field of clinical trials. The Task Force has striven to encourage, promote, and foster the use of creative and innovative methodology in dental studies. As individuals, members have published extensively on statistical methods relevant to design and/or analysis issues in clinical research, collaborated with other dental investigators on hundreds of scientific publications, provided statistical consultation services to countless others, and advised American Dental Association councils on the development of guidelines for protocols for the clinical testing of dental products. But most importantly, collectively through the Task Force, they have fostered a continuous dialogue between clinical and basic science researchers and statisticians involved in dental research. The Task Force has organized four major national and international conferences on clinical trials over the past two decades. These conferences have promoted communication between investigators from diverse disciplines in an exchange essential to high-quality dental science.

Beginning and early years

The Task Force's origins can be traced back to the late 1960s, when a small group of biostatisticians met as one of four subcommittees of the organizing committee of the 1968 Conference on Testing of Cariostatic Agents for Dental Caries. This conference was co-sponsored by the American Dental Association (ADA) and the US Public Health Service (PHS). One conference goal was to develop a standardized methodology for conducting field trials to evaluate the efficacy of products designed to prevent dental caries. Although the effectiveness of water fluoridation and fluoride dentifrices had been clinically demonstrated, there were no standard criteria for assessing dental caries or for recruiting and entering subjects into such trials. Nor were there widely accepted monitoring methods or reporting procedures for the collection, processing, description, and analysis of clinical data obtained in dental epidemiological studies.

The 1968 Conference was successful, and its proceedings were published in 1972 (ADA, 1972). Clinical criteria presented at this conference for detecting dental caries in epidemiological studies were widely accepted and became the gold standard for clinical trials conducted in the US. These criteria were shown to be practical, reliable, and reproducible when used by competent examiners. The more general clinical standards for assessing clinical caries that were formally described in the Conference Proceedings are still the standard for US clinical trials today.

Neal W. Chilton, who participated in the 1968 conference as a member of the statistical committee, was a research-minded, Board-certified, practicing periodontist with senior academic affiliations at Columbia and Temple Universities. He was motivated by a strong conviction of the importance of statistical methodology in dental research. This conviction had been instilled and nurtured by John W. Fertig, his mentor and long-time colleague at Columbia University.

Knowing that there were other dental researchers struggling with similar issues in the gingivitis and periodontitis arenas, Dr. Chilton recognized the need for convening a similar conference in which efficient study designs and better analytical methods appropriate for periodontal studies might be identified. Measurement issues such as the assessment of validity and reliability of clinical indices; trial management concerns such as effective methods for recruiting and retaining volunteer subjects, and methods for blinding subjects and examiners; and analytical issues such as efficient methods for analyzing longitudinal data were confronted by all clinical investigators, whether they were involved in studies of dental caries, periodontal diseases, tooth sensitivity, or craniofacial pain. The statisticians were eager to find new applications of statistical methods, recognizing that peculiar issues

confronted in large-scale dental clinical trials would inevitably lead to new theoretical research opportunities.

In 1971, Dr. Chilton obtained funds from the New Jersey Department of Health to organize a steering committee and two task forces to plan for an International Conference on Clinical Trials of Agents Used in the Prevention/Treatment of Periodontal Diseases. One Task Force, jointly chaired by Drs. John C. Greene and John D. Suomi, concerned itself with the indices used in periodontal clinical trials. The other Task Force, led by Drs. Fertig and Chilton, dealt with questions on the design and analysis of periodontal clinical trials. The conference was held at the Sugar Loaf Conference Center of Temple University in Philadelphia on April 2-3 of 1973. Organizing the scientific program for the conference went along rather smoothly, but obtaining financial support was more difficult. Eventually, funding was obtained from the US Public Health Service. The conference addressed methodological issues related to studies involving plaque, gingivitis, and periodontitis, and led to the participants' deeper understanding of the biological characteristics and statistical properties of common clinical indices of periodontal conditions. The proceedings of this conference were published in the *Journal of Periodontal Research* (Chilton, 1974).

The US Public Health Service, private research foundations, and commercial sponsors of clinical research welcomed these efforts, recognizing that they would undoubtedly lead to better-quality research and more efficient use of limited resources in the study of dental diseases. Subsequent to the Sugar Loaf Conference, Dr. Chilton obtained financial support from industry for the Task Force on Design and Analysis to hold regular semi-annual meetings. During the 1970s and 1980s, the Task Force meetings were small, consisting of roughly 12 to 15 members, with a few representatives of corporate sponsors and occasionally guests from Federal agencies, the ADA, and other universities. During the late 1980s, attendance at the Task Force meetings expanded, and currently these meetings draw between 45 and 50 participants. A Task Force meeting normally consists of from six to eight informal presentations dealing with specific aspects of clinical studies. Each presentation, lasting roughly 45 minutes, is a dialogue between the speaker and members of the audience. Statistical or methodological issues are usually the focus, and numerous suggestions are proposed regarding "solutions" to the particular design or analytical concern under discussion. During these discussions, the strengths and weaknesses of various approaches are debated. Often one strategy emerges and is recommended for further study. The process itself challenges each member intellectually, and individual members benefit by better understanding alternative views held by others. Presentations are given by Task Force members who are involved in a particular research question or project. Special guests are also invited on a regular basis to speak on substantive areas of dental research that may pose interesting methodological questions.

Divergent views regarding specific aspects of study design in dental research often occur, especially among the statisticians, but also between the statisticians and clinical investigators. Such disagreements are by no means unique to dental research. These individual perspectives are usually legitimate, reflecting important differences in philosophy, disciplinary perspective, or clinical judgment. However, in the absence of good communication, strongly held positions can lead to impasse and detract from the collaborative spirit necessary for the production of high-quality research. On occasion, sensitive topics have surfaced at the Task Force meetings. However, individual members are usually able to disagree without polarizing the group. This is in part due to the collegial atmosphere that has evolved at these meetings through the years. The fact that this group has been sustained for a quarter-century is remarkable, and largely due to the efforts of Drs. Chilton and Fertig.

Versions of most presentations made at the Task Force meetings are subsequently published in dental or statistical journals. Many statistical methods have been introduced to dental investigators through these publications, and tangible benefits have been realized by clinical dental researchers. More efficient experimental designs and better analytical methods are continually being introduced and used in dental clinical trials. Better study designs and more sensitive statistical analyses have resulted in more cost-effective research.

Parallel to the activities of the Task Force, Drs. Fertig and Chilton received support from the National Institute of Dental Research, NIH, through a series of grants to Columbia University on Statistical Methods in Dental Research. Papers were published in which new research designs and methods of statistical analysis were introduced to the dental literature. Dr. Chilton also wrote two editions of the textbook, **Design and Analysis in Dental and Oral Research** (Chilton, 1967, 1982), under contracts with the National Institute of Dental Research. In 1974, Dr. Chilton moved his clinical research from Temple University to the University of Pennsylvania School of Dental Medicine, continuing his research on statistical issues with Professor Fertig at Columbia University.

A second major international conference on clinical trials was organized by the Task Force in conjunction with the ADA. This conference was held in Chicago in 1983. Professor Fertig and Dr. Chilton spent numerous hours preparing the group for this conference. Primary funding was obtained from the National Institute of Dental Research, and Conference Proceedings were published in the *Journal of Dental Research* (Chilton, 1984). The conference provided clinical investigators with statistically state-of-the-art study designs and analytical methodologies for use in clinical caries trials.

Professor Fertig served as Chairman of the Task Force from its inception in 1971 until 1983, when ill health forced him to resign. An excellent teacher, he was a constant inspiration to the group, always demanding clarity of purpose, adequate attention to efficient study design, and analytical plans consistent with the statistical design. He demonstrated by example how to be an effective communicator with colleagues, and had a strong commitment to mentoring students and colleagues throughout his career. The success of Professor Fertig's mentoring efforts are most evident in dental research, where Drs. Neal W. Chilton, James P. Carlos, André Varma, Joseph L. Fleiss, and Stanley B. Heifetz, five of his prominent students, made substantial scientific contributions.

Changing of the guard

In 1983, the Task Force was fortunate to recruit Dr. Joseph L. Fleiss, John Fertig's successor as Chairman of the Division of Biostatistics at the Columbia University School of Public Health, as Task Force Chairman. Dr. Chilton, as Executive Director, continued to plan the programs, arrange meeting sites, and secure unrestricted contributions from industry to support meeting expenses.

A distinguished biostatistician and an exceptionally lucid writer, Professor Fleiss had recently published the second edition of his popular and highly regarded textbook, **Statistical Methods for Rates and Proportions** (Fleiss, 1981). Professor Fleiss' statistical research (*e.g.*, in measures of observer agreement) had immediate relevance to dental studies, and his activities at Columbia included greater involvement in large-scale clinical trials and dental research than Professor Fertig's. As Principal Investigator of an NIDR grant for development of statistical methods for dental research, with Chilton as co-investigator, Fleiss brought increased intensity and personal involvement in the substantive issues of dental investigations to the role of Task Force Chair. An excellent teacher and lecturer, he presented original research papers at these meetings, as did some of his graduate students. His widely read 1986 textbook, **The Design and Analysis of Clinical Experiments** (Fleiss, 1986), is a popular reference book among dental and medical researchers, illustrating design and analytical issues with clinical data from dental and medical studies. His cheerful but aggressive questioning of speakers and members stimulated lively discussions and stretched the intellectual horizons of all participants.

Under the direction of Dr. Fleiss, the main business of the Task Force continued to be the elaboration of methodology useful for investigators in dental and oral research. By the early 1980s, the Task Force had developed a renewed interest in periodontal clinical trials. New products and clinical approaches were being developed for the treatment of chronic adult periodontitis, but their effectiveness remained to be established. Consensus on how to measure periodontal diseases was lacking among the most active periodontal researchers. Little agreement existed on answers to basic design questions, such as what would constitute clinical improvement or be required to demonstrate the efficacy of a prophylactic or therapeutic product. There were few avenues for effective communication between the statisticians and the periodontal researchers involved in clinical testing. In response, the Task Force decided to organize a third major international conference on clinical trials, to stimulate broader exchange between methodologists and clinical investigators so that basic questions regarding aspects of study design could be confronted and resolved. Clarifications of some issues were needed before efficient study designs for such trials could be determined and rationally supported. The NIDR provided funds for planning the conference and fully endorsed its goals. This Conference on Clinical Trials in Periodontitis, hosted by the ADA in Chicago during May of 1985, was organized by the Task Force and totally funded by corporate sponsors. The proceedings appeared in the *Journal of Clinical Periodontology* (Chilton, 1986). Many of the basic designs for gingivitis and periodontitis clinical trials were introduced at this conference. Specific characteristics of the clinical measurements of periodontal disease were presented and discussed.

During the 1980s, new methods for demonstrating the equivalence of drugs were published. Regulatory agencies were considering approaches for demonstrating clinical equivalence of dental therapies. Proposed approaches borrowed heavily from the methodology used in comparative bioavailability drug studies. These methods were largely oriented to comparisons of bioavailability between proprietary pharmaceuticals and candidate generic competitors. The juxtaposition of superiority and equivalence concerns was causing subtle, but real, methodological difficulties as well as the usual ambiguities of interpretation associated with the meaning of "equivalence". These difficulties produced acute problems in the design of trials for the treatment or prevention of chronic adult periodontitis.

In response to this situation, the Task Force organized a fourth major international conference, held in Chicago during May of 1991, focusing on methodology for demonstrating superiority or equivalence of products for gingivitis and periodontitis. Co-sponsored by the Task Force and the ADA, this meeting was supported by commercial contributors. Background papers were presented dealing with conceptual and theoretical statistical issues regarding equivalence and superiority testing in general. Conference proceedings were published in the *Journal of Periodontal Research* (Chilton, 1992). One consequence of this meeting was the introduction of the "at least as good as" criterion when two drugs or treatments are compared.

In the 1960s, the ADA's Council on Dental Therapeutics began a policy of product endorsement. Initially, the ADA Seal of Approval was awarded to fluoride dentifrices shown in clinical trials to be effective in preventing dental caries. The program gained widespread acceptance over time, spreading to other classes of products, as clinical practitioners used the Seal to identify specific products to prescribe or recommend to patients. Dental product manufacturers realized the commercial importance of obtaining the ADA Seal of Approval for their products. The ADA policy of product endorsement provided an added incentive to manufacturers to continue developing more effective products for preventing dental diseases. Notable improvements in the oral health of the US population have resulted from the use of these products.

At the request of the ADA, the Task Force prepared recommendations for clinical trials to qualify gingivitis and chronic periodontitis for the ADA Seal. In November, 1991, the Task Force held a Workshop involving representatives from academia, independent research organizations, and industry, to develop a framework for its recommendations. Many ideas from the 1991 Conference provided a foundation for these deliberations. Further work on this issue spread over three years, with several drafts and solicitation of widespread comments from the periodontal research community. Attempts to achieve a balance between

the sometimes conflicting demands of methodological rigor and clinical reality produced consensus recommendations in most important areas, but left unresolved some key issues relating to chronic periodontitis. In 1994, separate publications recommending updates to the existing ADA guidelines for gingivitis trials, and proposing new guidelines for trials involving non-surgical therapeutic interventions for adult periodontitis, appeared in the *Journal of Periodontal Research* (Imrey *et al.*, 1994a,b).

The newly formed ADA Council on Scientific Affairs continues the product endorsement program. However, as changes in disease patterns and other characteristics of the US population occur, different strategies are needed to ensure that the protocols for clinical testing remain valid, practical, and affordable to public and private sponsors. Thus, the continued development of evaluation methodology is essential.

Financial support for the Task Force was highly variable during its first decade. The international conferences on clinical trials, especially the publication of their proceedings, were costly enterprises. Private and public sponsors were continually asked for financial support. Dr. Chilton practiced "doing more with less" and "leveraging resources" long before these phrases became clichés. The US Public Health Service continued to support the development of statistical methodology through individual grants, but widespread interest in clinical trials methodology developed within dentistry only when the National Caries Program (NCP) began conducting and funding clinical caries trials. Caries prevention trials were an integral portion of their research portfolio, as NIDR attempted to demonstrate the effectiveness of caries-preventive procedures such as fluoride mouthrinsing, fluoride tablets, fluoride dentifrices, and dental sealants.

Major funding for the Task Force has always been from commercial sponsors. These funds cover the costs of conducting the semi-annual meetings. Over the years, commercial sponsors have become increasingly aware of the tangible benefits that ultimately result from research fostered by Task Force activities. In the late 1980s, the level of corporate sponsorship increased substantially. In 1990, the Task Force re-organized itself formally as a non-profit research corporation with corporate officers and a Board of Directors. Dr. Chilton serves as Executive Director. Today, the Task Force benefits from a modest reserve account. This fund ensures coverage of the routine activities associated with meetings.

Broadening clinical research and uncharted waters

The Task Force is currently in a state of transition, both administratively and scientifically. Regrettably, Professor Fleiss recently resigned as chairman for health reasons. Known to many throughout dentistry as "Chilton's group", the Task Force dedicated its 25th anniversary meeting in November, 1996, to Chilton and Fleiss in recognition of their extraordinary contributions to dental statistics. Both have enjoyed remarkable careers as researchers, teachers, and writers whose personal qualities have endeared them to many. Professor Fleiss honored and enriched the tradition established by his mentor, Professor Fertig, as a role model of the statistician-scientist. The search for a new Chairperson is under way. Individual members of the Board of Directors are chairing meetings in the interim.

Scientifically, the Task Force is expanding its area of focus. A recent meeting included presentations on aspects of oral cancer and methods in genetic linkage analysis. Statistical methods for oral cancer clinical trials are well-established, but the field of oral cancer epidemiology continues to evolve. The search for biomarkers for disease and methods of early detection is rapidly expanding in oral cancer and in dental epidemiology more generally. These investigations could involve the identification of tumor suppressor genes and cell proliferation inhibitors for oral cancer, or the identification of multiple genetic loci associated with susceptibility to early-onset periodontitis, clefting of the lip or palate, and other oral diseases or malformations.

Statistical methods in genetic epidemiology are evolving rapidly, and improved modeling techniques appear frequently. New methodology will continue to proliferate so that the direct effects of alleles at specific genetic loci, effects of environmental contaminants and other stresses on the organism, and the interaction of genetic and environmental influences on the occurrence and severity of oral disease can be identified. Those who best anticipate the types of research tools needed for these problems may have extraordinary influence on dental research in the next two decades.

As multi-disciplinary approaches to dental research proliferate, improved communication among researchers becomes mandatory. The clinical testing of new products, when incorporating sophisticated technological assessment tools and biological risk markers for disease, will undoubtedly pose challenges for methodologists to develop new analytical methods relevant to such studies. The Task Force on Design and Analysis of Dental and Oral Research is in a unique position to embrace these trends and continue to foster high-quality dental research into the 21st century.

Acknowledgments

The current members of the Task Force are: Ronald Billings (Eastman Dental Center), Kenneth Burrell (ADA), Neal W. Chilton (Columbia University & University of Pennsylvania), Sebastian Ciancio (SUNY, Buffalo), Mark Cohen (Naval Dental Research Institute, Great Lakes, IL), Ralph D'Agostino (Boston University), Daniel Fine (UMDNJ), Stuart Fischman (SUNY, Buffalo), J. Max Goodson (Forsyth Dental Center), John Gunsolley (VA Commonwealth University), Peter B. Imrey (University of Illinois), Ralph Kent, Jr. (Forsyth Dental Center), William Killoy (UMKC), Albert Kingman (NIDR/NIH), Larry Laster and Max Listgarten (University of Pennsylvania), Irwin Mandel (Columbia University), Ronald Marks (University of Florida), Bruce L. Pihlstrom (University of Minnesota), Howard Proskin (Eastman Dental Center), André Varma (SUNY, Stony Brook), and Stuart Zimmerman (M.D. Anderson Cancer Center, University of Texas).

Important long-term scientific contributions have also been made by past members, including James P. Carlos*, John W.

*Deceased

Fertig*, Joseph L. Fleiss, Robert M. Grainger, Herschel Horowitz, Homer Jamison, David C. Korts, Kwo-Hua Lu*, Rick S. Senning*, and John W. Stamm, plus corporate-based researchers, including Louis Cancro, Diane Cummins, Robert W. Lehnhoff, Norton Ross*, and Anthony R. Volpe, as well as members of the FDA, including Robert T. O'Neill and Hoi M. Leung.

The Task Force would like to express formally its heartfelt appreciation for the financial support and scientific contributions bestowed by the numerous commercial sponsors over the last 25 years. Without this support, the Task Force would have been short-lived, and the many contributions made to the field of dental and oral research by the group might not have occurred.

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