Results of Expert Meetings

Data and safety monitoring committees: Philosophy and practice

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Introduction
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The science of clinical trials is evolving quickly. At the same time, the number and potency of therapeutic interventions is growing and the demands for evidence of therapeutic benefit are intensifying. In October 1998 these circumstances motivated us to convene a group of experts in the field of clinical trials; the principal objective of this group was to explore the purpose and function of the Data and Safety Monitoring Committee (DSMC), a key component in the organization of many trials.

Since that meeting, national interest in the ethics of clinical trials has increased enormously. After investigations by the Office for Human Research Protections at the National Institutes of Health (NIH), clinical research activities were suspended at several prominent institutions, including our own.1,2 Major news services have focused on the potential conflict between the financial interests of clinical investigators and the protection of the human subjects for whom investigators are responsible.3-5 After careful study, a special commission recommended a major commitment for a new infrastructure to monitor the activities of clinical trials and investigators in studies funded by the NIH. In addition, the Institute of Medicine published a recent report about medical errors6 that graphically points out the consequences of our ignorance about the best means for treating many diseases.

Because of the importance of DSMCs, we have devoted this series of articles to the 1998 meeting on these groups and to the pertinent issues that have arisen since that conference. Each article developed from the proceedings and was reviewed by those who chaired the relevant sessions and by other interested participants. The sponsors of this conference are listed in the title page footnotes to this article and participants are noted in an appendix at the end.
The first session, “Should All Trials Have a DSMC?” covered the rationale for and the charge of a DSMC in a clinical trial and emphasized the practical realities faced in different types of trials in different settings. The next session addressed the specifics of procedures: How should the proceedings of a DSMC be conducted? What information should it have at its fingertips? The third session reviewed the methods by which DSMCs make changes in ongoing trials. Knowing that the pace of clinical knowledge in the future will accelerate well beyond today’s level, it is more important than ever to understand how to cope with the dynamic nature of trials and the environment in which they are conducted. In the fourth session the statistical issues integral to DSMC deliberations were discussed. While decision making ultimately depends on clinical interpretations of the statistics, quantitative reasoning forms the basis for clinical trials and decisions about how they are performed. Our fifth session focused on the regulatory issues that affect DSMCs. The final session analyzed the essential terms of reference by which DSMCs operate. Surprisingly little information exists about the standards by which different components of clinical trials should fit together.

Because the deliberations of DSMCs have generally been mysterious to clinicians, we have chosen a pragmatic approach to the articles written for this series. Each poses a number of questions and then suggests answers that grew out of our conference discussions. In most cases, consensus was reached on basic issues, but finer points in the philosophy and practice of DSMCs inspired energetic dialogs and clear differences of opinion that remained unresolved. We hope that these articles stimulate greater discussion in the medical and clinical trial communities about the crucial work of DSMCs and generate many more publications about the practical issues that these committees face.

We also hope that these articles spur empiric research that illuminates which practices and procedures most benefit the important work of DSMCs.

The first article, “Should all trials have a DSMC?” follows this introduction. The remaining articles will appear in the next two issues and will conclude with a brief overview by DeMets and Yusuf.

References

Appendix
Participants in the October 1998 Duke Clinical Research Institute/American Heart Journal meeting on Data and Safety Monitoring Committees: Keaven Anderson, PhD, Centocor, Malvern, Pa; Juergen Armbruch, MD, Hoffman LaRoche Basel, Basel, Switzerland; Paul Armstrong, MD, University of Alberta; Paul Blake, MD, Proliance, Inc, Collegeville, Pa; Byron Brown, PhD, Stanford University; Rodney W. Butt, Boehringer Ingelheim (Canada), Burlington, Ontario; John A. Cairns, MD, University of British Columbia; Robert M. Califf, MD, Duke Clinical Research Institute; Winifred Castle, MD, PhD, SmithKline Beecham, Collegeville, Pa; Jain Chung, PhD, Hoffman LaRoche, Parsippany, NJ; Rory Collins, MB, BS, University of Oxford; Robert N. Daly, MS, PhD, DuPont Merck, Wilmington, Del; David DeMets, PhD, University of Wisconsin; Susan S. Ellenberg, PhD, US Food and Drug Administration; Jonas H. Ellenberg, PhD, Westat, Rockville, Md; Lloyd Fisher, PhD, University of Washington; Thomas R. Fleming, PhD, University of Washington; Michael J. Fox, MD, MBA, HealthCare Advisors, Weston, Mass; Stephen Freed, MD, US Food and Drug Administration; Curt D. Furburg, MD, PhD, Wake Forest University School of Medicine; Michael Gent, DSc, Hamilton Civic Hospitals Research Centre, Hamilton, Ontario, Canada; Christopher B. Granger, MD, FACC, Duke Clinical Research Institute; Sally Greenberg, PhD, Cor Therapeutics, San Francisco, Calif; Alfred Hallström, PhD, University of Washington; Victor Hasselbad, PhD, Duke Clinical Research Institute; Peter Held, PhD, Astra Hassle, Molndal, Sweden; Alan Hopkins, PhD; Genentech, South San Francisco, Calif; Ursula Hoppe, MD, BfArM, Berlin, Germany; Michael Klibaner, MD, PhD, Astra Merck, Wayne, Pa; Gene L. Knatterud, PhD, Maryland Medical Research Institute; Allen R. Kraska, PhD, Pfizer, Grotton, Conn; Henry H. Lee, PhD, Duke Clinical Research Institute; Robert Livingston, MD, Centocor, Malvern, Pa; Richard Malcolm, The Medicines Company, Cambridge, Mass; Clive Meanwell, MD, The Medicines Company, Cambridge, Mass; Christopher Mojck, MD, Alexion Pharmaceuticals, New Haven, Conn; Gunnar Olsson, MD, PhD, Astra Hassle, Molndal, Sweden; Milton Packer, MD, Columbia Presbyterian Medical Center, Marc A. Pfeffer, MD, PhD, Harvard Medical School; Stuart Pocock, PhD, London School of Hygiene and Tropical Medicine; Thomas J. Ryan, MD, Boston University School of Medicine; Corsee Sanders, PhD, Genentech, South San Francisco, Calif; Jay P. Siegel, MD, US Food and Drug Administration; John Simes, MD, National Health and Medical Research Council Clinical Trials Centre, University of Sydney; Allan Skene, PhD, Nottingham Clinical Trial Data Centre, Nottingham, UK; William Spickler, PhD, MD, Vascular Therapeutics, Mountainview, Calif; Robert J. Spiegel, MD, Schering Plough, Kenilworth, NJ; David C. Stump, MD, Genetech, South San Francisco, Calif; Jean-François Tambly, MD, Rhône-Poulenc Rorer, Collegeville, Pa; Jan G. P. Tijssen, PhD, University of Amsterdam; Diane Tipping, MS, Rhône-Poulenc Rorer, Collegeville, Pa; W. Douglas Weaver, MD, Henry Ford Health System, Detroit, Mich; Karl Wegscheider, PhD, BfArM Expert, Berlin, Germany; Janet Wittes, PhD, Statistics Collaborative, Washington, DC; Salim Yusuf, MD, McMaster University, Hamilton, Ontario, Canada.