The Harvard/Schering-Plough Partnership: A Broad and Beneficial Relationship

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The Harvard/Schering-Plough Partnership was initiated July 1, 1992, with the goal of establishing a long-term collaboration between the two institutions. It was based on the premise that joint collaborations between the pharmaceutical industry and academia have enormous potential for mutual benefit and important scientific advances. The activities and resources of the two establishments are complementary. Industry executives are aware of key scientific issues and problems that arise in the development and evaluation of new pharmaceutical products, and they have the resources to support research and training relevant to their mission. But industry scientists usually do not have adequate time or the mandate to develop the methodology needed to solve many of these critical problems. In contrast, academic institutions, especially public health and medical schools, have the breadth of technical and intellectual resources, as well as the social mandate, to play a key role in the solution of important, complex problems. In particular, the need to accurately assess the health effects of new and existing therapies represents a broad area of overlap between the pharmaceutical industry and the Department of Biostatistics at the Harvard School of Public Health. The Partnership facilitates the exploration of mutual research interests and the generation of new research projects which affect the practice of quantitative methods in the pharmaceutical industry.

The concept of a partnership between the Harvard Biostatistics Department and the Schering-Plough Research Institute evolved from relationships that were already in place before the Partnership was established. The Department was seeking to develop constructive, mutually beneficial alliances with industry, and several senior faculty members, including Professors Lagakos, Tsiatis, Walker and Weinstein had relationships with scientists at Schering-Plough. The Partnership was envisioned as an opportunity to move beyond the limitations inherent in short-term consulting arrangements and to promote long-term, productive interactions in the quantitative sciences. It was established to provide a framework that encouraged the Department's expertise in statistical methodology, clinical trials, and decision sciences to intersect with the challenges and demands of the pharmaceutical industry. The individuals who formalized this concept were Professors Laird, Lagakos, Weinstein, and Zelen from the Harvard School of Public Health and Dr. Dan Anbar, Senior Director of Statistics and Data Management at Schering-Plough Research Institute.

A defining characteristic of the Partnership is the extensive interactions between the two organizations that have evolved through the completion of supported activities. Solid working relationships between Harvard faculty and Schering-Plough scientists have developed, and scientific collaborations have augmented these relationships. The continuing goal of the Partnership is to build on the existing foundation and to nurture the long-term, interactive relationship between Schering-Plough and the Harvard School of Public Health.

The centerpiece of the Partnership is the annual Harvard/Schering-Plough Workshop, traditionally held in late May at the Harvard School of Public Health. In the view of many, the Workshop has emerged as a premier conference for clinical sciences in the pharmaceutical industry. It is a jointly organized and sponsored annual event that is designed to address important scientific topics which are controversial or for which there is no clear consensus. The enormous success of these workshops is reflected in the attendance, as well as the long list of prestigious speakers from academia, the FDA and international boards of health, government-sponsored and independent agencies that fund and run important clinical trials, and the pharmaceutical industry. The entire clinical trails community clearly benefits from the open exchange of ideas that this forum provides. In particular, the 'neutral' setting allows statisticians and other scientists from industry, the FDA, and academia to discuss issues and methodologies in an open and constructive manner, avoiding the somewhat adversarial tone that can arise when methods are discussed in the context of the results for a particular trial or drug. The two sponsoring organizations also benefit from working closely

together throughout the extensive planning process required to produce the workshop, from the interaction with highly regarded and influential participants, and from the substantial recognition associated with organizing this premier conference.

The Workshop has been sponsored annually since 1993. One popular topic has been on new approaches for the interim analysis and monitoring of clinical trials, including flexible design strategies (1993, 1996, 1998, and 2002). Over the past decade, Phase III trials are increasingly using formal methods for interim analysis and monitoring, and there have been some important new developments in this area that have allowed more flexibility in altering the design and evaluation of an evolving trial while preserving its statistical underpinnings. The 1994 workshop explored various methods for handling dropouts in a clinical trial, and introduced the participants to some of the new and robust methods that are being developed for missing data. Because of the increasing use of endpoints that represent multiple endpoints, such as a recurring event, the 1995 workshop summarized recent developments in semiparametric methodologies for multiple events, and the results were published as a special issue in the journal Statistics in Medicine. Two important changes in the field of biostatistics over the past decade have been the increased use of Bayesian methods and the development of methods for high dimensional data, such as those arising in genomic/microarray studies or in post-marketing studies. These topics were thus chosen as the focus of two of the workshops (1999 and 2001). The growing importance and utilization of quality-of-life methods in clinical trials was the focus of the 2000 workshop. For the past two years the workshop examined the influence of statistical research and thinking on the development and approval of pharmaceutical products for oncology (2003) and infectious diseases (2004). As noted above, the enormous success of these workshops can be attributed to the consistent ability to identify cutting-edge issues and attract speakers who are in the forefront of developing or applying novel methodologies for these issues.

The planning for each workshop begins one year in advance with the selection of the topic and the appointment of an organizing committee. The committee consists of three Harvard faculty and three Schering-Plough scientists. At least one planning session is held at Harvard or at Schering-Plough to establish a working outline and draw up a list of potential speakers. Other members from each organization are often used to consult on specific issues and to secure well-known speakers. Typically, weekly or biweekly teleconferences are held throughout October, November and January to develop the program, and announcements are sent out in February.

Each year several faculty and students from the Department of Biostatistics visit Schering-Plough Research Institute, and SPRI scientists visit the Harvard School of Public Health. Many of these visits focus on methodological approaches of common interest, and a seminar is usually presented to a broad Schering-Plough audience. Ample time is provided, however, for small group discussions geared to applying the visitor's expertise to specific drug development issues and challenges. Schering-Plough scientists are also invited to present seminars at HSPH, as well as to participate in workshops, conferences and short courses with faculty and students.

The visits by the Harvard faculty to Schering-Plough produce important and tangible benefits. The faculty benefit by presenting their own research to Schering-Plough scientists and by learning about new statistical problems encountered in practice. The visits also give Schering-Plough scientists the opportunity to discuss statistical issues arising in ongoing projects and to get feedback on proposed solutions. Many visits have focused on specific methodological approaches, such as surrogate endpoints, equivalence designs, multi-arm clinical trials, interim analyses of trials, adaptive designs, repeated measures data, population pharmacokinetics, missing data in survival studies, and alternatives to intent-to-treat methods. Other topics have included the analysis of microarray data, methods for analyzing failure time data based on imperfect diagnostics tests, bridging studies, statistical genetics, methods for analyzing interval censored data, analysis of clustered binary outcomes, model checking techniques based on cumulative residuals for general regression models, and testing for dependence between failure time and visit compliance with interval censored data. Some of these interactions led to the direct application of the statistical approaches discussed to specific Schering products under development, and the results of these

collaborations were submitted to regulatory authorities in support of product filings. Distinguished Harvard faculty who have visited Schering-Plough include Professors Wei, Lagakos, Tsitatis, Laird, Ware, and Zelen.

The Harvard faculty interacts in other ways with Schering-Plough scientists that provide important benefits to SPRI. For example, Drs. Anastasios Tsitatis and Stephen Lagakos worked with Schering-Plough scientists to develop a White Paper for a controversial oncology study. They found a serious flaw in the methodology of the study that helped to explain the controversial results. Another example was the presentation by Dr. Wei at an FDA Advisory Committee meeting on model testing methodologies in the evaluation of Schering-Plough's improved treatments for patients with Hepatitis C.

Another important aspect of the Partnership is the involvement of Harvard junior faculty and students. Funds from the Partnership have been used to provide junior faculty with support for their methodological research in areas relevant to problems in the pharmaceutical industry, and these faculty are expected to make one or more trips to Schering-Plough to present their work. The support of students also benefits both Schering-Plough and Harvard in numerous ways. The Department encourages students to take summer internships at Schering-Plough. This opportunity, as well as other activities sponsored by the Partnership, gives students greater exposure to the pharmaceutical industry in general, and to Schering-Plough in particular. This makes a career in the field more attractive, and students are better prepared for future collaborations. The funding also enables the Department to attract and retain high quality students. Federal support for training is steadily eroding and is not available at all for foreign students, making unrestricted funding from Schering-Plough especially valuable.

Schering-Plough scientists also receive invitations to Department-sponsored short courses, conferences, and workshops. In addition to the regular colloquia, the Department currently has twelve ongoing seminar series: Bayesian Methodology, Environmental Research, Genetics Epidemiology, HIV, Longitudinal Data, Nutrition on Obesity Research, Occupational Health Research and Environmental Biostatistics, Psychiatric Epidemiology, Psychiatric Biostatistics, Quantitative Issues in Cancer Research, Risk and Decision Analysis Research, and Statistical Methods in Epidemiology. This provides Schering-Plough statisticians and other scientists with access to a wide range of information and methodology that has potential applications in the discovery, development, and post-marketing surveillance of pharmaceutical products.

Funding for the Partnership is provided by a grant from Schering-Plough Research Institute which spans a five year period, with payments made each year to the Department of Biostatistics at the Harvard School of Public Health. The Partnership was initiated in 1992 when the first grant was awarded, and the agreement between the organizations, as well as the grant, was renewed in 1997 and 2002. The current grant runs through 2007.

The explicit plan is to carry on the major activities described above and to continue to build on the excellent working relationships that have been developed through this highly successful partnership. While all Harvard Biostatistics faculty are expected to participate in some aspect of the Partnership, a Coordinating Committee is appointed each year to plan and oversee Harvard's activity, with Stephen Lagakos and L.J. Wei acting as Co-Directors. Samuel Heft serves in this role for Schering-Plough, and he selects SPRI statisticians to participate in the planning and coordinating efforts.

At the beginning of each academic year, a joint planning session is held to select the workshop topic and its organizing committee, and to establish a schedule of visits by Harvard faculty to SPRI and by Schering-Plough scientists to HSPH. These structured activities provide a framework that allows Schering-Plough and Harvard to benefit from each other's research and expertise in the quantitative sciences. At the end of each academic year, the Biostatistics Department sends Schering-Plough a report on past, current, and planned activities sponsored under the Partnership. In addition, a review of general departmental activities, including a list of seminar series, faculty publications and technical reports, and student theses, is provided.