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Uneasy Alliance - Clinical Investigators and the Pharmaceutical Industry

[Health Policy Report]

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Clinical practice is changing rapidly. New cardiovascular drugs, antiinflammatory drugs, cancer chemotherapy, and other pharmacologic weapons are being added to physicians' therapeutic armamentarium virtually daily. Most clinical studies that bring new drugs from bench to bedside are financed by pharmaceutical companies. Many of these drug trials are rigorously designed, employing the skills of outstanding clinical researchers at leading academic institutions.

But academic medical centers are no longer the sole citadels of clinical research. The past 10 years have seen the spectacular growth of a new research model. Commercially oriented networks of contract-research organizations (CROs) and site-management organizations (SMOs) have altered the drug-trial landscape, forcing academic medical centers to rethink their participation in industry-funded drug research.

The infusion of industry dollars into an industry-investigator partnership has clearly improved clinical practice. Yet the medical literature contains many articles expressing concern about industrial funding of clinical research. Stelfox et al. found that authors whose work supported the safety of calcium-channel antagonists had a higher frequency of financial relationships with the drugs' manufacturers than authors whose work did not support the safety of these medications. [1] Davidson reported that results favoring a new therapy over a traditional one were more likely if the study was funded by the new therapy's manufacturer. [2] Cho and Bero demonstrated that articles from symposiums sponsored by a single drug company were more likely than articles without

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company support to have outcomes favorable to the sponsor's drugs. [3] Friedberg et al. reported that 5 percent of industry-sponsored pharmacoeconomic studies of cancer drugs reached unfavorable conclusions about the company's products, as compared with 38 percent of studies with nonprofit funding that reached similar conclusions. [4]

How much influence does industry have over the work and products of the research community? Can practicing physicians trust the information they receive about the medications they are prescribing? Does the shift from the academic to the commercial research sector give industry too much control over clinical drug trials?

In this report, I discuss some of the problems raised by pharmaceutical-industry funding of drug trials, problems that may deepen as trials are increasingly conducted by commercial organizations. I interviewed 39 participants in the process: 6 pharmaceutical executives, 12 clinical investigators, 9 people from university research offices, 2 physicians with CROs, 8 people who have studied the process of clinical drug trials, and 2 professional medical writers. Each interview consisted of standard questions plus an opportunity for the interviewees to discuss the industry-investigator relationship in a general way. Several interviewees preferred not to allow the use of their names in the article.

The Clinical-Drug-Trial System

The Food and Drug Administration (FDA) requires manufacturers to show that their products pass tests of efficacy and safety. [5,6] For such drugs as antibiotics for acute infections, large populations and long time lines are seldom needed to establish efficacy and safety. With the new emphasis on prevention and treatment of chronic diseases, however, clinical drug research has changed. Many people must take antihypertensive drugs and lipid-lowering drugs for many years in order to prevent relatively few undesired clinical end points. [7] To establish the efficacy and safety of preventive products and products designed to treat chronic disease, clinical trials must be large, lengthy, and conducted at multiple centers, because a single site cannot recruit enough patients to ensure statistical validity.

The average cost of developing one new drug is estimated to be \$300 million to \$600 million. [8] Of the \$6 billion in industry-generated money for clinical trials worldwide yearly, about \$3.3 billion goes to investigators in the United States. [9] Seventy percent of the money for clinical drug trials in the United States comes from industry rather than from the National Institutes of Health (NIH).

The Shift to Commercial Drug Networks

Until recently, the pharmaceutical industry needed academic physicians to perform drug trials for three reasons: companies did not have the in-house expertise to design trials themselves, academic medical centers provided patients as subjects for trials, and companies needed the prestige of academic publications to market their products. Lately, industry's dependence on academia has weakened: industry employs top-level research physicians to design and interpret drug trials, and community physicians have become a reliable source of patients.

Moreover, pharmaceutical firms are frustrated with academic medical centers. Most medical schools and teaching hospitals require that industry-investigator agreements be approved by an office of sponsored research. Slow review of industry proposals by academic research offices and institutional review boards (which must review all trials to protect patients' safety [10]) delays the starting dates of trials. Since academic physicians have multiple responsibilities in teaching,

research, and patient care, trials may proceed more slowly than the pharmaceutical firms desire. For each day's delay in gaining FDA approval of a drug, the manufacturer loses, on average, \$1.3 million. Speed is paramount for pharmaceutical firms.

To expedite trials, industry is turning from academic medical centers to a growing for-profit marketplace whose key players are CROs and SMOs. [11-13] In 1991, 80 percent of industry money for clinical trials went to academic medical centers; by 1998, the figure had dropped precipitously to 40 percent. [14] Evidence suggests that the commercial sector completes trials more rapidly and more cheaply than academic medical centers. [11]

Because multicenter trials may involve hundreds of sites and investigators, few pharmaceutical manufacturers choose to manage the trials themselves. CROs, which employ physician-scientists, pharmacists, biostatisticians, and managers, offer manufacturers a menu of services. Large drug companies often create their own study designs and contract with CROs to develop a network of sites, implement the trial protocol at those sites, and send report forms to the sponsoring company, which performs the data analysis. Smaller pharmaceutical firms may hire a CRO to manage the entire trial, including study design, data analysis, and preparation of FDA applications and journal articles. Several hundred CROs compete for the drug-trial business; the largest are Quintiles Transnational and Covance.

CROs may use both academic medical centers and community physicians to recruit patients for a trial. In the community arm of drug trials, yet another intermediary has entered the picture, the SMO. CROs may subcontract with for-profit SMOs to organize networks of community physicians, ensure rapid enrollment of patients, and deliver case-report forms to the CRO. Some trials have four layers (manufacturer, CRO, SMO, and physician-investigator), a situation reminiscent of the multitiered managed-care model (employer, health maintenance organization, independent practice association, and physician). Three of the largest SMOs are Clinical Studies Limited, Hill Top Research, and Affiliated Research Centers. SMOs provide community-physician investigators with administrative support and help market investigators' services to pharmaceutical companies. [15] They have been criticized for producing data of poor quality, inadequately training investigators, and costing more than a system of independent sites unassociated with an SMO. [13,15]

Competition for drug-trial money has stiffened as hundreds of CROs, SMOs, academic medical centers, and independent nonacademic sites scramble for a larger piece of the pie. According to Gregg Fromell of Covance, a leading CRO, "academic medical centers have a bad reputation in the industry because many overpromise and underdeliver." In contrast, critics, including Dr. Sidney Wolfe of Public Citizen, view CROs and the commercial drug-trial network as handmaidens of pharmaceutical companies, concerned with the approval and marketing of drugs rather than with true science. Whereas the academic and commercial drug-trial sectors can be seen as distinct networks with conflicting cultures, they also interlock, since CROs often act as intermediaries between drug companies and academic investigators.

Several academic medical centers are fighting to regain lost market share, transforming themselves into research networks to compete with the commercial drug-trial sector. [14,16] Columbia University, Cornell University, and New York Presbyterian Hospital have created a Clinical Trials Network as a joint venture. With funding from both industry and NIH sources, the network brings together academic researchers and community-based physicians in cardiology, hepatology, neurology, and oncology. The network has instituted required training for all participants and has centralized contracting, budgeting, and reimbursement systems. The network plans to be financially self-sufficient in a few years. Director Michael Leahey says, "Our goal is to take clinical research back from for-profit companies and place it where it rightfully belongs - in networks that are

partnerships between academic medicine and community practice. We are trying to formulate a real alternative to the for-profit drug-trial entrepreneurs."

In 1997 the University of Pittsburgh Medical Center Health System chartered the Pittsburgh Clinical Research Network (PCRN), a single point of contact between industry and clinical researchers in academic and community sites. PCRN provides the administrative procedures associated with clinical trials in such areas as contracting, institutional-review-board approval, and project management. Academic research expertise and a large hospital and community-practice network give PCRN resources unavailable to most commercial SMOs. PCRN's medical director, David Watkins, feels that "academic medical centers are sleeping giants that are beginning to awaken and respond to industry's needs."

Duke University and the University of Rochester are also leaders in developing academic clinical-research networks. Some academic medical centers will probably succeed in revamping their drug-trial business; others will fail.

Industry-Investigator Relationships

Trial Design

A company seeking FDA approval for a product often designs a clinical trial in its research division and circulates the proposed design to recognized investigators in that field. If the company has no in-house expertise, outside investigators are asked to design the trial. In some cases, company and academic investigators form a steering committee to discuss a trial protocol. In an interview, Dr. Thierry LeJemtel, of the Albert Einstein College of Medicine Division of Cardiology, said that 20 years ago outside investigators designed the studies, but that now companies write the protocols and bring in outside investigators pro forma, with little intention of changing the study design. In-house control is more likely in the commercial sector than in the academic sector, because of the limited expertise of many community-physician investigators.

Sometimes an investigator will propose a drug trial to the drug's manufacturer. Two investigators interviewed, including Steven Cummings, professor of medicine and epidemiology at the University of California at San Francisco, found that companies' marketing departments, which often rule on studies to be conducted after a drug has received FDA approval, declined to fund clinically important studies at least partly because the results might reduce sales of the drug.

Companies may design studies likely to favor their products. Bero and Rennie, in an article worth study by all physicians, catalogue the methods companies can use to produce desired results. [17]

If a drug is tested in a healthier population (younger, with fewer coexisting conditions and with milder disease) than the population that will actually receive the drug, a trial may find that the drug relieves symptoms and creates fewer adverse effects than will actually be the case. [17] Rochon et al. found that only 2.1 percent of subjects in trials of nonsteroidal antiinflammatory drugs were 65 years of age or older, even though these drugs are more commonly used and have a higher incidence of side effects in the elderly. [18]

If a new drug is compared with an insufficient dose of a competing product, the new drug will appear more efficacious. [17] Rochon et al. concluded that trials of nonsteroidal antiinflammatory drugs always found the sponsoring company's product superior or equal to the comparison product; in 48 percent of the trials, the dose of the sponsoring company's drug was higher than that of the comparison drug. [19] According to Johansen and Gotzsche, most trials comparing fluconazole with

amphotericin B used oral, not intravenous, amphotericin B, thereby favoring fluconazole, because oral amphotericin B is poorly absorbed. [20]

Clinical trials often use surrogate end points that may not correlate with more important clinical end points. Companies may study many surrogate end points and publish results only for those that favor their product. [7,17,21]

Data Analysis

A study's raw data are generally stored centrally at the company or CRO. Investigators may receive only portions of the data. Some principal investigators have the capacity to analyze all the data from a large trial, but companies prefer to retain control over this process.

A physician-executive at one company explained, "We are reluctant to provide the data tape because some investigators want to take the data beyond where the data should go." Several investigators, including Dr. LeJemtel, countered that industry control over data allows companies to "provide the spin on the data that favors them." In the commercial sector, where most investigators are more concerned with reimbursement than with authorship, industry can easily control clinical-trial data.

Publishing the Results

For academic investigators, publication in peer-reviewed journals is the coin of the realm. For pharmaceutical firms, in contrast, the essential product is the new-drug application to the FDA. In the absence of FDA approval, no journal article is worth a cent to a drug company. Yet publication in prestigious journals is important, to persuade physicians to prescribe the company's products.

Some multicenter trials have publication committees, which may be dominated by in-house or outside investigators, that write up the results for publication. In other cases, the company or CRO writes the reports for publication, circulating draft manuscripts to the investigators who will be listed as authors. Authorship may be determined by such criteria as who participated in designing the study, who enrolled the most patients, and who has a prominent name in the field.

Control over Publication

Many academic medical centers review contracts between industry and investigators, insisting on the investigator's right to publish the trial's results and allowing the company prepublication review, with a time limit of 60 to 90 days. Nikki Zapol, head of the sponsored-research office of Massachusetts General Hospital, estimates that 30 to 50 percent of contracts submitted by companies have unacceptable publication clauses that must be renegotiated.

In a survey of life-science faculty members, 27 percent of those with industry funding experienced delays of more than six months in the publication of their study results. [22] Chalmers argues that the results of substantial numbers of clinical trials are never published at all. [23]

In 1996, Canadian investigator Nancy Olivieri and colleagues found that deferiprone, used to treat thalassemia major, could worsen hepatic fibrosis. Apotex, the sponsoring company, threatened legal action if Olivieri published the findings. The contract between Apotex and Olivieri forbade disclosure of results for three years after the study without the company's consent. An article was eventually published. [24,25]

In 1987, the manufacturer of Synthroid (levothyroxine) contracted with University of California researcher Betty Dong to study whether Synthroid was more effective than competing thyroid preparations. In 1990, Dong found Synthroid to be no more effective than other preparations, including generic preparations. The sponsoring company refused to allow the findings to be published; the contract with Dong stipulated that no information could be released without the consent of the manufacturer. An article was finally published in 1997. [26]

Six investigators interviewed for this report cited cases of articles whose publication was stopped or whose content was altered by the funding company. In one case, according to Dr. Cummings, the company held up the prepublication review process for over half a year, then requested pages of detailed revisions that would have made the manuscript more favorable to the company's official marketing position. During the delay, the company secretly wrote a competing article on the same topic, which was favorable to the company's viewpoint.

In another case, the drug being investigated did not work. The investigator argued that scientific integrity required publishing the findings. The company never refused to publish, but it stalled until the investigator lost interest.

Another investigator, most of whose relations with industry have been without problems, related the case of two trials of the same drug, one more favorable to the company. Despite a protest from the investigator, the results of the less favorable trial were never published.

A fourth investigator found that a drug he was studying caused adverse reactions. He sent his manuscript to the sponsoring company for review. The company vowed never to fund his work again and published a competing article with scant mention of the adverse effects.

Dr. Curt Furberg, professor of public health sciences at Wake Forest University School of Medicine and principal investigator in a study whose results were unfavorable to the sponsoring company, refused to place his name on the published results of the study, because the sponsor was "attempting to wield undue influence on the nature of the final paper. This effort was so oppressive that we felt it inhibited academic freedom." [27]

A sixth investigator recounted two examples of suppressed manuscripts regarding negative studies whose results were sufficiently important to publish.

In scenarios such as these, the frequency of which is unknown, companies repeatedly delay publication, eventually exhausting investigators who are busy with other projects. One industry executive explained that such cases result from priority setting within the company; with limited personnel to produce publications, certain trials take precedence over others. However, as one investigator described it, "when results favor the company, everything is great. But when results are disappointing, there is commonly an effort to spin, downplay, or change findings." A CRO executive added that "industry obstruction to publishing is a big problem. They are nervous if bad data comes out and gets into the mass media." Investigators in the commercial sector may be less concerned than those in academia with contract clauses guaranteeing their right to publish, thereby giving industry greater control over publications.

Authorship

In the past, publications were written by a study's principal investigator. More recently, a practice that one might call the nonwriting author-nonauthor writer syndrome has developed. Many

interviews conducted for this report confirmed the wide prevalence of this syndrome in publications of drug-trial reports, editorials, and review articles. The syndrome has two features: a professional medical writer ("ghostwriter") employed by a drug company, CRO, or medical communications company, who is paid to write an article but is not named as an author; and a clinical investigator ("guest author"), who appears as an author but does not analyze the data or write the manuscript. [28-30] Ghostwriters typically receive a packet of materials from which they write the article; they may be instructed to insert a key paragraph favorable to the company's product.

The nonwriting author, who may be uninvolved in the research and have been requested to author the article to enhance its prestige, has final control over the manuscript. But many of these authors are busy and may not perform a thorough review. This guest-ghost syndrome [31,32] is a growing phenomenon, particularly in the commercial sector, where community-physician investigators have little interest in authorship.

In one study, 19 percent of the articles surveyed had named authors who did not contribute sufficiently to the articles to meet the criteria for authorship of the International Committee of Medical Journal Editors. Eleven percent had ghostwriters who contributed to the work but were not named as authors. [33,34] In justifying the nonwriting author-nonauthor writer syndrome, one industry executive explained that professional medical (ghost) writers are well trained, that investigators may be too busy to write, and that "nonwriting authors" are at fault if they do not carefully review ghostwritten manuscripts. An alternative view, articulated by Eric Campbell, of the Institute for Health Policy at Massachusetts General Hospital and Harvard Medical School, holds that "a manuscript represents the accumulation of the intellectual and physical processes conducted under the aegis of a study and should be produced by the people who have actually been involved in the design, conduct, and supervision of the research." Tim Franson, Vice President for Clinical Research and Regulatory Affairs at Eli Lilly, believes that "any parties, be they industry staff, investigators, or others who contribute to the content of articles should have their names listed on the article."

Conclusions \pm

Without industry funding, important advances in disease prevention and treatment would not have occurred. In the words of Lee Goldman, chairman of the Department of Medicine, University of California at San Francisco, "companies translate biologic advances into useable products for patients. They do it for a profit motive, but they do it, and it needs to be done." Investigators interviewed for this report confirmed that many collaborations with pharmaceutical companies were conducted on a high professional level.

But when results are disappointing for a company, conflicts may develop. Dr. Furberg, with years of experience in industry-funded drug trials, stated: "Companies can play hardball, and many investigators can't play hardball back. You send the paper to the company for comments, and that's the danger. Can you handle the changes the company wants? Will you give in a little, a little more, then capitulate? It's tricky for those who need money for more studies."

Although academic-industry drug trials have been tainted by the profit incentive, they do contain the potential for balance between the commercial interests of industry and the scientific goals of investigators. In contrast, trials conducted in the commercial sector are heavily tipped toward industry interests, since for-profit CROs and SMOs, contracting with industry in a competitive market, will fail if they offend their funding sources. The pharmaceutical industry must appreciate the risks inherent in its partnership with the commercial drug-trial sector: potential public and

physician skepticism about the results of clinical drug trials and a devaluation of the insights provided through close relationships with academic scientists.

A number of authors have recommended changes to resolve the problems of clinical drug trials. [11.35-37] An essential ingredient of any solution is increasing the independence of investigators to conduct and publish their research. Some investigators interviewed for this article felt that drug trials should be funded by industry but that design, implementation, data analysis, and publication should be controlled entirely by academic medical centers and investigators. The rise of the commercial sector - which reduces rather than enhances the independence of investigators - appears to be moving drug trials in the opposite direction.

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