

## Health Policy Report

### UNEASY ALLIANCE

#### Clinical Investigators and the Pharmaceutical Industry

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**C**LINICAL 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.<sup>1</sup> 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.<sup>2</sup> Cho and Bero demonstrated that articles from symposiums sponsored by a single drug company were more likely than articles without company support to have outcomes favorable to the sponsor's drugs.<sup>3</sup> 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.<sup>4</sup>

How much influence does industry have over the work and products of the research community? Can practicing physicians trust the information they re-

ceive 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.<sup>5,6</sup> 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.<sup>7</sup> 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.<sup>8</sup> Of the \$6 billion in industry-generated money for clinical trials worldwide yearly, about \$3.3 billion goes to investigators in the United States.<sup>9</sup> 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<sup>10</sup>) 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.<sup>11-13</sup> 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.<sup>14</sup> Evidence suggests that the commercial sector completes trials more rapidly and more cheaply than academic medical centers.<sup>11</sup>

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.<sup>15</sup> They have been criticized for producing data of poor quality, in-

adequately training investigators, and costing more than a system of independent sites unassociated with an SMO.<sup>13,15</sup>

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.<sup>14,16</sup> 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 Lehey 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.<sup>17</sup>

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.<sup>17</sup> 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.<sup>18</sup>

If a new drug is compared with an insufficient dose of a competing product, the new drug will appear more efficacious.<sup>17</sup> 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.<sup>19</sup> 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.<sup>20</sup>

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.<sup>7,17,21</sup>

### 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.<sup>22</sup> Chalmers argues that the results of substantial numbers of clinical trials are never published at all.<sup>23</sup>

In 1996, Canadian investigator Nancy Olivieri and colleagues found that deferiprone, used to treat thal-

