# Position/Policy Statement

**Adopted December 14, 1999**

**Policy Of The American Society of Gene Therapy on Financial Conflict of Interest in Clinical Research**

Potential conflicts of interest may arise in the course of all clinical research, including gene therapy. In principle, the ethical standards for clinical research in gene therapy should be the same as those demanded in all areas of medicine. Therapeutic agents used in clinical trials are often produced by for-profit companies, which can give rise to circumstances that present a financial conflict of interest to the investigators. An extreme case would be that a clinical reagent, be it a small molecule, a protein or a gene transfer vector, that is manufactured by a company wholly or partly owned by the Principal Investigator conducting the clinical trial. The guiding principle is clear: clinical investigators must be able to design and carry out clinical research studies in an objective and unbiased manner, free from conflicts caused by significant financial involvement with the commercial sponsors of the study.

Clinical trials are often sponsored by industry, where legitimate costs in conducting the research are covered. The Regulations on Objectivity in Research and the Investigator Financial Disclosure Policy adopted by the National Institutes of Health and the National Science Foundation on July 3, 1996 have established that: "Investigators are required to disclose to the institution a listing of Significant Financial Interests (and those of his/her spouse and dependent children) that would reasonably appear to be affected by the research proposed for funding by the PHS. The institution will review those disclosures and determine whether any of the reported financial interests could directly and significantly affect the design, conduct, or reporting of the research and if so, the institution must report the existence of such conflicting interests to the PHS Awarding Component and act to protect PHS-funded research from bias due to the conflict of interest". The same documents also established significant financial interests as equity ownership in companies exceeding 5%, and/or aggregate payments received from companies in excess of $10,000/year. Academic institutions have also established policies governing investigators' financial conflicts of interest that are consistent with these federal regulations.

The American Society of Gene Therapy is not a regulatory body and it should beware from becoming one. However, in order to pursue its mission to promote gene therapy research and development, the Ethics Committee recommends to the Board of Directors to adopt the following resolution:

"In Gene Therapy trials, as in all other clinical trials, the best interest of the patients must be always primary. International, national and institutional guidelines on standards of care must be rigorously followed, approved protocols strictly adhered to, serious adverse events promptly reported to all appropriate regulatory and review bodies. Relevant federally and institutionally established regulations and guidelines in financial conflicts must also be abided by. In addition, all investigators and team members directly responsible for patient selection, the informed consent process and/or clinical management in a trial must not have equity, stock options or comparable arrangements in companies sponsoring the trial. The American Society of Gene Therapy requests its members to abstain from or to discontinue any arrangement that is not consonant with this policy."

For Immediate Release

Contact: Elizabeth Dooley

Ph. 414/278-1341

April 13, 2000

# American Society of Gene Therapy establishes ethical policy to guide clinical trials

MILWAUKEE—The Board of Directors of the American Society of Gene Therapy (ASGT) has approved a policy for ethical standards involving gene therapy clinical studies. The policy, which was developed by the Ethics Committee of ASGT, will help ensure the safety of all patients participating in gene transfer studies and that researchers involved in clinical studies are free from financial conflicts of interest. Members of the Society have been notified of the new policy.

According to ASGT president, Savio L. C. Woo, Ph.D., "This policy is a significant step forward in addressing the safety and interests of the many patients who volunteer in such trials. Patients should know that investigators have their best interest in mind, are practicing in an objective manner and are not in any way influenced by financial incentives."

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clinical research, including gene therapy. In principle, the ethical standards for clinical research in gene therapy should be the same as those demanded in all areas of medicine. Therapeutic agents used in clinical trials are often produced by for-profit companies, which can give rise to circumstances that present a financial conflict of interest to the investigators. An extreme case would be that a clinical reagent, be it a small molecule, a protein or a gene transfer vector, that is manufactured by a company wholly or partly owned by the Principal Investigator conducting the clinical trial. The guiding principle is clear: clinical investigators must be able to design and carry out clinical research studies in an objective and unbiased manner, free from conflicts caused by significant financial involvement with the commercial sponsors of the study.

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Gene therapy is a revolutionary approach to fight and prevent disease. The ASGT is the largest medical professional organization representing researchers and scientists dedicated to discovering new gene therapies. ASGT was established in 1996, and has grown to more than 2,000 members. It is committed to promoting and fostering the exchange and dissemination of information and ideas related to gene therapy, to encouraging the general field of research involving gene therapy and to promoting professional and public education in all areas of gene therapy.

Editor's Note: The Policy of the American Society of Gene Therapy on Financial Conflict of Interest in Clinical Research can be viewed on the society's Web site at www.asgt.org/policy .

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# U.S. Representative

# Diana DeGette

**First Congressional District of Colorado**


**PRESS RELEASE**


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**FOR IMMEDIATE RELEASE**
May 23, 2000


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# DeGETTE ANNOUNCES SUPPORT FOR HHS HUMAN RESEARCH REFORMS

**WASHINGTON, D.C.** - U.S. Rep. Diana DeGette (D-CO) announced today support for the Department of Health and Human Services' (HHS) initiative to increase education, training and consent in human subject research programs across the country.

Secretary Donna Shalala announced this week that the Department of Health and Human Services is taking steps to improve human subject protections in medical research. The specific measures include:

- Increasing education and training of investigators, research staff and Institutional Review Board (IRB) members;
- Improving the informed consent process; and,
- Addressing conflict of interest concerns.

"This is an important first step for improving our nation's human subject protections in medical research and I welcome these measures, as they will undoubtedly address some critical problems with our nation's medical research system," according to Rep. Diana DeGette.

"A rash of recent reports have brought the nation's attention to unfortunate incidences of abuse by some researchers and institutions. These incidences have raised concerns that human subject research requires a more thorough informed consent process and IRB review.

"I believe the HHS proposals address some of the concerns raised by their Inspector General in the report entitled, *Protecting Human Research Subjects: Status of Recommendations*. However, as the Inspector General noted, legislation is needed to address some of its recommendations.

"As a result, I am preparing bipartisan legislation to overhaul and improve our nation's regulation of human research programs. While I applaud the Administration for taking this critical step, there are additional measures that require legislative action and I hope that Congress will address the issue this year."

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# STATEMENT ON RESEARCH SUBJECT PROTECTION

## SENATOR EDWARD M. KENNEDY

## MAY 23RD, 2000

Patients who volunteer to participate in gene therapy and other clinical trials deserve to be fully informed about the trials and fully protected from unnecessary risks. The Administration deserves credit for acting promptly to address these problems. We need to do all we can to ensure the safety of patients in research projects throughout clinical medicine.

Health Policy Report

# UNEASY ALLIANCE

## Clinical Investigators and the Pharmaceutical Industry

THOMAS BODENHEIMER, M.D.

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 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 thal-

assemia 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

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.

*I am indebted to Janice Kohn for research assistance.*

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*Roadside View, Southwestern Ontario*

RUPERT KAUL, M.D.

# NATIONAL CENTER FOR HUMAN GENOME RESEARCH, NIH

## FAX TRANSMITTAL SHEET

DATE: May 19, 2000

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# Congress of the United States
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HENRY A. WAXMAN
29th District, California

COMMITTEE ON GOVERNMENT REFORM
MEMBER
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DEMOCRATIC STEERING COMMITTEE

May 23, 2000

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STATEMENT OF CONGRESSMAN HENRY A. WAXMAN
ON SECRETARY SHALALA'S ANNOUNCEMENT ON ENHANCING
HUMAN RESEARCH SUBJECT PROTECTIONS

"Secretary Shalala is taking important steps to protect Americans who volunteer to help advance medical progress. I know she is also committed to making whatever changes are needed in the law for patient welfare.

We cannot conduct research without the public's confidence, and that confidence is not justified unless researchers, universities, companies and the government do everything they can to assure research is conducted responsibly and ethically. That is why the Administration's actions today are so important."

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TOTAL P.02

The Boston Herald

View Related Topics

**May** 4, 2000 Thursday ALL EDITIONS

**SECTION:** NEWS; Pg. 010

**LENGTH:** 525 words

**HEADLINE:** Human **gene therapy** trials placed under the microscope

**BYLINE:** By Michael Lasalandra

**BODY:**

**Gene therapy** researchers must be more careful in protecting patients, ethicists said yesterday in the aftermath of problems found by the Food and Drug Administration at St. Elizabeth's Medical Center in Brighton.

"**Gene therapy,** because it has been pushing hard to advance fast, has clearly gotten sloppy in many areas of subject protection," said Arthur Caplan of the University of Pennsylvania.

"They've got to get on top of things because, if they don't, the whole field is going to be set back a decade."

Such experiments must be subject to stronger oversight and should be limited to only a few institutions, said George Annas, an ethicist at Boston University.

"They're not doing what they say they're doing," he said. "You have a protocol, you follow it."

The FDA cited St. Elizabeth's researchers, led by Dr. Jeffrey Isner, with numerous violations of the protocol for their study. The work involves giving genetically engineered DNA to cardiac patients to grow new blood vessels.

The trial was halted in March, after the government started taking a closer look at **gene therapy** trials following the death of a subject in Pennsylvania.

A "warning letter" dated April 28 explained why the St. Elizabeth's program was shut down.

The violations noted by the FDA included the enrollment of a cancer patient and the failure to report the death of a patient to the hospital's internal review board.

Isner declined to comment yesterday, but is filing an official response to the FDA letter.

According to Annas, acceptance of the cancer patient into the study had to be a mistake.

"They're either sloppy or fraudulent," he said. "I like to think they're sloppy."

The FDA said the **gene therapy,** which involves injections of VEGF, or vascular endothelial growth factor, may have caused the cancer patient's tumor size to double.

The FDA said inclusions of ineligible subjects not only harm patients, but also skew study results.

Concerning the failure to report a patient's death to the hospital's review board, Annas said he doubts Isner was trying to hide the fact, since he had reported it elsewhere.

"But researchers have a hard time taking these IRBs (internal review boards) seriously," he said. "They've always been treated as a bureaucratic hurdle rather than an integral part of research."

Caplan said IRBs are underfunded. "They're all volunteers," he said. "All they get is their cookies and coffee. IRBs are underfunded, understaffed, overworked and overwhelmed. They do what they can, but they don't have the resources. It's a flea trying to steer a dinosaur."

Caplan said IRBs must be sufficiently funded and said all researchers should be required to take a course in **human-subject** experimentation and be certified.

But Caplan said the problem of protecting **human subjects** is not limited to **gene therapy** trials.

"These are problems that you find across the board in medical research," he said.

Annas decried the secrecy surrounding such experiments, which he said is fueled by the profit motive.

The St. Elizabeth's trials are co-sponsored by Vascular Genetics, of Durham, N.C., a company Isner co-founded.

**LOAD-DATE:** May 04, 2000

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**May** 4, 2000

**SECTION:** No. No. 87, Vol. Vol. 11; Pg. NA

**IAC-ACC-NO:** 61905759

**LENGTH:** 748 words

**HEADLINE:** FDA ISSUES WARNING LETTER IN VEGF **GENE THERAPY** TRIAL; Government Activity; Brief Article

**BYLINE:** Seachrist, Lisa



**BODY:**

WASHINGTON - With **gene therapy** protocols under intensified scrutiny ever since an 18-year-old volunteer died from participating in an experiment at the University of Pennsylvania, the FDA has issued a warning letter to Jeffrey Isner, chief of vascular medicine at St. Elizabeth's Medical Center in Boston, documenting deficiencies in **gene therapy** studies he is conducting with Vascular Genetics Inc.'s angiogenic vector, vascular endothelial growth factor plasmid (VEGF-2).

The warning letter comes in response to deficiencies noted following a March 22, inspection of the studies in cardiac and peripheral artery disease, and addresses Isner's role as a clinical investigator. The agency will address deficiencies of the sponsors - Vascular Genetics, St. Elizabeth's and Isner - in a separate letter. The four **gene therapy** studies were placed on clinical hold in February.

The letter highlights the failure to enroll only patients who met the protocol eligibility criteria, the failure to report adverse events, including a death, to the institutional review board, irregularities with an informed consent document, and the failure to maintain adequate case histories. The letter notes that the "deviations in these studies appear to be the result of a serious lack of knowledge of your responsibilities as principal investigator including supervision of personnel."

"We are working with all of our sites to ensure they understand their responsibilities," said John Cumming, president of privately held, Durham, N.C.-based Vascular Genetics - a study sponsor. "We've offered all of our resources to help him address any problems."

The warning letter details deficiencies found at St. Elizabeth's for which Isner, as principal investigator, is responsible. The agency highlights a patient who was enrolled in the study despite evidence of potential lung cancer. Because VEGF-2 spurs the growth of new blood vessels, the protocol for the study prohibits patients with any signs of cancer from enrolling, in order to prevent the **gene therapy** from fueling cancer growth.

The patient in question was diagnosed with lung cancer after treatment with the study vector. Cumming said he doesn't know what happened in the case of this particular patient and why investigators found the former smoker eligible for the study. But he called the event "troubling."

"We are, as the sponsors, very concerned that every patient meets the very strict eligibility criteria in the protocol," Cumming said. "That in no way minimizes what happened to this patient. We are working

very hard with all of our trial sites to ensure there are no more problems. When something like this happens you ask yourself, 'have we failed somewhere to educate our investigators?'"

In addition, the letter documents a patient who suffered cardiac arrest in the perioperative period following a direct injection of VEGF-2 into the heart. The patient ultimately suffered multi-system organ failure and died more than four months following the **gene therapy** procedure. The agency found the death hadn't been reported to the Institutional Review Board (IRB). While not commenting on the IRB matter, Cumming said the death had been reported to the FDA in a timely manner.

In addition, the FDA took issue with Isner conducting an anatomic and histopathologic examination of the heart of this patient when Isner isn't board certified in pathology.

The agency also found the case histories and medical records were incomplete for some of the subjects in a number of the four clinical trials Isner oversaw.

"I've talked to some people who said if this study had been conducted at another time we wouldn't be on clinical hold right now," Cumming said. "I don't know about that. But we are in a period of significant scrutiny - we aren't the only **gene therapy** company on hold - and we must be sure we are complying with FDA."

As with all FDA warning letters issued to clinical investigators, Isner has 15 business days to respond to the issues raised in the warning letter. If Isner fails to correct the deficiencies identified by the agency, he risks losing his right to investigate new drugs and the termination of the VEGF-2 **gene therapy** IND.

BioWorld Today was unable to contact Isner. Cumming said Vascular Genetics had completed enrollment for three of the four trials currently on hold, and is working to gather the information necessary to get the hold on the final study lifted. n

**LANGUAGE:** ENGLISH

**IAC-CREATE-DATE:** May 5, 2000

**LOAD-DATE:** May 06, 2000

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The Boston Globe

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**May** 9, 2000, Tuesday ,THIRD EDITION

**SECTION:** HEALTH/SCIENCE; Pg. E4

**LENGTH:** 923 words

**HEADLINE: GENE THERAPY** REDIRECTS FOCUS ON SAFETY OF ALL RESEARCH

**BYLINE:** By Richard Saltus, Globe Staff

**BODY:**

Allegations of misconduct in **gene therapy** experiments at St. Elizabeth's Medical Center in Boston and a death after gene treatment in Pennsylvania have intensified public unease about the new unproven technology, but scientists and science officials say the problems reflect a much broader concern about the safety of all research on human beings.

They say the public shouldn't conclude that **gene therapy** researchers are particularly lax or the technology is inherently dangerous. Instead, regulators are growing less tolerant of exposing people to hazardous research of all kinds, and the high profile field of **gene therapy** is just caught in the spotlight. "This is a problem of clinical medicine, not a problem of **gene therapy,**" said Dr. Harold Varmus, until recently the director of the National Institutes of Health.

He was referring to allegations that **gene therapy** researchers at the University of Pennsylvania had failed to take proper precautions in an experiment that caused the death of an 18-year-old volunteer last September.

But Varmus' statements could equally apply to the Food and Drug Administration's harsh warning letter to Dr. Jeffrey Isner, a heart researcher performing **gene therapy** research at St. Elizabeth's. The FDA accused Isner, who is also at Tufts University, of failing to report one death properly and endangering patients' lives in research designed to see if gene implants can grow new blood vessels in the heart.

A St. Elizabeth's spokeswoman said yesterday that Isner has already given his responses to the April 28 warning letter alleging that Isner and his subordinates had violated regulations on a number of grounds, including failing to monitor some volunteers' health closely enough, and admitting a patient into a trial who should have been excluded for health reasons.

**Gene therapy,** which attempts to reprogram patients' DNA to reverse genetic disorders and fight disease, has had little to boast about despite a great deal of hype and investment since the 1980s. Only last month, researchers claimed their first big success as **gene therapy** apparently restored normal immune systems to two French babies born with a rare, lethal immune disease sometimes called the bubble boy disease.

But **gene therapy** pioneer Dr. W. French Anderson of the University of Southern California said people such as Isner are making more progress than they get public credit for.

Anderson predicted that the federal investigation of Isner's work by the FDA and the Office of Protection from Research Risks will determine that there is "a lot of smoke and minuscule fire."

"There do appear to have been infractions with the Tufts program, but Isner is a highly respected individual," Anderson said, adding that Isner and colleagues "have extraordinarily exciting results" in improving blood flow in the heart.

Anderson contended that Isner's results in tests aimed at growing new heart vessels to bypass clogged ones are among the most promising so far in the decades-long history of **gene therapy** research.

The federal official in charge of protecting human test subjects, however, said it's too soon to absolve Isner. Gary Ellis, the director of the Office of Protection from Research Risks, said there is an "open investigation" underway into the St. Elizabeth's gene research.

In an effort to shore up protection of patients in **gene therapy** trials, the FDA and the NIH, of which Elllis is a part, announced in March they will require sponsors to submit monitoring plans. Under the plans, research sponsors would choose people to serve as monitors, making sure the well-being of volunteers is being protected and that the trial is being carried out according to the protocol.

Ellis said in an interview that "the concern over human gene transfer experiments gained greater currency because of the mounting concerns about human experimentation in general."

"We are collectively coming to grips with what it means to take the **human subjects** regulations seriously," Ellis said. For example, Ellis' office halted all clinical research at Duke University School of Medicine for several days after a probe found violations of **human subjects** protection.

His office in the last five years has found commonly occurring lapses in protection of **human subjects.** The two surprises were the breadth of the problems across so many research institutions, and how fundamental the shortcomings are, Ellis said.

Regulations to minimize risk to human volunteers are enforced by the FDA and the Office of Protection from Research Risks, but the day-to-day monitoring of such research is the task of each research facility's institutional review board.

George Annas, professor of health law at the Boston University School of Public Health, said that many researchers see **human subjects** regulations and review board requirements "like hurdles you jump through before you can do research."

"Most [researchers] haven't taken the regulations very seriously," Annas added, "because there really aren't any serious consequences to investigators."

Anderson, the **gene therapy** pioneer, noted that the spotlight on the field comes just as the first success has been recorded - gene implants in France that appear to have cured two young girls of severe immune deficiency.

"In the long run, I think all of this super-careful scrutiny is a good thing," Anderson said, "because it does look like **gene therapy** is starting to turn the corner. It will be done better" because of the glare of regulatory attention.

**LANGUAGE:** ENGLISH

**LOAD-DATE:** May 9, 2000

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**May** 19, 2000, Friday ,THIRD EDITION

**SECTION:** METRO/REGION; Pg. A1

**LENGTH:** 1028 words

**HEADLINE:** DOCTOR REBUTS FDA CITATIONS LAPSE TIED TO GENE PATIENT'S DEATH REPORT

**BYLINE:** By Richard Saltus, Globe Staff

***BODY:***

Boston **gene therapy** researcher Dr. Jeffrey Isner, slapped last month with federal allegations of failing to protect human research subjects, yesterday conceded lapses in reporting a patient's death but said most of the Food and Drug Administration's findings against him are wrong.

Isner's comments, his first since the FDA made its accusations, are in a 19-page response to the agency's warning letter of April 28 - a letter that said he violated regulations governing clinical trial procedures. In an interview yesterday, Isner agreed that the stress of chest surgery to perform the gene implants might have played a role in the deaths of two people in the program. But he maintained that the FDA found no evidence that the therapy actually caused the fatalities.

Isner, 52, a superstar cardiologist at St. Elizabeth's Medical Center and professor of medicine at Tufts University, said he and the hospital were eager to cooperate with regulators. Isner also said they wanted to resume the experimental trials. If successful, he said, the **gene therapy** "is likely to change the way medicine is practiced."

The clinical **gene therapy** trials test a method aimed at growing new blood vessels to bypass arterial blockages in the heart or the leg. The trials are sponsored by Vascular Genetics Inc. of Durham, N.C., a company Isner co-founded in 1997. The American Society of **Gene Therapy** has said Isner's financial stake in the company is a potential conflict of interest, but Isner and hospital officials say the link does not influence the research. The hospital also has a financial stake in the company.

Isner contended that two deaths out of the 85 treated in several **gene therapy** trials were a good record, given that the patients were chronically ill. It was a mistake, he acknowledged, not to report one of those deaths to a hospital watchdog committee. But Isner added that the deaths were properly reported to the FDA.

In the written response to the FDA, the hospital and Isner say 16 of the FDA's 21 findings were in error: Some were minor issues of documentation while others involved whether patients not medically eligible for the research were wrongly admitted to the trials.

Isner also said a chain of lapses led to a patient undergoing the **gene therapy** despite having a lung tumor that enlarged subsequent to the therapy. Patients with cancer are supposed to be excluded from the therapy trials, because the genes produce a protein that potentially could speed the growth of a tumor. Among the mistakes, the response said, was a "communications error" in which a report of a chest X-ray was never filed in the patient's chart. The letter added that in the course of screening patients for the trial, doctors diagnosed many other cancer cases and the one cancer victim admitted to the trial has survived.

Isner, who was interviewed with hospital president Michael F. Collins, said St. Elizabeth's **gene therapy** trials differ significantly from highly publicized trials at the University of Pennsylvania, in which a healthy 18-year-old patient died last fall.

"We're not dealing with healthy, young patients," Isner said. St. Elizabeth's trial volunteers were either about to lose their legs because of blocked arteries or suffered from terminal heart disease.

"This is as sick as you get," Isner said, adding that in every case he told the patients that the experiment was "a roll of the dice."

One patient died in October 1998, four months after she suffered an abnormal heart rhythm and two days after receiving the gene implants. It was this death that the FDA said researchers failed to report to the hospital's Institutional Review Board.

In February, the FDA directed St. Elizabeth's to halt all **gene therapy** trials: Six have already been completed, and two active ones remain on hold, said a hospital spokeswoman. FDA investigators spent five days in March scrutinizing research records at St. Elizabeth's.

Their conclusions were in the warning letter that accused Isner of "a serious lack of knowledge of your responsibilities as a principal investigator."

In responding to the FDA, Isner and hospital officials said they had already, or would in the future take a number of corrective actions.

Among them were plans to follow all research protocols and enforce the criteria for admission to a trial; report all serious adverse events, including deaths, as soon as they are discovered; communicate more effectively with a patient's other doctors to check on the patient's health; and to train staff in following protocol rules. Regarding the missed cancer diagnosis, hospital officials said a committee will focus on the health histories of all patients in whom "suspicious lesions" are revealed during screening.

In addition, Collins and Isner said that research volunteers will be informed about previous adverse events or deaths of patients receiving the treatment. They will also be advised that Isner and St. Elizabeth's have a financial interest in the research because they hold equity in Vascular Genetics.

Collins, the hospital president, said he takes "full responsibility" for the flaws highlighted by the FDA. "I'm not happy that things were found that could be improved upon, but we have taken a good faith effort to review all of our policies and practices."

The next move in the case is up to the FDA, which can impose penalties or simply re-open the trials if it is satisfied with the response and plan for corrections.

In the most recent gene transfer experiments, Isner and his team have been inserting the genes into the heart via a catheter, avoiding the more invasive chest surgery previously used. Isner said imaging tests on the patients who have received the genes show significant improvement in blood flow to the heart, and that they have been able to walk longer on treadmill tests.

"I think it's intriguing and encouraging," Isner said of the research. But he, along with others in the field, say the true value of the gene implants will not be known until the treatment is compared against an inactive placebo in studies where neither patient nor researchers know who received the genes.

**GRAPHIC:** PHOTO, 1. Dr. Jeffrey Isner (left) and St. Elizabeth's Hospital chief Michael Collins at a media conference yesterday. / GLOBE STAFF PHOTO/DAVID L. RYAN 2. Dr. Jeffrey Isner, in his office at St. Elizabeth's Hospital, says he is eager to cooperate with FDA regulators. / GLOBE STAFF PHOTO/DAVID L. RYAN

**LANGUAGE:** ENGLISH

**LOAD-DATE:** May 19, 2000

The New York Times



**March** 2, 2000, Thursday, Late Edition - Final

**SECTION:** Section A; Page 20; Column 1; National Desk

**LENGTH:** 646 words

**HEADLINE:** Panel Seeks Better Monitoring Of Experiments Using People

**BYLINE:** By PHILIP J. HILTS

**BODY:**

Citing failures of scientists to report problems, federal health officials and members of the National Bioethics Advisory Commission said yesterday that changes were needed in the monitoring of research on people.

The commission heard testimony as part of its review of the safety and ethics of human research.

It has been working for more than a year, holding hearings around the country, but in that time several problems in experiments involving people have emerged. Federal regulators have halted experiments at several major institutions, citing violations of ethics rules. Certain trials involving **gene therapy** were halted after a patient died.

After hearing testimony from witnesses representing the National Institutes of Health and the Food and Drug Administration, Dr. Harold T. Shapiro of Princeton University, chairman of the bioethics commission, said: "One problem we have heard again and again is that, once an experiment is approved, there is a failure to follow what's going on with the patients. I think there is a growing consensus that something must be done."

Dr. Lana R. Skirboll, director of the Office of Science Policy, acknowledged that there had been some serious problems with experiments in **gene therapy,** which is designed to treat inherited defects by giving patients infusions of working genes. She said that the institutes had begun to change procedures to deal with the problems and noted that the Department of Health and Human Services would soon announce further changes needed to protect participants in the experiments.

The central issue of yesterday's discussion was the disclosure, after the death of Jesse Gelsinger, a patient in a gene expeirment at the University of Pennsylvania, that scientists had often failed to inform federal agencies of "serious adverse effects" involving patients.

Adverse events can include anything that happens to a subject while an experiment is under way, even things seemingly unrelated to the research. (Sometimes a serious event may not appear to be related to an experiment, but is later found to be related. For example, if a patient falls down the stairs and is injured, that may be a accident, but if the patient was given a drug in an experiment that brought on dizziness, the experimental drug could be considered the cause of the fall.)

Until yesterday, the N.I.H. said there had been 691 "serious adverse events" in **gene therapy** experiments involving the use of adenovirus, a weakened cold virus used to carry genes into the body, but that scientists had reported only 39.

Dr. Skirboll said the number for last year was 970 in adenovirus experiments, and an additional 100 in other **gene therapy** experiments.

**Gene therapy** experiments are among the hottest in medicine, and the number is rising. Dr. Claudia

Mickelson of the Massachusetts Institute of Technology, who is chairman of the N.I.H.'s Recombinant DNA Advisory Committee, which helps make policy on what kind of gene experiments should be permitted, said that in 1988 there was one experiment, but last year there were 91. In that period, there have been more than 300 experiments, he said.

There are few reports of success, but there is hope for the experimental treatments in a variety of conditions, from cancer to hemophilia.

Dr. Skirboll said most of the reporting failures discussed yesterday involved potential problems, rather than harm to patients. But she said the reporting is important both to understand which types of experiments might be more hazardous, and in building trust that scientists are carefully watching for problems.

"This research, we think, is very exciting and may produce huge benefits to human health ultimately," she said. "But to get there we have to go through the door of clinical trials with human patients. And we can't go through there if we don't have the patients' trust."

http://www.nytimes.com

**LANGUAGE:** ENGLISH

**LOAD-DATE:** March 7, 2000

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The Boston Herald

View Related Topics

**May** 3, 2000 Wednesday ALL EDITIONS

**SECTION:** NEWS; Pg. 005

**LENGTH:** 428 words

**HEADLINE:** FDA: Docs violated protocol

**BYLINE:** By Michael Lasalandra

**BODY:**

Researchers at St. Elizabeth's Medical Center violated FDA rules for the conduct of **gene-therapy** experiments, according to a "warning letter" dated April 28 that explains for the first time why the program was put on hold in March.

One of the violations involves the acceptance of a cancer patient into the study that involves an attempt to grow new arteries to carry blood to the hearts of cardiac patients.

The FDA is concerned the **gene-therapy** treatment may have caused the patient's lung tumor to grow. "The outcome of the FDA inspection raised concerns about the quality of your clinical research," says the letter to Dr. Jeffrey Isner, the program's chief investigator, obtained by the Herald yesterday.

The harshly worded FDA letter says corrective action must be taken or Isner could be disqualified as a clinical investigator.

According to the FDA, Isner's study violated regulations designed to protect **human subjects.**

"Deviations in these studies appear to be the result of a serious lack of knowledge of your responsibilities as principal investigator . . ." says the letter, signed by Steven A. Masiello, director of the Office of Compliance and Biologic Quality.

The study involves giving genetically engineered DNA - known as VEGF or vascular endothelial growth factor - to cardiac patients to help them grow new blood vessels to the heart. About 82 patients have been enrolled in the studies dating back to 1998. Two of the patients have died.

Among violations cited:

The study accepted a patient who had cancer, even though the protocol bars subjects with any evidence of the disease.

Failure to notify the hospital's internal review board in a timely manner of the increase in the size of the patient's lung mass.

Failure to notify the review board of the death of a patient.

Isner performed the autopsy on one of the patients who died, although he is not board certified in pathology and has no hospital privileges for doing autopsies.

Some patients did not get proper physical exams or have blood samples taken as required.

Two subjects signed consent forms without a witness.

The warning letter describes several violations as "major," particularly those involving the admission of ineligible subjects into the study.

Isner could not be reached for comment. St. Elizabeth spokeswoman Sonia Hagopian said the hospital is taking the letter seriously.

"It raises some questions about some aspects of care and record-keeping and the medical center is in the process of putting together a thoughtful and thorough response."

**LOAD-DATE:** May 03, 2000

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The New York Times

View Related Topics

**May** 4, 2000, Thursday, Late Edition - Final
Correction Appended

**SECTION:** Section A; Page 20; Column 1; National Desk

**LENGTH:** 1015 words

**HEADLINE:** F.D.A. Says Researchers Failed to Report a Second Death Linked to **Gene Therapy**

**BYLINE:** By PHILIP J. HILTS

**DATELINE:** BOSTON, May 3

**BODY:**

Researchers at St. Elizabeth's Medical Center here failed to report the death of a patient in **gene therapy** experiments and might have contributed to the growth of cancer in another patient, whose condition was also reported improperly, investigators for the Food and Drug Administration have said.

Their accusations were made in April in a letter to the hospital and the chief researcher in the experiment, Dr. Jeffrey M. Isner, and were recently posted on the agency's Web site. The experiment has been stopped.

The news comes as scientists, hospitals and companies sponsoring **gene therapy** experiments have been working to assure the public of the safety of the experiments after the death of a patient in a gene experiment at the University of Pennsylvania last year.

Jack Cumming, president of the Vascular Genetics Inc. of Durham, N.C., the company sponsoring the experiment at St. Elizabeth's, acknowledged today that there had been some "problems" in the **gene therapy** experiment. Mr. Cumming said the company would do everything it could to satisfy the F.D.A. in correcting the problems. He said he was "very optimistic" that positive results would be presented to the agency this summer.

Mr. Cumming said he would not dispute the agency's findings and said that his company had hired two outside groups to audit and monitor all the experiments it had begun around the country, including the one at St. Elizabeth's. The groups were hired after the company learned that the federal agency was writing a warning letter, he said.

Sonia Hagopian, a spokeswoman for the St. Elizabeth's, said the hospital took the warning letter very seriously, and added: "We are focusing all our resources on producing a thorough and thoughtful response to the F.D.A."

The hospital's public relations office said Dr. Isner would not be available for comment at this time.

The problems in the experiment were reported on Tuesday in The Washington Post and The Boston Herald.

About 300 **gene therapy** experiments are under way around the country. Troubles with some of the experiments have become public, especially since the death of a patient, Jesse Gelsinger, 18, in the University of Pennsylvania experiment.

In the experiment at St. Elizabeth's, which was jointly sponsored by Tufts University, a gene that makes a substance called V.E.G.F. (for vascular endothelial growth factor) was injected directly into the hearts

of patients with blocked heart vessels. Researchers hoped the gene would start making the growth factor, which is the body's natural substance to make blood vessels grow.

Inspectors for the federal agency said they found several violations of the rules of the experiment in a routine check in March. One patient in the experiment died two months after receiving the experimental therapy, but the researchers did not report the death to the agency. The agency is investigating to determine if the treatment was the cause of the death.

In another case, a patient was included in the study although he should have been kept out under the rules of the experiment. The patient was a heavy smoker and a small mass had appeared in one lung, the agency said. Because the experimental therapy used a chemical designed to increase the growth of blood vessels, the agency said, it was possible that it increased the supply of blood to the growing tumor.

The agency's warning letter noted that the St. Elizabeth's researchers saw the mass when it was less than a centimeter in July 1999, then again in August when it was two centimeters in diameter, but went ahead with the treatment on Sept. 21, 1999. Two months later, the agency said, the patient was hospitalized with chest pain, and the mass was found to have grown to five centimeters.

There was no evidence in the patient's records or the experiment records that either the patient or his doctor was notified of the growth of the mass, investigators said.

Instead, one of the researchers sent a letter to the patient's doctor saying that the patient was doing better with his heart problem since receiving the therapy. The letter did not mention the lung mass.

In addition, the agency noted that in the experiment records the growth in the mass was noted and marked as a "severe" change for the patient. This word should have set off an immediate call to the F.D.A. Instead, the agency said, the word "severe" was struck out and the word "mild" substituted.

The agency's letter also noted that because the researchers apparently did nothing to notify the patient or his doctor, "your site appears to have failed to provide adequate medical care for this subject."

In another case, a patient in the study had a heart attack just after getting the experimental injection. The attack led to multiple organ failure, a long hospitalization, and death a few months later.

But the researchers reported to authorities only that the patient was hospitalized, not that she had died.

Such events are required to be reported because it is possible the therapy itself was the cause of death, and it would be urgent to consider whether to take precautions with other experimental subjects.

In addition, the agency reported that Dr. Isner himself carried out an autopsy on the woman's heart, although he is not a certified pathologist and has no hospital privileges to carry out autopsies.

The inspectors also cited several other problems with the methods of enrolling patients in the experiment: needed tests were not done in some cases, and other patients enrolled might not have been eligible for the study.

The hospital and the researchers have 15 days to tell the agency how they will correct the problems in the experiment. There is no set punishment for the violations, but the F.D.A. has the authority to ban the researchers from future work using federal money.

This and three other experiments carried on by Dr. Isner were stopped when the agency first began its inspection in February and have not resumed.

Dr. Isner is a founder of the company leading the trials and is a major stockholder in it.

http://www.nytimes.com

**CORRECTION-DATE:** May 6, 2000, Saturday

**CORRECTION:**
An article on Thursday about the death of a patient in a **gene therapy** experiment at St. Elizabeth's Medical Center in Boston misidentified the authority to which the hospital failed to report the death. It is the institutional review board of St. Elizabeth's, not the Food and Drug Administration.

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*Editorials*

## Is Academic Medicine for Sale?

In 1984 the *Journal* became the first of the major medical journals to require authors of original research articles to disclose any financial ties with companies that make products discussed in papers submitted to us.[1] We were aware that such ties were becoming fairly common, and we thought it reasonable to disclose them to readers. Although we came to this issue early, no one could have foreseen at the time just how ubiquitous and manifold such financial associations would become. The article by Keller et al.[2] in this issue of the *Journal* provides a striking example. The authors' ties with companies that make antidepressant drugs were so extensive that it would have used too much space to disclose them fully in the *Journal*. We decided merely to summarize them and to provide the details on our Web site.

Finding an editorialist to write about the article presented another problem. Our conflict-of-interest policy for editorialists, established in 1990,[3] is stricter than that for authors of original research papers. Since editorialists do not provide data, but instead selectively review the literature and offer their judgments, we require that they have no important financial ties to companies that make products related to the issues they discuss. We do not believe disclosure is enough to deal with the problem of possible bias. This policy is analogous to the requirement that judges recuse themselves from hearing cases if they have financial ties to a litigant. Just as a judge's disclosure would not be sufficiently reassuring to the other side in a court case, so we believe that a policy of caveat emptor is not enough for readers who depend on the opinion of editorialists.

But as we spoke with research psychiatrists about writing an editorial on the treatment of depression, we found very few who did not have financial ties to drug companies that make antidepressants. (Fortunately, Dr. Jan Scott, who is eminently qualified to write the editorial,[4] met our standards with respect to conflicts of interest.) The problem is by no means unique to psychiatry. We routinely encounter similar difficulties in finding editorialists in other specialties, particularly those that involve the heavy use of expensive drugs and devices.

In this editorial, I wish to discuss the extent to which academic medicine has become intertwined with the pharmaceutical and biotechnology industries, and the benefits and risks of this state of affairs. Bodenheimer, in his Health Policy Report elsewhere in this issue of the *Journal*,[5] provides a detailed view of an overlapping issue — the relations between clinical investigators and the pharmaceutical industry.

The ties between clinical researchers and industry include not only grant support, but also a host of other financial arrangements. Researchers serve as consultants to companies whose products they are studying, join advisory boards and speakers' bureaus, enter into patent and royalty arrangements, agree to be the listed authors of articles ghostwritten by interested companies, promote drugs and devices at company-sponsored symposiums, and allow themselves to be plied with expensive gifts and trips to luxurious settings. Many also have equity interest in the companies.

Although most medical schools have guidelines to regulate financial ties between their faculty members and industry, the rules are generally quite relaxed and are likely to become even more so. For some years, Harvard Medical School prided itself on having unusually strict guidelines. For example, Harvard has prohibited researchers from having more than $20,000 worth of stock in companies whose products they are studying.[6] But now the medical school is in the process of softening its guidelines. Those reviewing the Harvard policy claim that the guidelines need to be modified to prevent the loss of star faculty members to other schools. The executive dean for academic programs was reported to say, "I'm not sure what will come of the proposal. But the impetus is to make sure our faculty has reasonable opportunities."[7]

Academic medical institutions are themselves growing increasingly beholden to industry. How can they justify rigorous conflict-of-interest policies for individual researchers when their own ties are so extensive? Some academic institutions have entered into partnerships with drug companies to set up research centers and teaching programs in which students and faculty members essentially carry out industry research. Both sides see great benefit in this arrangement. For financially struggling medical centers, it means cash. For the companies that make the drugs and devices, it means access to research talent, as well as affiliation with a prestigious "brand." The time-honored custom of drug companies' gaining entry into teaching hospitals by bestowing small gifts on house officers has reached new levels of munificence. Trainees now receive free meals and other substantial favors from drug companies virtually daily, and they are often invited to opulent dinners and other quasi-social events to hear lectures on various medical topics. All of this is done with the acquiescence of the teaching hospitals.

What is the justification for this large-scale breaching of the boundaries between academic medicine and for-profit industry? Two reasons are usually offered, one emphasized more than the other. The first is that ties to industry are necessary to facilitate technology transfer — that is, the movement of new drugs and devices from the laboratory to the marketplace. The term "technology transfer" entered the lexicon in 1980, with the passage of federal legislation, called the Bayh–Dole Act,[8] that encouraged academic in-

stitutions supported by federal grants to patent and license new products developed by their faculty members and to share royalties with the researchers. The Bayh–Dole Act is now frequently invoked to justify the ubiquitous ties between academia and industry. It is argued that the more contacts there are between academia and industry, the better it is for clinical medicine; the fact that money changes hands is considered merely the way of the world.

A second rationale, less often invoked explicitly, is simply that academic medical centers need the money. Many of the most prestigious institutions in the country are bleeding red ink as a result of the reductions in Medicare reimbursements contained in the 1997 Balanced Budget Act and the hard bargaining of other third-party payers to keep hospital costs down. Deals with drug companies can help make up for the shortfall, so that academic medical centers can continue to carry out their crucial missions of education, research, and the provision of clinical care for the sickest and neediest. Under the circumstances, it is not surprising that institutions feel justified in accepting help from any source.

I believe the claim that extensive ties between academic researchers and industry are necessary for technology transfer is greatly exaggerated, particularly with regard to clinical research. There may be some merit to the claim for basic research, but in most clinical research, including clinical trials, the "technology" is essentially already developed. Researchers are simply testing it. Furthermore, whether financial arrangements facilitate technology transfer depends crucially on what those arrangements are. Certainly grant support is constructive, if administered properly. But it is highly doubtful whether many of the other financial arrangements facilitate technology transfer or confer any other social benefit. For example, there is no conceivable social benefit in researchers' having equity interest in companies whose products they are studying. Traveling around the world to appear at industry-sponsored symposiums has much more to do with marketing than with technology transfer. Consulting arrangements may be more likely to further the development of useful products, but even this is arguable. Industry may ask clinical researchers to become consultants more to obtain their goodwill than to benefit from their expertise. The goodwill of academic researchers is a very valuable commodity for drug and device manufacturers. Finally, it is by no means necessary for technology transfer that researchers be personally rewarded. One could imagine a different system for accomplishing the same purpose. For example, income from consulting might go to a pool earmarked to support research or any other mission of the medical center.

What is wrong with the current situation? Why shouldn't clinical researchers have close ties to industry? One obvious concern is that these ties will bias research, both the kind of work that is done and the way it is reported. Researchers might undertake studies on the basis of whether they can get industry funding, not whether the studies are scientifically important. That would mean more research on drugs and devices and less designed to gain insights into the causes and mechanisms of disease. It would also skew research toward finding trivial differences between drugs, because those differences can be exploited for marketing. Of even greater concern is the possibility that financial ties may influence the outcome of research studies.

As summarized by Bodenheimer,[5] there is now considerable evidence that researchers with ties to drug companies are indeed more likely to report results that are favorable to the products of those companies than researchers without such ties. That does not conclusively prove that researchers are influenced by their financial ties to industry. Conceivably, drug companies seek out researchers who happen to be getting positive results. But I believe bias is the most likely explanation, and in either case, it is clear that the more enthusiastic researchers are, the more assured they can be of industry funding.

Many researchers profess that they are outraged by the very notion that their financial ties to industry could affect their work. They insist that, as scientists, they can remain objective, no matter what the blandishments. In short, they cannot be bought. What is at issue is not whether researchers can be "bought," in the sense of a quid pro quo. It is that close and remunerative collaboration with a company naturally creates goodwill on the part of researchers and the hope that the largesse will continue. This attitude can subtly influence scientific judgment in ways that may be difficult to discern. Can we really believe that clinical researchers are more immune to self-interest than other people?

When the boundaries between industry and academic medicine become as blurred as they now are, the business goals of industry influence the mission of the medical schools in multiple ways. In terms of education, medical students and house officers, under the constant tutelage of industry representatives, learn to rely on drugs and devices more than they probably should. As the critics of medicine so often charge, young physicians learn that for every problem, there is a pill (and a drug company representative to explain it). They also become accustomed to receiving gifts and favors from an industry that uses these courtesies to influence their continuing education. The academic medical centers, in allowing themselves to become research outposts for industry, contribute to the overemphasis on drugs and devices. Finally, there is the issue of conflicts of commitment. Faculty members who do extensive work for industry may be distracted from their commitment to the school's educational mission.

All of this is not to gainsay the importance of the spectacular advances in therapy and diagnosis made possible by new drugs and devices. Nor is it to deny the value of cooperation between academia and industry. But that cooperation should be at arm's length, with both sides maintaining their own standards and ethical norms. The incentives of the marketplace should not become woven into the fabric of academic medicine. We need to remember that for-profit businesses are pledged to increase the value of their investors' stock. That is a very different goal from the mission of medical schools.

What needs to be done — or undone? Softening its conflict-of-interest guidelines is exactly the wrong thing for Harvard Medical School to do. Instead, it should seek to encourage other institutions to adopt stronger ones. If there were general agreement among the major medical schools on uniform and rigorous rules, the concern about losing faculty to more lax schools — and the consequent race to the bottom — would end. Certain financial ties should be prohibited altogether, including equity interest and many of the writing and speaking arrangements. Rules regarding conflicts of commitment should also be enforced. It is difficult to believe that full-time faculty members can generate outside income greater than their salaries without shortchanging their institutions and students.

As Rothman urges, teaching hospitals should forbid drug-company representatives from coming into the hospital to promote their wares and offer gifts to students and house officers.[9] House officers should buy their own pizza, and hospitals should pay them enough to do so. To the argument that these gifts are too inconsequential to constitute bribes, the answer is that the drug companies are not engaging in charity. These gifts are intended to buy the goodwill of young physicians with long prescribing lives ahead of them. Similarly, academic medical centers should be wary of partnerships in which they make available their precious resources of talent and prestige to carry out research that serves primarily the interests of the companies. That is ultimately a Faustian bargain.

It is well to remember that the costs of the industry-sponsored trips, meals, gifts, conferences, and symposiums and the honorariums, consulting fees, and research grants are simply added to the prices of drugs and devices. The Clinton administration and Congress are now grappling with the serious problem of escalating drug prices in this country. In these difficult times, academic medicine depends more than ever on the public's trust and goodwill. If the public begins to perceive academic medical institutions and clinical researchers as gaining inappropriately from cozy relations with industry — relations that create conflicts of interest and contribute to rising drug prices — there will be little sympathy for their difficulties. Academic institutions and their clinical faculty members must take care not to be open to the charge that they are for sale.

MARCIA ANGELL, M.D.

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## TREATMENT OF CHRONIC DEPRESSION

THE majority of persons who have an acute episode of a major depressive disorder will have a response to the first or second treatment tried.[1] In patients with mild or moderately severe episodes, treatment with antidepressant drugs and brief psychotherapies are equally effective; in those with severe episodes, medication is usually recommended.[2] The treatment of chronic depression is more problematic, since in 20 to 30 percent of initial episodes, there is incomplete remission after two years.[3,4] Patients with chronic depression have marked impairments in psychosocial function, poor responses to single therapies, and very high rates of use of health care resources.[3] Furthermore, even if they have a partial remission, they have a risk of relapse of 50 to 80 percent.[4]

The poor response of patients with chronic depression to treatment with antidepressant drugs alone is not fully understood, but it cannot be explained solely on the basis of inadequate dosing or the failure of patients to take their medication.[1] Psychotherapy has been advocated as an alternative. Unfortunately, a review of nine studies of psychotherapy for chronic depression that were published before 1998 revealed that in only two trials were patients appropriately randomized, and the combined sample size was only 126 subjects.[5]

Given the lack of empirical data, establishing the relative efficacy of pharmacotherapy and psychotherapy for this disorder has been difficult.[6] Nonetheless, two trends in research results are apparent. First, there is a relatively low rate of response to placebo (about

Special Article

# CONFLICT OF INTEREST IN THE DEBATE OVER CALCIUM-CHANNEL ANTAGONISTS

HENRY THOMAS STELFOX, M.D., GRACE CHUA, M.D., KEITH O'ROURKE, M.B.A., AND ALLAN S. DETSKY, M.D., PH.D.

## ABSTRACT

***Background*** Physicians' financial relationships with the pharmaceutical industry are controversial because such relationships may pose a conflict of interest. It is unknown to what extent industry support of medical education and research influences the opinions and behavior of clinicians and researchers. The recent debate over the safety of calcium-channel antagonists provided an opportunity to examine the effect of financial conflicts of interest.

***Methods*** We searched the English-language medical literature published from March 1995 through September 1996 for articles examining the controversy about the safety of calcium-channel antagonists. Articles were reviewed and classified as being supportive, neutral, or critical with respect to the use of calcium-channel antagonists. The authors of the articles were asked about their financial relationships with both manufacturers of calcium-channel antagonists and manufacturers of competing products (i.e., beta-blockers, angiotensin-converting–enzyme inhibitors, diuretics, and nitrates). We examined the authors' published positions on the safety of calcium-channel antagonists according to their financial relationships with pharmaceutical companies.

***Results*** Authors who supported the use of calcium-channel antagonists were significantly more likely than neutral or critical authors to have financial relationships with manufacturers of calcium-channel antagonists (96 percent, vs. 60 percent and 37 percent, respectively; $P<0.001$). Supportive authors were also more likely than neutral or critical authors to have financial relationships with any pharmaceutical manufacturer, irrespective of the product (100 percent, vs. 67 percent and 43 percent, respectively; $P<0.001$).

***Conclusions*** Our results demonstrate a strong association between authors' published positions on the safety of calcium-channel antagonists and their financial relationships with pharmaceutical manufacturers. The medical profession needs to develop a more effective policy on conflict of interest. We support complete disclosure of relationships with pharmaceutical manufacturers for clinicians and researchers who write articles examining pharmaceutical products. (N Engl J Med 1998;338:101-6.)



THE safety of calcium-channel antagonists in the treatment of cardiovascular disorders has recently become a controversial issue. A case–control study suggested a possible association between the use of calcium-channel antagonists to treat hypertension and an increased risk of myocardial infarction.[1] A meta-analysis of randomized, controlled trials in patients with ischemic heart disease and a case–control study of antihypertensive medications in the elderly raised further questions about the safety of calcium-channel antagonists.[2,3] An intense debate followed in both the medical literature and the lay press.

A Canadian television documentary, *The Fifth Estate*, reported on Health Canada's review of calcium-channel antagonists and suggested that the public was not being adequately protected from potentially dangerous medications. The allegation that an academic advisor to the Health Protection Branch of Health and Welfare Canada (the body that reviews the safety of all pharmaceutical products) had financial relationships with manufacturers of calcium-channel antagonists raised an important question about physicians' objectivity in assessing the safety of drugs.

Physicians' interactions with pharmaceutical manufacturers are controversial. The pharmaceutical industry provides substantial financial support for both medical education and research. What is unknown is the extent to which support by the drug industry influences physicians' opinions and behavior. Limited scientific evidence suggests that physicians may be influenced by pharmaceutical promotions.[4-7] For example, a study by Chren and Landefeld demonstrated that physicians' requests to add particular drugs to hospital formularies were associated with interactions between physicians and manufacturers.[4]

The debate about the safety of calcium-channel

From the Departments of Medicine (H.T.S., G.C., A.S.D.), Health Administration (K.O., A.S.D.), and Public Health Sciences (K.O.), University of Toronto; the Department of Medicine, Mount Sinai Hospital (A.S.D.); and the Department of Medicine, Toronto Hospital (A.S.D.) — all in Toronto. Address reprint requests to Dr. Detsky at Mount Sinai Hospital, Rm. 427, 600 University Ave., Toronto, ON M5G 1X5, Canada.

antagonists provided an opportunity to study financial conflicts of interest in medicine. Our project was designed to examine the relation between authors' published positions on the safety of calcium-channel antagonists and their financial interactions with the pharmaceutical industry.

## METHODS

### Study Questions

The primary question we addressed was whether there was an association between authors' published positions on the safety of calcium-channel antagonists and their financial relationships with the pharmaceutical industry. Authors were surveyed about their financial relationships with pharmaceutical manufacturers, and this information was compared with their published positions. We asked three specific questions: Were authors who supported the use of calcium-channel antagonists more likely than other authors to have financial relationships with manufacturers of calcium-channel antagonists? Were authors who criticized the use of calcium-channel antagonists more likely than other authors to have financial relationships with manufacturers of competing products (i.e., beta-blockers, angiotensin-converting–enzyme inhibitors, diuretics, and nitrates)? Were authors who supported the use of calcium-channel antagonists more likely than other authors to have financial relationships with any pharmaceutical manufacturer?

### Selection and Review of Articles

Authors were identified by reviewing articles on calcium-channel antagonists published between March 10, 1995, and September 30, 1996. Pertinent articles (reports of original research, reviews, and letters to the editor) were identified with the use of the Medline data base and reference lists from published articles. Seventy-seven articles were initially selected.[1-3,8-81] Seven articles were excluded because they were primarily news related, the authors could not be identified, or the authors were officially writing on behalf of the pharmaceutical industry.[8-14] Seventy articles were included in the study.[1-3,15-81]

The articles were reviewed with the use of a predefined classification system (Table 1). Each article was classified as being supportive, neutral, or critical with respect to the use of calcium-channel antagonists. The articles were independently assessed by two of us without knowledge of the authors' survey responses. Discrepancies were discussed, and a third author was consulted if an agreement was not reached. Authors were identified and assigned a classification (supportive, neutral, or critical) according to the classification of their articles. Thirty authors had more than one article, but each author was assigned a single classification. Authors classified as neutral on the basis of one article but critical or supportive on the basis of another were classified as critical or supportive.

### Survey Instrument

A survey instrument based on Chren and Landefeld's[4] questionnaire was developed to examine the authors' financial interactions with pharmaceutical companies. The manufacturers of drugs used to manage angina and hypertension were identified. Forty companies were identified in Canada and the United States: 28 manufactured only products that compete with calcium-channel antagonists (beta-blockers, angiotensin-converting–enzyme inhibitors, diuretics, or nitrates), and 12 manufactured calcium-channel antagonists; 9 of the 12 also manufactured at least one competing product. The pharmaceutical manufacturers were listed alphabetically; the nature of their products was not revealed. For each of the 40 manufacturers, authors were asked whether they had received any of five types of funding in the past five years: support to attend a symposium (i.e., funds for travel expenses), an honorarium to speak at a symposium, support to organize an educational program, support to perform research, and employment or consultation. The questionnaire and the list of manufacturers are available from the National Auxiliary Publications Service (NAPS).*

**TABLE 1.** CLASSIFICATION OF AUTHORS' POSITIONS ON THE SAFETY OF CALCIUM-CHANNEL ANTAGONISTS.

| |
|---|
| **Critical** |
| Emphasizes concern about safety |
| Recommends use of alternative medications |
| Criticizes authors emphasizing the safety of calcium-channel antagonists |
| **Neutral** |
| Concludes that there is insufficient information to assess safety |
| Makes no recommendation about medication use |
| Equitably assesses opposing views |
| **Supportive** |
| Emphasizes safety |
| Recommends continued use of calcium-channel antagonists |
| Criticizes authors questioning safety |

The addresses of the corresponding authors were obtained from the articles, and the addresses of coauthors were requested from the corresponding authors. All authors were mailed the survey questionnaire with a cover letter explaining the purpose of the study. Reminder letters and questionnaires were mailed to authors who did not respond to the first mailing within eight weeks.

### Statistical Analysis

The strategy for the primary analysis was to answer each of the three specific study questions by determining associations between the authors' positions on the safety of calcium-channel antagonists and their reported financial relationships with pharmaceutical manufacturers. The authors' survey responses were coded according to the presence or absence of at least one relationship with a manufacturer of a calcium-channel antagonist, a manufacturer of a competing product, or any pharmaceutical manufacturer. Logistic regression was performed individually for each group of manufacturers, with the classification of the authors (supportive, neutral, or critical) treated as both strictly linear (coded as 2, 1, or 0) and nominal (unordered).[82-84] The results are reported only as linear chi-square values and P values, since the results of the nominal analyses were similar. For the authors who reported financial relationships with pharmaceutical manufacturers, the number of relationships was assessed by linear regression.

The rate of response to the survey was analyzed according to the classification of the authors with the use of logistic regression (linear and nominal). Agreement on the classification of the authors was assessed with Spearman's rank-correlation test. Data were analyzed with S-PLUS software.[85]

## RESULTS

### Classification of Authors

Seventy articles (5 reports of original research, 32 review articles, and 33 letters to the editor) were included in the study; 30 were classified as support-

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ive,[32-61] 17 as neutral,[15-31] and 23 as critical.[1-3,62-81] Agreement on the classification of the articles by the two reviewers was initially 81 percent (agreement on 57 of the 70 articles) and increased to 96 percent (67 of 70) after the reviewers had discussed the discrepancies. A third reviewer was required to resolve the disagreement on the classification of three articles. Interobserver variation was small for the initial reviewer agreement on article classification (Spearman's rank-correlation coefficient, 0.82). Eighty-nine authors of the 70 articles were identified and assigned a classification according to that of their articles; 36 authors were classified as supportive, 19 as neutral, and 34 as critical.

### Response Rates

Addresses were available for 86 of the 89 authors, and all 86 were mailed questionnaires. Three coauthors (one supportive, one neutral, and one critical) were not mailed surveys because their addresses were not provided by the corresponding authors. Of the 86 authors who were mailed surveys, 71 (83 percent) responded. Two authors (one supportive and one critical) refused to participate in the study. A total of 69 authors (80 percent) completed the survey. Table 2 shows the response rate according to the classification of the authors. Sixty-nine percent of the authors who were supportive of calcium-channel antagonists completed the survey, as compared with 83 percent of the neutral authors and 91 percent of the critical authors ($P=0.02$).

**TABLE 2.** RATES OF RESPONSE TO THE SURVEY.

| VARIABLE | SUPPORTIVE | NEUTRAL | CRITICAL | CHI-SQUARE FOR LINEAR TREND | P VALUE |
|---|---|---|---|---|---|
| No. of articles | 30 | 17 | 23 | | |
| No. of authors surveyed | 35 | 18 | 33 | | |
| No. of respondents | 24 | 15 | 30 | | |
| Response rate (%) | 69 | 83 | 91 | 5.60 | 0.02 |

**TABLE 3.** AUTHORS WITH FINANCIAL RELATIONSHIPS WITH PHARMACEUTICAL MANUFACTURERS.

| MANUFACTURER | SUPPORTIVE AUTHORS (N=24) | NEUTRAL AUTHORS (N=15) | CRITICAL AUTHORS (N=30) | CHI-SQUARE FOR LINEAR TREND | P VALUE FOR TREND |
|---|---|---|---|---|---|
| | no. of authors (%) | | | | |
| Manufacturer of calcium-channel antagonist | 23 (96) | 9 (60) | 11 (37) | 22.02 | <0.001 |
| Manufacturer of competing product | 21 (88) | 8 (53) | 11 (37) | 14.84 | <0.001 |
| Any manufacturer | 24 (100) | 10 (67) | 13 (43) | 22.68 | <0.001 |

### Study Questions

The first question we addressed was whether supporters of calcium-channel antagonists were more likely than other authors to have financial relationships with manufacturers of calcium-channel antagonists. The answer was yes. Ninety-six percent of the supportive authors had financial relationships with manufacturers of calcium-channel antagonists, as compared with 60 percent of the neutral authors and 37 percent of the critical authors ($P<0.001$) (Table 3).

Our second question was whether critics of calcium-channel antagonists were more likely than other authors to have financial relationships with manufacturers of competing products (beta-blockers, angiotensin-converting–enzyme inhibitors, diuretics, and nitrates). The answer was no. In fact, supportive and neutral authors were more likely than critical authors to have financial interactions with manufacturers of competing products (88 percent and 53 percent, respectively, vs. 37 percent; $P<0.001$).

Our third question was whether supporters of calcium-channel antagonists were more likely than other authors to have financial relationships with any pharmaceutical manufacturer. The answer was yes. One hundred percent of the supportive authors, as compared with 67 percent of the neutral authors and 43 percent of the critical authors, had financial interactions with at least one pharmaceutical manufacturer ($P<0.001$).

The associations between the authors' positions on the safety of calcium-channel antagonists and the presence or absence of financial relationships with pharmaceutical manufacturers were consistent in the five categories of funding (funds for travel expenses, honorariums for speeches, support for educational programs, research grants, and employment or consultation) (Table 4). Sixty-seven percent of the supportive authors reported three or more of the five types of interactions, as compared with 40 percent of the neutral authors and 13 percent of the critical authors ($P<0.001$). In the group of authors who had at least one relationship with any pharmaceutical manufacturer, there were no significant associations between an author's position on the safety of calcium-channel antagonists and the mean number of relationships.

## DISCUSSION

Our study was designed to examine financial conflicts of interest in the debate over calcium-channel antagonists. The results demonstrate a strong association between authors' opinions about the safety of

**TABLE 4.** AUTHORS' FINANCIAL RELATIONSHIPS WITH PHARMACEUTICAL MANUFACTURERS.

| INTERACTION AND MANUFACTURER | SUPPORTIVE AUTHORS (N=24) | NEUTRAL AUTHORS (N=15) | CRITICAL AUTHORS (N=30) | CHI-SQUARE FOR LINEAR TREND | P VALUE FOR TREND |
|---|---|---|---|---|---|
| | % of authors | | | | |
| Support to attend symposium | | | | | |
| Manufacturer of calcium-channel antagonist | 67 | 33 | 20 | 12.39 | 0.002 |
| Manufacturer of competing product | 50 | 27 | 13 | 8.84 | 0.01 |
| Any manufacturer | 67 | 47 | 27 | 8.87 | 0.01 |
| Honorarium to speak at symposium | | | | | |
| Manufacturer of calcium-channel antagonist | 71 | 27 | 13 | 19.82 | <0.001 |
| Manufacturer of competing product | 62 | 40 | 13 | 14.66 | <0.001 |
| Any manufacturer | 75 | 40 | 17 | 19.62 | <0.001 |
| Support for educational program | | | | | |
| Manufacturer of calcium-channel antagonist | 46 | 20 | 7 | 11.92 | 0.003 |
| Manufacturer of competing product | 37 | 13 | 10 | 6.16 | 0.04 |
| Any manufacturer | 50 | 20 | 10 | 11.26 | 0.003 |
| Research funding | | | | | |
| Manufacturer of calcium-channel antagonist | 79 | 33 | 17 | 22.45 | <0.001 |
| Manufacturer of competing product | 50 | 33 | 20 | 5.45 | 0.07 |
| Any manufacturer | 87 | 40 | 20 | 26.09 | <0.001 |
| Employment or consultation | | | | | |
| Manufacturer of calcium-channel antagonist | 21 | 33 | 7 | 2.13 | 0.07 |
| Manufacturer of competing product | 21 | 33 | 17 | 0.19 | 0.46 |
| Any manufacturer | 25 | 33 | 17 | 0.60 | 0.45 |

calcium-channel antagonists and their financial relationships with pharmaceutical manufacturers. Supportive authors were much more likely than critical authors to have financial associations with manufacturers of calcium-channel antagonists, as well as with manufacturers of other products. Conversely, critical authors were much less likely to be financially associated with manufacturers of competing products.

### Limitations of the Study

The results of this study need to be interpreted within the context of its limitations. First, the survey instrument used was simple and perhaps imperfect. Author–manufacturer relationships were assessed simply as being present or absent. No estimates of monetary value were assigned to the relationships to assist in quantification. We also realized later that the authors' business interests in pharmaceutical companies (e.g., equities) were not assessed. The most serious weakness of the survey instrument, however, was that it provided only self-reported data on financial relationships. Independent verification of these relationships would be very difficult. Self-reporting could potentially have biased the study results since the authors were more likely to underreport than overreport interactions with manufacturers. Most of the critical authors (91 percent) completed the survey, and we believe it is unlikely that they underreported their financial relationships, as compared with the other authors. The supportive authors had a lower response rate (69 percent), yet all the supportive authors who responded to the survey reported a financial relationship with at least one manufacturer. We therefore believe that self-reporting is unlikely to have significantly influenced our study findings.

Second, we were unable to determine the temporal relation between authors' published opinions and their financial interactions with pharmaceutical manufacturers. The authors may have formulated their opinions after having financial interactions with drug manufacturers. However, it is equally plausible that the pharmaceutical companies sought relationships with clinicians and researchers who had already expressed favorable opinions of their products.

### Guidelines for Disclosing Conflicts of Interest

The medical profession has failed to develop and enforce strict guidelines for disclosing conflicts of interest. Furthermore, many conflicts of interest may go unrecognized. In our study, the majority of authors (63 percent) had a financial relationship with either a manufacturer of a calcium-channel antagonist or a manufacturer of a competing product. However, only 2 of the 70 articles included in the study disclosed the authors' potential conflicts of interest.[41,53] Clearly, our current disclosure policies are inadequate.

We propose a disclosure mechanism in the form of a questionnaire for authors: a simple two- or three-page document, similar to the one used in our study, listing pharmaceutical manufacturers and in-

quiring about specific financial relationships with them. A questionnaire posing simple, concrete questions facilitates the disclosure of conflicts of interest. With this approach, ambiguity and accidentally missed conflicts, as recently noted in the *New England Journal of Medicine*,[86] would be avoided. Editorial staff would be in possession of all information on potential conflicts of interest and would be able to make an appropriate decision about disclosure for each article published.

We believe that the pharmaceutical industry has an important and constructive role in academic medicine. Pharmaceutical manufacturers provide important support for both medical education and research. We also believe that medical journals risk severely limiting the pool of experts available to debate medical issues if they restrict the publication of articles by clinicians and researchers with conflicts of interest. Physicians and researchers simply need to disclose their financial relationships with pharmaceutical manufacturers appropriately. Medical professionals should be able to evaluate the merit of individual articles in the light of the authors' disclosure of conflicts of interest.

The extent to which the pharmaceutical industry influences clinicians' and researchers' opinions cannot be determined by the results of our study. We believe that the authors we surveyed expressed their own opinions and were not influenced by financial relationships with pharmaceutical manufacturers. However, it is our opinion that scientific authors are naive about public perceptions concerning such relationships. We wonder how the public would interpret the debate over calcium-channel antagonists if it knew that most of the authors participating in the debate had undisclosed financial ties with pharmaceutical manufacturers. The medical profession needs to develop a strong policy governing conflict of interest. Full disclosure of relationships between physicians and pharmaceutical manufacturers is necessary to affirm the integrity of the medical profession and maintain public confidence.

This study received no financial support from the pharmaceutical industry. Dr. Stelfox has no financial relationships with the pharmaceutical industry; he has attended numerous Department of Medicine educational rounds sponsored by pharmaceutical manufacturers. Dr. Chua has received funding for travel from both manufacturers of calcium-channel antagonists and manufacturers of competing products. Mr. O'Rourke has no financial relationships with the manufacturers of calcium-channel antagonists or the manufacturers of competing products; he has attended industry-sponsored functions when invited by clinicians. Dr. Detsky has received honorariums for speeches and consulting fees from manufacturers of calcium-channel antagonists and manufacturers of competing products; he has received research grants from Rhone–Poulenc Rorer Pharmaceuticals, Searle, and SmithKline Beecham Pharmaceuticals.

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ORIGINAL CONTRIBUTION

# Evaluation of Conflict of Interest in Economic Analyses of New Drugs Used in Oncology

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**Context** Recent studies have found that when investigators have financial relationships with pharmaceutical or product manufacturers, they are less likely to criticize the safety or efficacy of these agents. The effects of health economics research on pharmaceutical company revenue make drug investigations potentially vulnerable to this bias.

**Objective** To determine whether there is an association between pharmaceutical industry sponsorship and economic assessment of oncology drugs.

**Design** MEDLINE and HealthSTAR databases (1988-1998) were searched for original English-language research articles of cost or cost-effectiveness analyses of 6 oncology drugs in 3 new drug categories (hematopoietic colony-stimulating factors, serotonin antagonist antiemetics, and taxanes), yielding 44 eligible articles. Two investigators independently abstracted each article based on specific criteria.

**Main Outcome Measure** Relationships between funding source and (1) qualitative cost assessment (favorable, neutral, or unfavorable) and (2) qualitative conclusions that overstated quantitative results.

**Results** Pharmaceutical company–sponsored studies were less likely than nonprofit-sponsored studies to report unfavorable qualitative conclusions (1/20 [5%] vs 9/24 [38%]; $P = .04$), whereas overstatements of quantitative results were not significantly different in pharmaceutical company–sponsored (6/20 [30%]) vs nonprofit-sponsored (3/24 [13%]) studies ($P = .26$).

**Conclusions** Although we did not identify bias in individual studies, these findings indicate that pharmaceutical company sponsorship of economic analyses is associated with reduced likelihood of reporting unfavorable results.

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FINANCIAL CONFLICT OF INTEREST is a pressing issue for the medical research community.[1,2] Physicians' economic ties to tobacco, alcohol, baby formula, and pharmaceutical companies have all been criticized as possible nonscientific influences on medical research.[3-6] Recent studies of research on calcium channel antagonists in cardiology, nonsteroidal anti-inflammatory drugs for the treatment of arthritis, and the health effects of secondhand smoke all found that physicians with financial ties to manufacturers were significantly less likely to criticize the safety or efficacy of these agents.[7-9] Similarly, a study of clinical trial publications determined that there was a significant association between positive results in general internal medicine clinical trials and funding from a pharmaceutical manufacturer.[10]

While the debate over financial conflict of interest has surrounded issues of clinical efficacy and safety, only 1 prior study has addressed concerns related to reports on cost-effectiveness.[11] In that study, Azimi and Welch[11] reported that industry-financed cost-effectiveness analyses were more likely to support additional expenditures with investigational drugs than standard treatments. To further examine the existing pharmacoeconomic literature, we evaluated cost studies for 3 recent breakthrough areas in oncology: hematopoietic colony-stimulating factors, serotonin antagonist antiemetics, and taxanes. Economic studies of these agents have reported varying assessments of costs and cost-effectiveness.[12-17] This study was designed to determine whether the apparent financially motivated bias seen in clinical efficacy and safety evaluations is also evident in economic analyses in oncology.

The major objective of this study was to determine whether there was an association between pharmaceutical industry sponsorship and economic assessments of breakthrough oncology drugs. The following questions were addressed: were pharmaceutical company–funded economic studies more likely than nonprofit-funded studies to report favorable qualitative assessments and less likely to report unfavorable qualitative assessments? and were pharmaceutical company–sponsored studies more likely than nonprofit-funded studies to state qualitatively favorable

**For editorial comment see p 1474.**

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conclusions despite neutral or unfavorable quantitative results?

## METHODS

Economic analyses of 6 recently marketed breakthrough cancer drugs in 3 categories were chosen. The agents included hematopoietic growth factors (granulocyte colony-stimulating factor [G-CSF] and granulocyte-macrophage colony-stimulating factor [GM-CSF]), serotonin antagonist antiemetics (ondansetron hydrochloride and granisetron), and taxane chemotherapy agents (paclitaxel and docetaxel). These drugs were chosen because their cost-effectiveness is controversial, and they account for a large fraction of total pharmaceutical expenditures in many hospital pharmacies. Clinical reports have demonstrated efficacy in specific settings, but high acquisition and administration costs have raised concern about the widespread use of these agents.

We searched the MEDLINE (1988-1998) and HealthSTAR (1988-1998) databases to identify original research articles that contained an economic analysis of 1 or more of the study drugs. The following terms were searched: *cost(s)*, *cost-effective(ness)*, *economic(s)*, *dollar(s)*, *pharmacoeconomic(s)*, and *cost-benefit*. Drugs were searched under generic and brand names. Abstracts, letters, editorials, review articles, and non–English-language articles were excluded. Abstracts from the remaining articles were reviewed, and all articles including an actual analysis of costs were identified. This search yielded 54 articles, of which 8 were head-to-head comparisons between drugs in a given category (eg, G-CSF vs GM-CSF) and 46 were comparisons with placebo or standard treatment. Head-to-head comparisons were excluded because they could not be classified according to our criteria; ie, the results would always be either favorable or neutral for 1 or the other of the study drugs. Another 2 articles[18,19] were excluded because we were unable to obtain information about the funding source, despite repeated requests. Of the 44 articles studied, there were 28 articles for hematopoietic colony-stimulating factors,[12,13,20-45] 11 articles for antiemetics,[14,15,46-54] and 5 articles for taxanes.[16,17,55-57] The types of analyses included were cost-minimization or cost-identification (a comparison of the costs of treatment for 2 different agents with similar efficacy or outcomes) and cost-effectiveness (comparison of the costs of treatment for 2 agents normalized by their effectiveness, typically reported as cost per life-year gained). All of the articles fit 1 of these types, based on generally accepted definitions.[58,59]

Two investigators (M.F. and W.N.) independently abstracted information from each of the articles based on distinct, written, preset criteria. Information was collected on (1) the qualitative conclusion as stated in the abstract or manuscript conclusion, (2) the quantitative numerical results, (3) the timing of the study, and (4) the funding source.

Qualitative conclusions were rated according to the following criteria: favorable (the new drug "reduces costs" or is "cost-effective"), neutral (the new drug "is cost equivalent" or "may be cost-effective," or "does not require additional costs" over standard therapy), or unfavorable (the new drug has "higher costs" or is "not cost-effective"). Whenever the 2 investigators disagreed over an article's qualitative conclusion, a third investigator made the final decision.

Quantitative numerical results were also rated as favorable, neutral, or unfavorable. For cost-minimization studies, numerical results were classified as favorable when the costs of use of the new drug were less than standard treatment, neutral when there was no difference between the new drug and the standard, and unfavorable when the costs of use of the new drug were more than standard treatment. The total cost of treatment for each arm of the study was compared, including the cost of the study drug. When tests of statistical significance were available, significant differences were interpreted as favorable or unfavorable. Statistically insignificant differences were interpreted as neutral. For articles that did not include statistical analyses (typically, decision analyses), robust differences were interpreted as favorable or unfavorable. Nonrobust differences (which reversed direction under sensitivity analyses) were interpreted as neutral. For cost-effectiveness studies, any cost estimate of less than $50 000 per life-year gained was considered favorable, as is generally accepted in the literature.[60] More expensive results were considered unfavorable.

Study timing was interpreted as either prospective (the study was initiated alongside the clinical trial) or retrospective (the economic study was begun after the results of the clinical study were known).

Funding source was abstracted after recording a study's qualitative conclusion, quantitative results, and timing. Investigators were not specifically blinded as to funding source during abstraction. Articles were classified as either pharmaceutical company–sponsored or nonprofit-sponsored (government agency, professional organization, nonprofit foundation, or academic institution). For publications not including an acknowledgment of funding (17/46), first and last authors were contacted via mail, e-mail, and/or telephone and queried regarding the funding source of their study. Authors from 13 of 17 articles replied that their studies were either not externally funded or funded by nonprofit sources, while authors of 2 of 17 articles reported that their studies were funded by pharmaceutical companies. Authors of the remaining 2 articles[18,19] did not reply, and their studies were not included in our analyses.

Relationships between funding source and (1) qualitative conclusion (favorable, neutral, or unfavorable), (2) overstatement of results (a favorable qualitative conclusion despite neutral or unfavorable quantitative results or a neutral qualitative conclusion despite unfavorable quantitative results), (3) study agent (hematopoietic growth factor, antiemetic, or taxane), (4) study timing (prospective or retrospective), (5) analysis type (cost minimization or cost-effectiveness), (6) journal type (peer-reviewed or non–peer-reviewed), and (7) author affiliations (all academic, or at least 1 pharmaceutical company or

consulting firm employee) were analyzed using Fisher exact tests (for 2 × 2 tables with an expected cell value less than 5) or Pearson $\chi^2$ tests. A 2-sided *P* value (against the null hypothesis of no relationship between conclusion and funding source) less than .05 was considered significant.

## RESULTS

Of the 44 articles, 20 were funded by pharmaceutical companies and 24 by nonprofit organizations. For those studies funded by pharmaceutical companies, the funding source was always the manufacturer of the investigational drug. Approximately 65% of studies analyzed hematopoietic growth factors, 25% antiemetics, and 10% taxanes (TABLE). This distribution was similar for both pharmaceutical- and nonprofit-sponsored studies. Study timing, analysis type, and journal type also did not differ significantly by funding source. All authors of nonprofit-sponsored studies had academic affiliations, whereas 40% of pharmaceutical company–sponsored studies had at least 1 author with a pharmaceutical company or consulting firm affiliation (divided evenly between pharmaceutical company and consulting firm employees).

There was a statistically significant relationship between funding source and qualitative conclusions (*P* = .04). Unfavorable conclusions were reached by 38% (9/24) of nonprofit-sponsored studies but by only 5% (1/20) of pharmaceutical company–sponsored studies (Table). Reports including only authors who had an academic affiliation appeared more likely to report unfavorable conclusions (28% [10/36]) than those including pharmaceutical or consulting firm employees (0% [0/8]), although this difference was not significant (*P* = .18). The 2 investigators agreed on the classification of qualitative conclusions in 87% of the articles, with the third investigator determining the classification of the remaining 13%.

In addition, pharmaceutical company–sponsored studies were somewhat more likely than nonprofit-sponsored studies to overstate quantitative results; ie, a favorable qualitative conclusion when quantitative results were neutral or unfavorable, or a neutral conclusion when quantitative results were unfavorable (30% [6/20] vs 13% [3/24]), although this finding was not statistically significant (*P* = .26).

## COMMENT

This study investigated financial conflicts of interest in the debate over economic analyses of breakthrough oncology drugs. We found a significant association between authors' stated qualitative conclusions regarding the costs and cost-effectiveness of these drugs and study sponsorship by the drugs' manufacturers. Studies funded by pharmaceutical companies were nearly 8 times less likely to reach unfavorable qualitative conclusions than nonprofit-funded studies and 1.4 times more likely to reach favorable qualitative conclusions. We also determined that 1 in 5 articles contained qualitative overstatements of quantitative results.

A number of hypotheses can help explain our findings. First, the retrospective methods used in 89% of our sample studies allow investigators and pharmaceutical companies "early looks" at clinical results and associated resource profiles. These early clinical data can be used to selectively identify the trials most likely to yield positive outcomes, and the pharmaceutical companies can fund economic studies accordingly and therefore, can potentially exercise a limited power to censor unfavorable studies simply by withholding financial support.

Second, there is an evident bias in the body of pharmacoeconomics research (also seen in other areas of medical research) toward the publication of studies with "positive" results. Regardless of funding source, studies with unfavor-

**Table.** Study Set Characteristics and Conclusions*

| Characteristic | Study: Pharmaceutical Company Sponsored (n = 20) | Study: Nonprofit Sponsored (n = 24) | *P* Value |
|---|---|---|---|
| Agent | | | |
| Hematopoietic growth factors | 65 | 63 | .97 |
| Antiemetics | 25 | 25 | |
| Taxanes | 10 | 13 | |
| Study timing | | | |
| Prospective | 5 | 17 | .36 |
| Retrospective | 95 | 83 | |
| Analysis type | | | |
| Cost minimization | 75 | 58 | .24 |
| Cost-effectiveness | 25 | 42 | |
| Journal type | | | |
| Non–peer-reviewed | 15 | 17 | .99 |
| Peer-reviewed | 85 | 83 | |
| General medical | 0 | 8 | |
| Oncology | 40 | 25 | |
| Hematology | 15 | 17 | |
| Supportive care | 5 | 17 | |
| Pharmacy | 25 | 16 | |
| Author affiliation | | | |
| All academic | 60 | 100 | <.002 |
| ≥1 Pharmaceutical or consulting firm employee | 40 | 0 | |
| Conclusion | | | |
| Favorable | 60 | 42 | .04 |
| Neutral | 35 | 21 | |
| Unfavorable | 5 | 38 | |
| Overstatement of quantitative results | 30 | 13 | .26 |

*All data are presented as percentages unless otherwise indicated. Numbers may not sum to 100 due to rounding.

able preliminary evidence are less likely to be completed, less likely to be submitted for peer review, and, once submitted, less likely to be published.[61]

Third, pharmaceutical companies can influence research in a variety of ways. Studies may be funded through unrestricted research grants, educational funds, or consultancies (paid directly to investigators). These may include contractual agreements requiring pharmaceutical company review of manuscripts before being submitted for publication. Researchers also may receive funding from the same companies in the form of honoraria or travel awards for scientific meetings and have equity interests in companies and profit directly from increased drug sales.[62] It is possible that these factors may result in some unconscious bias (perhaps when qualitatively interpreting results) that could influence study conclusions.

Fourth, the pharmaceutical companies can collaborate directly with investigators in devising protocols for economic analyses and indirectly shape the economic evaluation criteria.

Our study has several limitations. First, we considered only 1 type of economic relationship between pharmaceutical companies and researchers: direct funding of the analysis reported. Second, our ability to investigate direct financial sponsorship of the individual studies was limited because we were unable to review contracts or grants. While we used published information and direct communication with authors, the nature and degree of the financial relationship were not investigated.

The correlation between pharmaceutical company funding and favorable study conclusions might add to public uncertainty regarding company-sponsored medical research.[63,64] Although other sources of funds for pharmacoeconomic studies are needed, limiting the publication of pharmaceutical company–sponsored studies is probably not feasible or practical. Pharmaceutical companies provide valuable resources to many areas of academic medicine and are a primary source of funding for pharmacoeconomic studies.[7,58] To improve the credibility of economic analyses, policies promoting full disclosure of all financial interests should be pursued. Conducting more prospective pharmacoeconomic analyses (in conjunction with phase 3 trials) would also increase credibility by eliminating the opportunity for selective funding based on clinical results.[65] Finally, pharmacoeconomic literature would be more balanced if managed care organizations, government agencies, and nonprofit groups increased their support for high-quality prospective pharmacoeconomic studies.

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**HEADLINE:** Money Is Putting People at Risk in Biomedical Research

**BYLINE:** LORI B. ANDREWS

**BODY:**

When the Food and Drug Administration halted research into human-gene therapy at the University of Pennsylvania in January, after the death of a research subject, Jesse Gelsinger, administrators at universities across the United States took notice. If a research program at an Ivy League institution, run by a scientist as prominent as James M. Wilson, was being accused of serious breaches of law and ethical standards, what problems lurked in the growing number of studies at their own institutions? The Universities of Alabama, Colorado, and Illinois, as well as Duke and Virginia Commonwealth Universities, also have recently faced embarrassing public disclosures about their research programs. For example, federal regulators charged scientists at the University of Illinois at Chicago with failing to obtain subjects' informed **consent** in a study of an antipsychotic drug, and charged Duke's institutional review board with not monitoring continuing research.

Can other institutions stay out of trouble by giving researchers more education about their ethical and legal obligations? Or do we need radical new laws to remedy the situation?

The number of research studies on campuses is soaring, and the potential risks for subjects are increasing. In the 1970's, as an undergraduate majoring in psychology, I earned either course credit or a few dollars by participating in studies in which the major risk was inconvenience or boredom. Now, healthy college students can earn upwards of $ 2,000 for taking part in medical studies -- but may face permanent harm.

The financial incentives for researchers are escalating, too. Last year, The New York Times reported that pharmaceutical companies often pay doctors handsomely -- in some cases, $ 1-million per year -- for enrolling patients in studies. The results: Doctors from one field enroll their patients in drug trials in another field. For example, asthma specialists run studies on psychiatric medications. Patients who are not appropriate candidates for a study have received drugs for conditions they did not have, sometimes without even being told that the drugs were experimental. That not only subjected them to unnecessary risks, which is malpractice, but also compromised the study results.

Even $ 1-million a year is small potatoes, though, in light of the incentives created for university researchers in the 1980's by the federal laws governing technology transfer. Before that time, research conducted at universities and supported by public funds belonged to the public. But the new laws give academic researchers intellectual-property rights; now they can, for example, patent a gene they discover or an invention they make, even if the entire enterprise has been financed by taxpayers through the National Institutes of Health or another federal agency.

Academic researchers can form biotech companies or enter into joint ventures with them. Penn's James Wilson, for example, founded a gene-therapy company. Many university biologists have become millionaires, with stock options and fees as directors of corporations far exceeding their university salaries.

Is it any wonder, then, that federal investigators from the Food and Drug Administration and the N.I.H.'s Office for Protection from Research Risks find that, even though federal regulations require scientists to disclose the risks of participating in research to potential subjects, the researchers often underplay the

risks and enroll inappropriate candidates? At Penn, the informed-**consent** form that Jesse Gelsinger signed did not disclose the fact that two monkeys had died after receiving the gene-therapy vector that he, too, was given. And researchers had accepted Gelsinger as a subject despite the fact that, according to the government, his liver function was not good enough to meet the study's criteria.

Other universities have covered up the risks of gene therapy in studies conducted on their campuses. Disregarding federal rules, researchers reported promptly to the N.I.H. only 39 of the 691 deaths and illnesses suffered by participants in gene-therapy research who had received the same vector as Gelsinger.

At Congressional hearings in February, sponsored by Sen. Bill Frist, a Republican from Tennessee, the testimony by federal regulators was disappointing. It sounded almost exactly like that of the biotech companies. Jay Siegel, of the F.D.A., pointed to the "potential for tremendous patient benefit" of gene therapy. He reported that "since the first human gene transfer in the late 1980's, human gene therapy products have become one of the fastest growing areas of product development."

Referring to "products" makes it seem as if valid gene therapies are being marketed already. In reality, gene therapy has been a dud -- not one successful experiment has been reported in a peer-reviewed journal. Yet, thanks to hype by companies and regulators alike, 36 percent of the public, according to a survey conducted by the National Center for Genome Resources, thinks that gene-therapy treatments have already succeeded in curing human diseases. Research volunteers thus may not realize the preliminary nature of the experiments they have agreed to participate in.

The business perspective among researchers is even more obvious. As far back as September 1995, at a meeting at Stanford University on genetics research, faculty members and graduate students filled the auditorium when George Poste, of SmithKline Beecham, was speaking. But when Nancy Wexler, then chair of the N.I.H.-D.O.E. Working Group on the Ethical, Legal, and Social Implications of the Human Genome Project, took to the stage to discuss the risks to participants in genetic research, many members of the audience left. I overheard researchers in the hall discussing how to handle psychological risks -- not to their subjects, but to the researchers themselves when there was a dip in the value of their biotech stock.

Whether the corporate mentality of many researchers is part of the reason for the abuses recently uncovered in research with **human subjects,** or whether investigators have simply become more aggressive, is an interesting question. It is clear, however, that the violations of the federal regulations protecting **human subjects** are serious.

According to the American Bar Association's Coordinating Group on Bioethics and the Law, between January 1997 and June 1999 the F.D.A. issued 36 warning letters to investigators undertaking research with drugs, medical devices, and biological products. The reported violations are similar to those found by the Office for Protection from Research Risks for human research in general. They include failures to submit studies to an institutional review board, obtain informed **consent,** report adverse effects of the research, and determine the suitability of research subjects, as well as inappropriate promotion to solicit subjects' participation, and inadequate record-keeping.

The F.D.A. and the risk-protection office also found that some universities did not seem to be taking seriously the review of **human-subjects** research. Their I.R.B.'s had too few members for the volume of studies they were expected to review, and their researchers had inappropriately claimed that studies fell within regulatory exceptions and so did not need to be approved by the institution's I.R.B.

Administrators and researchers at many colleges and universities seem to think that they should be exempt from regulation because they work at nonprofit institutions. Yet human research subjects deserve protection no matter who is conducting the study. That is particularly true in an era when universities are acting more and more like businesses, even to the point of forming for-profit companies to commercialize their professors' research.

The University of Minnesota developed, manufactured, and sold an antirejection drug for use in

transplants, making more than $ 85-million. It was forced to stop marketing the drug when federal investigators found that the university had failed to get F.D.A. approval for the drug, and had not properly reported serious adverse reactions, including deaths. The government sued the university for allegedly selling an unlicensed drug, fraudulently billing Medicare for the drug, and submitting false grant applications -- claiming that Minnesota was distributing the drug at cost rather than making a profit -- to the N.I.H. The university settled the suit in 1998 for $ 32-million.

The academics involved in the affair seemed to feel that they were above the law. An internal university report suggested that "cost recovery in any form is strictly illegal, but . . . when it is done on behalf of the University, the FDA probably will not take action."

What can be done to better protect the subjects of academic research? Individual colleges and universities need to put more resources -- both people and money -- into their institutional review boards. They need to do a better job of educating their employees about the federal regulations and state laws that govern human research.

Academe as a whole should also devote more effort to the question of I.R.B.'s. We need research on how well the system is working, mechanisms to evaluate the performance of individual boards, and new ways to reward faculty members who serve on I.R.B.'s -- such as offering them release time from other duties, and counting I.R.B. service in promotion and tenure decisions.

Universities must also guard against conflicts of interest among members of I.R.B.'s. The risk-protection office found that some review-board members do not recuse themselves from voting when they have such conflicts. At Duke, both the director and the assistant director of the medical center's Office of Grants and Contracts, which is responsible for bringing in grants, had improperly served as voting members of the medical center's I.R.B.

The government needs to do a better job of monitoring research -- including periodic reviews of I.R.B. files -- and making available information about the risks involved. Serious side effects uncovered in studies paid for by industry are sometimes labeled proprietary information and -- though they are reported to the F.D.A. -- are not disclosed to the public. Such censorship should not be allowed.

The Department of Health and Human Services has not provided sufficient personnel or resources -- in their Office of Biotechnology Activities, for example -- to complete important public databases about research risks. Such data are crucial both to people's decisions about whether to participate in research, and to investigators' determinations about when research is too dangerous to continue.

More generally, Congress needs to reconsider the laws governing technology transfer. By trying to ensure that products are brought to market quickly, lawmakers have so commercialized academe that there are now few neutral scientists who can provide credible assessments of the risks and benefits of new medical developments. We should revise the laws so that academics and universities cannot profit from the sale of treatments created through research that the taxpayers have paid for.

The federal regulations developed in the mid-1970's for use by a kinder, gentler generation of researchers may be outdated now. Last August, the bar association's Coordinating Group on Bioethics and the Law initiated a major project to analyze the research abuses of the past three years. The group is assessing what proportion of abuses violate existing regulations, and what proportion could have been prevented only by new regulations. Many things have changed since the current federal regulations were adopted, including greater financial incentives for researchers, more and larger conflicts of interest, more research on tissue samples collected for other purposes, and greater risks to people's privacy when genetic information about them is obtained.

"When lives are at stake, and my son's life was at stake," Paul Gelsinger told Senator Frist and his colleagues in February, "money and fame should take a back seat. The concern should not be on getting to the finish line first, but on making sure no unnecessary risks are taken, no lives filled with potential and promise are lost forever, no more fathers lose their sons."

Academic researchers seem to be focusing on their new role as business people. Universities and regulators need to remind them of their obligations to their subjects and society.

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