



Issue Analysis

Shackling Innovation

The Regulation of Industry- Supported Clinical Trials

By Sigrid Fry-Revere, Alison Mathey and David Malmstrom

February 2010

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Executive Summary

Over the past three decades, collaborative arrangements between academic biomedical researchers and private industry have grown dramatically, resulting in medical innovations that have benefited society greatly. However, a growing chorus of criticism directed at private companies that sponsor and conduct biomedical research casts doubt on the very ethos of science. Academics and anti-business activists have waged a campaign against industry-sponsored clinical trials that denies the fundamentally commercial nature of such research and hinders medical progress. These critics point to a small number of unfortunate and tragic cases in which financial conflicts of interest may have played a role in research-related injuries and deaths in order to unjustifiably condemn the profit motive in biomedical research as a whole.

The debate over conflicts of interest, once confined to the pages of medical journals, has jumped aboard a runaway train. In response to public outcry, the Obama administration and the 111th Congress have promised stronger federal regulation and a far more aggressive role for federal and state governments in the nation's biomedical economy. Industry critics, however, are pushing for even stricter regulations, including the abolishment of industry-sponsored clinical trials all together.

Prohibition or even greater regulation of industry sponsorship makes no sense. Given the paucity of evidence linking financial conflicts of interest to research-related mishaps, these new regulations elevate isolated incidents to the norm, and confuse correlation with causation. The way to prevent dangerous or ineffective drugs from reaching the market is not to eliminate financial incentives, but quite the opposite—to make well-conducted successful research so rewarding, both financially and otherwise, and errors in research so costly, that the only logical choice for researchers is to do their absolute best to produce accurate results. If the profit motive is removed, so is the most immediate benefit of doing good work and the long-term cost of doing poor work. The net result of policies that restrict industry sponsored clinical trials will be a slowing of medical advances and a delay in the development and marketing of new medical technologies that have the potential to save thousands of lives. Suggestions for restricting financial incentives are being made without any clear evidence, let alone proof, that doing so will prevent the tragic incidents that fuel today's movement to restrict industry-sponsored clinical trials.

After a careful analysis of both the facts and the arguments for and against restricting industry-sponsored clinical, we suggest that regulators should be moving in a totally different direction. Educating people about drug development, clinical trials, risks and benefits, and figuring out ways to increase compliance with medical instructions is likely to go much further toward reducing adverse reactions to medications than trying to eliminate conflicts of interest.

Introduction

Collaborative arrangements between biomedical academic researchers and private industry have grown dramatically over the past three decades, resulting in medical innovations that have benefited society as a whole. However, a chorus of growing criticism directed at private companies that sponsor and conduct biomedical research casts doubt on the very ethos of science. Some academics and anti-business activists have waged a campaign against industry-sponsored clinical trials. That criticism denies the fundamentally commercial nature of such research, and therefore hinders medical progress.

These critics point to a small number of unfortunate and tragic cases in which financial conflicts of interest may have played a role in research related injuries and deaths in order to unjustifiably condemn the profit motive in biomedical research as a whole. In response to claims that unchecked industry research has led—and will continue to lead—to disastrous outcomes, the Obama administration and the 111th Congress have promised stronger federal regulation and a far more aggressive role for the federal and state governments in the nation's biomedical economy.

Contrary to the anti-industry zealots' claims, financial incentives lead to innovation and progress. In those instances in which industry-sponsored trials have gone awry, money played no more a part than did other potential motivations, such as professional ambition or a fear of failure. Therefore, there is no reason to believe that mistakes or malfeasance are more likely in industry-sponsored, or other for-profit, research than in the public or nonprofit sector.

A conflict of interest is a clash of competing interests in which a socially sanctioned goal could potentially be compromised by a more personal goal. Conflicts of interest exist in every form of human interaction. Therefore, the question should be not whether conflicts exist, but whether relevant individuals will succumb to the temptation to satisfy more immediate personal desires at the expense of long-term personal benefit and long-term social goals.

The most effective way to manage conflicts of interests is to create a social order in which personal interests and social interests coincide—that is, a social order where striving to achieve one's personal goals (at least one's long-term goals), also benefits society. To encourage long-term investment in serving social goals, two conditions must be present: 1) a potential for long-term personal gain, and 2) a certainty of negative

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consequences for those who choose short-term personal interests that violate social norms over long-term ones that coincide with societal goals.

Critics of industry-supported clinical trials who seek to reduce or eliminate financial incentives are throwing the proverbial baby out with the bathwater. The way to reduce the potential for harm to clinical trial participants and to prevent dangerous or ineffective drugs from reaching the market is not to eliminate financial incentives, but quite the opposite—to make well-conducted successful research so rewarding, both financially and otherwise, and errors in research (whether accidental or intentional) so costly, that the only logical choice for researchers is to do their absolute best to produce accurate results. Eliminating the profit motive also eliminates both the most immediate benefit of doing good work and the long-term cost of doing poor work.

Furthermore, there is no evidence to support the notion that reducing or eliminating financial incentives in research will prevent the rare shortsighted researcher from sacrificing long-term goals for short-term gains. First, not all research mistakes are intentional, and second, financial gain is not the only factor that could motivate an unwise choice. Alternative negative influences—such as ambition, fear of failure, a need for job security, or glory seeking—all can just as easily contribute to shortsighted errors in judgment.

Policies that restrict industry-sponsored clinical trials will slow the development of medical advances that could dramatically improve the lives of millions—and they would do so without any clear evidence that reduction or elimination of financial incentives will prevent the tragic incidents that anti-industry activists often cite. The real threat to social well-being is not financial relationships between industry and biomedical research, but the proposed restrictions on industry-sponsored clinical trials.

Many criticisms of industry-supported biomedical research are based on factual mistakes and erroneous arguments. A few recent notorious cases have lent the movement for restrictions on industry-sponsored research an air of urgency, but a more level-headed approach and thorough analysis indicates that such regulation is unjustified and potentially very harmful.

The Tragedies Are Real, but the Proposed Solutions Are a Dangerous Stab in the Dark

There are a few notorious cases in which financial conflicts of interests may have played a role in research-related misconduct. Examples include the cases of patients at the Fred Hutchinson Cancer Center in Seattle,

consumers of the painkiller Vioxx, and a gene therapy test subject named Jesse Gelsinger at the University of Pennsylvania. These and a few other similar cases are often cited as grounds for limiting industry sponsorship of clinical trials. Yet, when reviewing the facts of these isolated cases, it is impossible to say whether financial interests were partially, let alone principally, to blame for these incidents.

Fred Hutchinson Cancer Center

In 2001, a scientist and former employee of the Fred Hutchinson Cancer Center in Seattle wrote to federal and state regulators and to members of Congress, telling them that researchers at the Center had failed to fully warn patients of the risks of two experimental cancer treatment drugs they tested during the 1980s and 1990s.² Both the Center and several of its top researchers had financial interests in the tested drugs. Most patients who participated in the trials died, including some who may have survived with more conventional treatment. The Food and Drug Administration (FDA) temporarily halted some of the Center's other ongoing experiments, and the families of several patients sued, citing "systemic problems" in the Center's approach to clinical trials as part of their claims.

In response to FDA demands, the Center created an independent committee, comprised of community leaders and patients or family members of patients, to review its practices. The Patient Protection Oversight Committee (PPOC),³ as it was called, recommended that the Center's board adopt what would become the nation's toughest bans on financial interests for clinical trials.⁴ The PPOC's new conflict-of-interest policy prohibited researchers from owning stock or receiving payments arising from intellectual property interests that directly and significantly related to any clinical trial in which researchers were involved.⁵

Vioxx

In September 2004, the arthritis drug Vioxx was voluntarily withdrawn from the market by its developer, Merck. Pre-market clinical trials did not indicate any reason for concern, but five years after its commercial introduction, post-market testing indicated a significant risk of heart disease, strokes, and even death arising from long-term use of the drug.⁶ Millions of patients depended upon Vioxx for relief of their arthritis symptoms (92.8 million Vioxx prescriptions were filled between 1999 and 2003).⁷ So, when the FDA reviewed the situation, it decided that Merck could continue marketing Vioxx, but with an added black box

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warning. However, after further consideration Merck decided on its own to withdraw Vioxx from the market.⁸

Most Vioxx investigations focused on whether warning potential users of the risk of serious side effects such as heart disease and strokes provided sufficient protections or whether it was necessary to pull the drug off the market altogether. Clinical trials are done on a sample of potential users. Therefore, while common side effects are likely to surface even in a small sample of patients, sometimes rare side effects may not surface at all or only in statistically insignificant numbers. Unfortunately, Vioxx's dangerous side effects only became evident once there were hundreds of thousands of users. Critics seem to suggest that Merck put its desire for profits ahead of patient safety, but that allegation is difficult to support. Did Merck initially hesitate to take Vioxx off the market because doing so would mean the end of a profitable product? Very likely yes. But Merck did take Vioxx off the market despite the FDA's determination that an added warning would suffice, probably because Merck felt an obligation to its customers and because it feared costly lawsuits.⁹

Jesse Gelsinger

The unfortunate death of 18-year-old Jesse Gelsinger during a gene-therapy experiment at the University of Pennsylvania put an end to most gene-therapy research in the United States. In 1999, Jesse, who had a rare, genetic metabolic disorder, volunteered for an experimental gene therapy knowing there was not much chance that the treatment could help him personally, but that the knowledge gained from the experiment had the potential to help future generations of children born with the same disorder.¹⁰ During litigation over Jesse's death, it was discovered that principal investigator Dr. James Wilson and the University of Pennsylvania both held stock in Genovo, the study's sponsor.¹¹ Critics were quick to blame the errors in judgment that took place during Jesse's care on the financial interests that Wilson and the University had in Genovo. However, the Gelsinger case involved so many different potential conflicts of interest that it is impossible to know which, if any, contributed to Jesse's tragic death.

While it is possible that shortsighted greed clouded the judgment of Jesse's physicians, it is equally plausible that their eagerness to advance medical research caused them to undervalue the danger to Jesse. Jesse's father, in his wrongful death lawsuit, claimed there was insufficient informed consent because researchers failed to mention that in mouse

trials several of the mice had died, and that as a result Jesse and his family were under the false impression that the trials were safer than they actually were.¹² There were also questions regarding whether Jesse was healthy enough to undergo the trial in the first place and whether researchers reacted too slowly once there were indications that Jesse was having a bad reaction to the gene therapy.¹³ All these complicating factors are tied to what is commonly called the “therapeutic misconception”—a situation in which there is a clear conflict between the obligation researchers owe to society (to learn as much as possible from their research) and the obligation physicians owe to their patients—that is, their therapeutic obligation to put the patient’s well being first, even if doing so means stopping experimental treatment before any useful information is obtained.

One final set of potential non-financial conflicts of interest that may have clouded the judgment of researchers was the desire for success in the pursuit of cutting-edge research, and the prestige, fame, and renown inherent in such an enterprise. Ultimately, it is impossible to say whether financial conflicts of interests, non-financial conflicts of interests, the inherent risks associated with experimental gene-therapy, some combination of these, or other factors, caused Jesse’s death.

Critics of the profit motive used the fear and anger the public felt at hearing about these tragic incidents to make a case for curtailing industry-sponsored clinical trials. The next section assesses some of their proposed solutions, all of which would do more harm than good.

The Public Outcry for Change is Met by Suggestions for Counterproductive Regulation

Careful and well-reasoned solutions are not only a scholarly imperative, but also the only approach that is truly in the public interest. Nonetheless, industry critics hastily present solutions for curtailing financial conflicts of interest that range from increased regulation and oversight of industry-sponsored trials to a total prohibition of industry sponsorship. Critics have also disparaged medical journal publication of research results based on industry-funded trials, proposed limits on corporate sponsorship of university research centers, and recommended that clinical trials be totally funded and run by government.

The most common suggestion is to limit corporate sponsorship of university research centers. One critic, University of Michigan law professor Rebecca Eisenberg, argues that potential financial gain from

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innovations will cause researchers to suppress research results that might displease their corporate sponsors.¹⁴ According to Eisenberg, “These outside funds often come with strings attached, and such externally funded academic research can threaten academic values by distorting the viewpoints, claims, and research agendas of scholars and by insisting that research results be kept secret.”¹⁵ Eisenberg and other such critics suggest that regulations should at least require a demonstration of legitimate justification for financial relationships between universities and industry, and some propose a total prohibition of financial ties.¹⁶ For example, Howard Brody, director of the Institute for Medical Humanities at the University of Texas Medical Branch, in his book, *Hooked*, envisions a future where, “The funding of clinical trials will have been taken in part or in whole out of the hands of the drug firms, so that physician-investigators who want research money will no longer feel beholden to individual companies for their support.”¹⁷

In her book *Riding the Green Wave*, Patricia Tereskerz of the University of Virginia Health System proposes allowing industry to continue paying for clinical testing but otherwise removing it from the process by preventing industry from having any role in choosing researchers or exercising any oversight of trials.¹⁸ Tereskerz, argues for the establishment of “a U.S. government research brokerage firm or clearing house” that would “rank all the proposals for new drugs it receives, based on scientific merit” and then decide which investigators would be granted the privilege of doing the necessary clinical trials at the company’s expense. Funding for the government clearing house would come from a “required indirect cost rate added to all study budgets.”¹⁹

And, finally, Dr. Marcia Angell, professor at Harvard Medical School and a former editor of the *New England Journal of Medicine*, in her book *The Truth About Drug Companies*, proposes an Institute for Prescription Drug Trials to be established within the National Institutes of Health (NIH) to administer clinical trials for all prescription drugs.²⁰ Angell has gone so far as to advocate a ban on industry-sponsored clinical trials, arguing that, “Drug companies should no longer be permitted to control the clinical testing of their own drugs.”²¹

If the ideal of banning all industry sponsorship of clinical trials cannot be achieved, Angell suggests that the financial ties between industry and researchers should at least be heavily regulated. In a speech at NIH, Angell suggested that at least six areas of regulation are needed.²²

1. Those medical investigators who receive grant support from industry should have no other financial ties to those companies (particularly, no equity stakes in those companies).
2. Investigators should design and analyze their own studies, write their own papers, and decide about publication on their own without industry input.
3. Consultancy arrangements, in which academic researchers are indirectly paid for “pro-industry” research, should be carefully limited. Angell believes that consultancies in academic medicine are virtually ubiquitous because they are more about income supplementation—and the goodwill that money generates—than about technology transfer. Income from limited consulting might instead go to a pool earmarked to support the mission of the institution.
4. Institutions should not become outposts for industry by allowing investor-owned companies to set up teaching or research centers in their hospitals or by giving them access to students, house officers, and patients.
5. Research institutions and senior officials should have no investments in the health care industry.
6. Educational institutions need to collaborate on this issue and develop a common policy.

While serious movement towards implementing some of these suggestions has only gained momentum recently, the underlying demonization of the profit motive is already affecting how research is conducted in the United States. Researchers are having second thoughts about availing themselves of financial incentives because their integrity is automatically questioned simply for engaging in industry-sponsored clinical trials—regardless of whether or not there is any evidence of wrong doing. Even as mild a requirement as disclosure of financial ties can hinder progress because of the unfounded belief that such ties compromise a researcher’s objectivity.

Organizations like the International Committee of Medical Journal Editors (ICMJE), which consists of approximately 700 medical journal members, have succumbed to anti-profit sentiments and developed manuscript submission requirements that include financial conflict of interest disclosures for authors, editors, and reviewers.²³ One ICMJE

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member, Arthur Schafer, suggests that the best strategy for mitigating the problem of increasingly close ties between research universities and the corporate world is the outright elimination of corporate sponsorship, and he argues that reputable medical journals should cease publishing articles that report on clinical research findings performed with private industry dollars.²⁴

The Government Response

Regulation of the pharmaceutical industry is nothing new, but until relatively recently, laws concentrated more on adequate testing and labeling than the regulation of research itself. The Pure Food and Drug Act of 1906 gave the government control over the labeling of drugs.²⁵ The Federal Food Drug and Cosmetic Act of 1938 (FFDCA) gave the FDA authority to oversee the safety of food, drugs and cosmetics. And the creation of the National Institutes of Health in 1930 and the National Science Foundation in 1950 gave the federal government a sustained role in funding and conducting basic science research.

By the late 1970s, the federal and state governments provided billions of dollars annually to fund basic research by public-sector and university-based scientists, but there were few incentives to encourage academic researchers to share their findings with those in industry who could turn the basic science into marketable technologies and realize their public utility. That recognition led to passage of the Bayh-Dole Act in 1980.²⁶ Its purpose was to encourage academic institutions to pursue patents for federally funded research and to license their inventions to private firms for commercialization.²⁷ The Act recognized the crucial role that industry plays in turning scientific discoveries into usable products, and it established a mechanism to facilitate the commercialization of federally funded research.²⁸

Now that trend is reversing. In the last few years, the number of guidelines and regulations promulgated or proposed that seek to curb financial incentives has increased exponentially. For example, in 2005, the National Institutes of Health introduced stringent new ethics rules that prohibit certain employees from engaging in consulting arrangements with, or accepting research grants from, pharmaceutical and biotechnology companies, and prohibit employees and their spouses from owning stock in those companies.²⁹ And in 2007, President George W. Bush signed into law the Food and Drug Administration Amendments Act of 2007 (FDAAA), which gives the Secretary of Health and Human Services (HHS) authority to regulate financial conflicts of interest—specifically

those in government-run review boards, but also potentially those that could arise in industry-sponsored clinical trials.³⁰

In May 2004, the HHS Office for Human Research Protections promulgated guidelines governing financial relationships and conflicts of interest in research involving human subjects. These guidelines include a recommendation for universities to establish conflict of interest committees.³¹ Similarly, HHS regulations issued in May 2009, which are intended to promote objectivity in research supported by the Department's Public Health Service (PHS),³² and establish standards to ensure that the design, conduct, or reporting of research funded under PHS grants or cooperative agreements are not biased by any conflicting financial interest of an investigator.³³ Also in May 2009, the NIH issued an Advanced Notice of Proposed Rule Making (ANPRM) and a request for comments concerning the responsibility of applicants for promoting research objectivity related to certain government-funded projects.³⁴ The proposed rules would require grantees to provide assurances that their institutions have policies to address conflicts that arise due to industry financial support.³⁵ The ANPRM discusses the need to expand the scope of the regulation of financial ties to industry,³⁶ and raises the question of whether all financial interests should be disclosed, in contrast to current regulations that require disclosure only when the dollar amount involved reaches a certain level.³⁷

Despite this flurry of activity, more efforts to curtail industry sponsorship of clinical trials are in the works. The results of the 2008 presidential and congressional elections emboldened critics of the profit motive, and Congress has been flooded with new proposals to curb industry-sponsored clinical trials. Even the 2009 stimulus bill (known officially as the American Recovery and Reinvestment Act) contains measures that would address how medical products research is conducted in the United States.³⁸ A June 2009 Institute of Medicine report, which was mandated by the Act, suggests that Congress and HHS develop infrastructure to carry out national Comparative Effectiveness Research (CER),³⁹ which is intended to test the relative effectiveness of different forms of treatment.⁴⁰ On April 2, 2009, HHS Secretary Kathleen Sebelius told the Senate Finance Committee, during her confirmation hearing, that CER is necessary to curb the profit motive in medicine.⁴¹ And Sens. Max Baucus (D-Mont.) and Kent Conrad (D-N.D.) have made it clear that they consider excluding private companies from follow-up research on the effectiveness of approved products to be the best way to ensure the

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integrity of clinical trials. The Patient-Centered Outcomes Research Act of 2009, which Baucus and Conrad introduced in June 2009, would establish a “private, nonprofit corporation, called the Patient-Centered Outcomes Research Institute, to generate scientific evidence and new information on how diseases, disorders and other health conditions can be treated to achieve the best clinical outcome for patients.”⁴²

Representatives in the House have also taken action to curb industry-sponsored clinical trials. Rep. Diana DeGette (D-Colo.) has introduced the Protection for Participants in Research Act of 2009, to help harmonize all clinical trials, and, among other things, require the Secretary of Health and Human Services to review the differences that exist in how the private and public sectors control financial conflicts of interest in clinical trials.⁴³ It seems unlikely that the “harmonizing” Rep. DeGette has in mind is to make the public sector more like the private by increasing the financial incentives for successful clinical trials.

The Evidence and Arguments Provided for these “Solutions” Are Flawed

In a rush to stave off future tragedies, policy makers have accepted poor arguments and weak evidence to support limitations on industry funding of clinical research. We surveyed over 100 articles and dozens of books and studies and found none that could serve as an adequate foundation either for the types of regulatory proposals described above or for already existing regulatory restrictions on industry-sponsored clinical trials. Nor did we find any proof that such restrictions have had any positive impact.

The main deficiencies in arguments for regulating industry-sponsored research fall into three categories:

1. Some authors hold their conclusions to be self-evident and without need for evidentiary support;⁴⁴
2. Some openly assume certain facts;⁴⁵ and
3. Others are quite forthright about the lack of evidence, but nevertheless go on to make very specific suggestions.⁴⁶

For example, Justin Bekelman, Yan Li, and Cary Gross, of the Yale University School of Medicine, admit that, “Despite the prevalence of these [conflict of interest] relationships and the broad concerns they have generated, a relative paucity of data has been published describing the impact of financial ties on biomedical research.”⁴⁷ Several studies note that industry support of clinical trials is common, but those studies

do not show any correlation between financial support and inappropriate conduct.⁴⁸ The authors just assume that the mere existence of financial ties will increase the instances of research misconduct and therefore allow a greater number of substandard drugs on the market.⁴⁹

One recent study published in the *Journal of the American Medical Association* found that nearly two-thirds of academic leaders and researchers surveyed at U.S. medical schools and teaching hospitals have financial ties to the pharmaceutical or medical-device industry.⁵⁰ The authors offered this finding as an indication of pervasive wrongdoing without any evidence that financial ties had led to actual misconduct. This argument assumes, without any proof, as though it were self-evident, that any scientist who takes monetary considerations into account must be corrupt.

For a study to show that there is a significant causal connection between financial interests and researcher misconduct, it would have to find a way to control for other types of biased motivations that could possibly lead to misconduct, such as ambition, glory-seeking, a desire for more respect, or higher academic standing. But no researchers have tried to account for these other conflicts. These errors in evidence and argument are compounded by conceptual errors. The most obvious are those that assume causal connections where they do not exist, but others involve confusing foresight for bias and grossly underestimate the value of the profit motive.

Errors of Causation

Errors of causation are the most common mistakes in reasoning made by proponents of limiting industry-sponsored clinical trials. One error is to assume correlation implies causation, or what logicians call the *post hoc ergo propter hoc* fallacy. Thus, it is a mistake in reasoning to assume that financial incentives cause conflicts of interest simply because they are present or that the mere existence of conflicts of interest causes biased results. It is further mistaken to assume that biased results necessarily result in dangerous outcomes or that the number of bad outcomes that actually can be attributed to financial conflicts of interest is significant enough to justify restricting industry-supported clinical trials.

Another error of causation is known as the fallacy of complex causes. This is based on the assumption that one of many possible causes is the *necessary and sufficient* cause of the bad outcome one seeks to avoid. Conflicts of interest can have many causes, such as a researcher's desire to spend more time doing things other than research (thus neglecting

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his research), ambition, glory-seeking, a desire for academic standing, or professional recognition by one's peers. Any one of these factors, or a combination of them, may exist alongside a possible financial conflict of interest, making it impossible to know whether the financial conflict caused the undesirable outcome.

Bias or Foresight

Some conflict-of-interest studies have seized upon the fact that a higher proportion of industry-sponsored than non-industry-sponsored clinical trials show a positive outcome for the drugs being studied as evidence of researcher bias.⁵¹ However, the higher occurrence of positive outcomes may have more to do with foresight than with bias. Company executives are not interested in spending their firm's money on pure science for science's sake. They are interested in results and are most valuable to their employers if they have a knack for choosing to test drugs that are likely to be found safe and effective. Likewise, they have good reason to stop trials on drugs that are not likely to succeed. The existence of this valuable form of foresight says nothing about the integrity or bias of the scientists doing the clinical trials. It is in company executives' best interest to have thorough, reliable research so they can pull the plug as early as possible on any drug that may cause problems down the road.

It is also worth noting that government-sponsored clinical trials are not immune to conflicts of interest,⁵² as government funding may give rise to similar types of bias. Consider the need to control costs as an example. It could lead to a government-funded study being biased to show that the least expensive drug for a given indication is as good as a costlier alternative,⁵³ or that the life-extending potential of an expensive drug is low.

It may not be easy to design a study that measures both potential negative and positive effects of industry involvement in clinical trials, but it is intellectually dishonest to disregard potential benefits simply because they may be hard to quantify. In fact, a study conducted by NIH researcher Lindsay A. Hampson and her colleagues that focused on the clinical trial volunteer's perspective of this conflict, found that more than 90 percent of patients in cancer trials expressed little or no worry about financial relationships between researchers or their institutions and industry partners.⁵⁴ They noted that, "[P]atients trusted their physicians and, moreover, viewed ties with industry as a positive factor in enabling the physicians to provide access to the newest treatments."⁵⁵

The Profit Motive

When critics disparage the “profit motive” to discredit industry-sponsored research, they ignore the fact that, without industry funded research, many advances in disease prevention and treatment would never occur.⁵⁶

The Bayh-Dole Act recognizes that public-sector researchers are not well suited to developing marketable products from basic research. Public funding of pure science permits researchers to explore basic observations of nature, such as the relationship between genetics and disease, free from the need to produce marketable products that can justify high research costs. However, the profit motive’s existence in private sector research provides an incentive for investors to supply the even larger financial resources needed for developing new medicines and medical devices, while giving the researchers themselves appropriate incentive to spend those sums on activities most likely to yield products consumers value enough to pay for.⁵⁷ The discovery of new medications, devices, and techniques is therefore funded primarily by for-profit companies, as is the testing of new modalities of treatment.⁵⁸ According to a Congressional Budget Office study, the pharmaceutical industry spent an estimated \$49 billion on research and development in 2004, compared with total federal health-related research expenditures of just \$25 billion in 2005.⁵⁹ Lee Goldman, chairman of the Department of Medicine at the University of California at San Francisco, explains, “Companies translate biological advances into useable products for patients. They do it for a profit motive, but they do it, and it needs to be done.”⁶⁰

In fact, our very economic system rests on the principle that financial interests lead to good decisions.⁶¹ Financial interests motivate employees to do a good job. Employees who provide substandard service damage both their reputations and the reputations of their employers. Business owners who encourage employees to misrepresent the safety of their products are equally guilty of consumer fraud whether the product is a car or a drug. And any employee or company executive who cooks the books for whatever reason risks criminal penalties and substantial tort liability.

Researchers and pharmaceutical companies face similar motivations and constraints on their conduct. If a drug is not going to be safe and effective, or has a significant chance of posing risks that outweigh its health-enhancing benefits, the sooner the project is abandoned the better. The product, even if it is approved, is either going to give the company a bad name because it is ineffective or result in litigation because of adverse side effects.⁶²

When critics disparage the “profit motive” to discredit industry-sponsored research, they ignore the fact that, without industry funded research, many advances in disease prevention and treatment would never occur.

Slowing the development of useful, but potentially dangerous, medications allows time for latent adverse effects to surface, but it also prevents them from helping those whose lives could be improved or saved.

Consider the case of the generic drug manufacturer Able Laboratories. After the FDA raised questions about the quality control over the data Able used to obtain approval for its drugs, Able had to withdraw every one of its products from the market and eventually dissolve its entire business, even though the errors discovered never endangered any customers.⁶³ In the words of Roger J. Porter, former Deputy Director of the National Institute of Neurological Disorders and Strokes at the National Institutes of Health, whether misrepresentations are intentional or not, the “truth will out.”⁶⁴ One way or another, companies that fail to discover the limitations of their products will pay the consequences.

It is worth noting that financial conflicts of interest are more easily identified, measured, and controlled, than other types of conflicts of interest, regardless of whether they are more or less likely to contribute to either good or bad outcomes.⁶⁵ This makes financial conflict of interest an easy scapegoat for many unfortunate mishaps that have their origins in a more complex set of factors that is more difficult to identify and control. But, while limiting industry-sponsored clinical trials is likely to do little or nothing to reduce the number of adverse drug reactions, it may inadvertently reduce the supply of life-saving drugs, since seventy percent of all money spent on drug research and development in the United States is privately funded,⁶⁶ and almost two-thirds of all clinical trials are sponsored by industry.⁶⁷

The Costs of Stifling Innovation

Regulating drug development to prevent dangerous adverse events may be closer to a zero-sum game than many people think. New drugs are developed to save and improve lives, but they also entail inherent risks that can harm those they are intended to help. Slowing the development of useful, but potentially dangerous, medications allows time for latent adverse effects to surface, but it also prevents them from helping those whose lives could be improved or saved. In a speech before Congress on May 9, 2007, the late Sen. Edward Kennedy (D-Mass.) noted that, “Every day that a new medicine is needlessly delayed is another day that a patient does not receive a treatment that could well mean the difference between health and continued illness.”⁶⁸

One study by Harvard and MIT researchers examining the benefits of hypertension treatments reported that high blood pressure medicines prevented 86,000 premature deaths in 2001 and 833,000 hospitalizations for heart attack and stroke in 2002. The study estimated that antihypertensive

medicines, when used correctly, could prevent 89,000 additional deaths annually and avoid 420,000 additional hospitalizations.⁶⁹ Even when the negative outcomes associated with drugs eventually taken off the market are expressly factored in, the benefits of medical innovation are still tremendous. A study published by the National Bureau of Economic Research (NBER) looked at all 662 drugs approved by FDA from 1979 to 2002 and concluded that, even if every withdrawn drug provided no benefits at all, the faster pace of approvals spurred by FDA reforms of the early 1990s benefited patients with an extra 180,000 to 310,000 years of life—three to five times greater than the worst case estimate of harms.⁷⁰ And another NBER study published in 2003 attributes a 40-percent increase in worldwide life expectancy between 1982 and 2001 to drug innovations. How many more lives might have been saved if these drugs had become available days, weeks, months, or even years earlier? Undoubtedly learning about and preventing adverse events saved lives, but those lives were saved at the expense of others that were not saved or improved.

Banning or heavily curtailing industry-sponsored clinical trials will have as many potential negative consequences as good ones, so it would be foolish to only consider the potential benefits of such policies. It simply does not follow that all researchers and industry sponsors should be restricted in conducting clinical trials because of the short-sightedness of a few, particularly if doing so stifles innovation leading to new drugs that are beneficial to the population at large.

Conclusion

Regulations designed to prevent conflicts of interests through the regulation of financial ties between industry and researchers are misguided and likely to hinder rather than promote patient well being. This is true of such policies whether they are existing disclosure requirements or more aggressive proposals to make certain types of clinical trials the purview of government or an outright ban on industry-sponsored clinical trials, as suggested by professors Brody, Tereskerz, and Angell.

A careful analysis of the facts and arguments for and against restricting industry-sponsored clinical trials suggests that regulators should be moving in a totally different direction than they are now. While not an easy fix, educating people about drug development, clinical trials, risks, and benefits, as well as figuring out ways to increase compliance with medical instructions, are likely to go much further towards reducing adverse reactions to medications than trying to eliminate conflicts of

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interest.

Harsh punishments for fraud in research should remain the rule, but patients and those who care for them also need to learn to take more responsibility—that is, they need to ask questions rather than assume physicians and researchers will see risks and benefits the same way they do. Some of these possible solutions may be better than others, but one thing seems certain—further limiting industry sponsorship of clinical trials is not the solution. To discourage financial incentives in research is to strangle the proverbial goose that lays the medical golden egg.

Notes

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About the Authors

Sigrid Fry-Revere is the founder and president of the non-partisan Center for Ethical Solutions, a 501(c)(3) nonprofit organization devoted to educating the public on ethical issues in medicine. Prior to starting the Center, Fry-Revere was the director of bioethics studies at the Cato Institute. She has taught bioethics and law at the university level, been a consultant to hospitals, hospices and home health agencies, and practiced health and FDA law. Fry-Revere has published more than 100 articles in newspapers, journals and trade publications such as the *New York Times*, *Los Angeles Times*, *Wall Street Journal*, *Cambridge Quarterly of Healthcare Ethics*, *Journal of Clinical Ethics*, *Pediatric Nursing*, and *Genetic Engineering News*. She has also written a book and edited another on bioethics consultation. Fry-Revere holds a Ph.D. in philosophy and a law degree, both from Georgetown University.

Alison Mathey is a third-year law student at the Catholic University of America, Columbus School of Law. She graduated cum laude from the College William and Mary in 2007. Mathey is the Preemption Editor of the *Journal of Contemporary Health Law and Policy* at the Columbus School of Law. She is also editor of *Legal Trends in Bioethics*, published by the Center for Ethical Solutions. Mathey has recently interned at organizations such as the American Association for Retired Persons and the National Council on Aging.

David Malmstrom is currently a constitutional law fellow at the Institute for Justice in Seattle, Washington. He received his juris doctor. from George Mason University School of Law and his bachelor of arts in international relations magna cum laude from Florida International University. He is co-author, with Sigrid Fry-Revere, of an earlier version of this study, “More Regulation of Industry-Supported Biomedical Research: Are We Asking the Right Questions?” which was published by the *Journal of Law, Medicine and Ethics* in 2009. Before co-authoring this paper, he worked with Fry-Revere at the Cato Institute in Washington, D.C.

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