From Bench to Bedside: Impact of Conflict-of-Interest Restrictions at Academic Medical Centers on Clinical Trials

By

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SUBMITTED TO THE HARVARD-MIT DIVISION OF HEALTH SCIENCES AND TECHNOLOGY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER IN HEALTH SCIENCES AND TECHNOLOGY

At the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

September 2012

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Abstract

Successful translation of scientific discovery into new medicines is most successful with collaboration between academics – scientists and physicians – and industry. In recent years, there has been increasing concern at academic medical centers about the impact of relationships with industry on patient care and student education. This has generally resulted in more stringent conflict-of-interest rules. This paper seeks to better understand the impact of these conflict-of-interest rules. In the first part, it explores research to-date on the importance of relationships between industry and academia and discusses some of the concerns that have arisen. In the second part, this relationship is better characterized with clinical trial data. The findings suggest that there is a strong trend towards schools with higher conflict-of-interest rules having fewer clinical trials. This suggests that although there may be benefits to stricter regulation, there are trade-offs in terms of clinical translation.

Acknowledgements

First, I would like to thank my advisors, Prof. Fiona Murray and Prof. Anthony Sinskey, for their guidance and support throughout this process. I would also like to thank Julian Kolev for his assistance with the statistical analysis, and Paul Lapinski for his help in converting the xml files to xls.

Furthermore, I'd like to extend my deep gratitude to Prof. Martha Gray and the Harvard-MIT Health Sciences and Technology IDEA^2 program for their generous support. I am very grateful to my many catalysts, including Dr. Stossel, Paul Citron, Sandy Bodner, Adrian Gottschalk, Mehmet Toner and Genevieve Pham-Kanter for all their insight and advice.

In addition, I would like to thank Ryan Coelhepp at Millennium Pharmaceuticals and Bhavesh Ashar at Sanofi for giving me the opportunity to intern, and gain insight from an industry perspective into running clinical trials and interacting with medical professionals.

Finally, my thesis would not have been possible without the support of my friends and family. I would like to thank my wonderful friends Mike Belinsky and Laura Quinby and my parents, without whom I would not have been able to complete this.

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1. Introduction

In the healthcare industry, progress in finding new treatments is spurred by close collaboration between industry, and academia. Unfortunately, such arrangements can create conflicts-of-interest. As a consequence, numerous entities, including academic medical centers, states, and government and physician bodies have stated and implemented guidance to restrict the interaction of industry representatives with physicians.

This paper evaluates the impact of conflict-of-interest (COI) restrictions at academic medical centers (AMCs) on innovation in the life sciences, as measured by clinical trials. Informing the controversy regarding conflict-of-interest, I analyze whether and to what extent these policies influence the translation of research into the clinic.

1.1 History of Industry Collaborations with Academia

It is important to recognize that industry and academic institutions have a long history, with both sides recognizing that close industry-academic ties facilitate translation of scientific research into clinical innovations. For instance, in the 1920s Eli Lilly worked with academics at the University of Toronto to manufacture insulin; the university then issued royalty-free patents to other companies to extend the drug's availability (NRC).

These interactions were spurred by the Bayh-Dole Act of 1980 and the birth of biotechnology in the 1990s. In the 1990s, industry ties were widespread, with one study finding that 60% of department chairs at academic medical centers had relationships with industry (usually serving as a consultant or member of an advisory board) (Blumenthal 1996). A survey among faculty in the 50 most research intensive universities found that 28% of respondents received some research support from industrial sources, and 43% received research related gifts independent of research grants. Likewise, senior administrators and academic leaders often have

financial interest in companies whose products and services are related to their responsibilities (Campbell 2004a).

Universities have been increasing their commercial activities. From 1991 to 2000 universities became more active in commercializing technology, with patent applications and licenses approximately tripling (from 1,033 patents to 3,643, and 907 licenses to 2,343). (Campbell 2004b) From 1976 to 2003, the number of patents granted to medical faculty increased from 122 to 2,175, and the share of medical patents out of all patents increased from 29% to 53% (Azoulay 2007). Universities with a technology transfer office increased from 25 in 1980 to 200 in 1990, and by 2000 "virtually every US university had such an office" (Bulut and Moschini 2006).

Concurrently, the share of industry funding relative to government funding has been increasing, from 27 percent in 1999 to 43 percent in 2002 (White 2007). In the early 1990s, more than 90 percent of life science companies paid for a service rendered by a university, usually via consulting agreements with faculty. More than half also sponsored research projects. Blumenthal et al. estimated that the life science industry spent more than $1.5 billion on over 6,000 research projects in 1994, out of a total of $12.8 billion in funding (11.7 percent) (Blumenthal 1996). A search of registered drug trials in 2010 found that 63% were primarily funded by industry (Bourgeois 2010).

While concerns about medical marketing are not new (e.g. when Merck's Manual of the Materia Medica was published in 1899 one reviewer wrote "[a]lthough this little book is gotten out by a manufacturing firm and with some view towards its advertising value, it nonetheless is of such merit that it is deserving of mention" (quoted by Lane and Berkow [1999, p. 112] in

NRC)), the growth of industry academic collaborations have brought heightened scrutiny to their interactions, and potential conflicts of interest created.

"The interest is exponentially more now than it was five years ago, which was exponentially more than it was five years before that."
-- Richard Krugman, who has served as dean of the University of Colorado School of Medicine for 20 years (O'Connor 2010)

1.2 Conflicts of Interest

As physicians have many roles, their interactions with industry can create a number of conflicts-of-interest, or occasions when financial ties might influence their decision making in other areas.

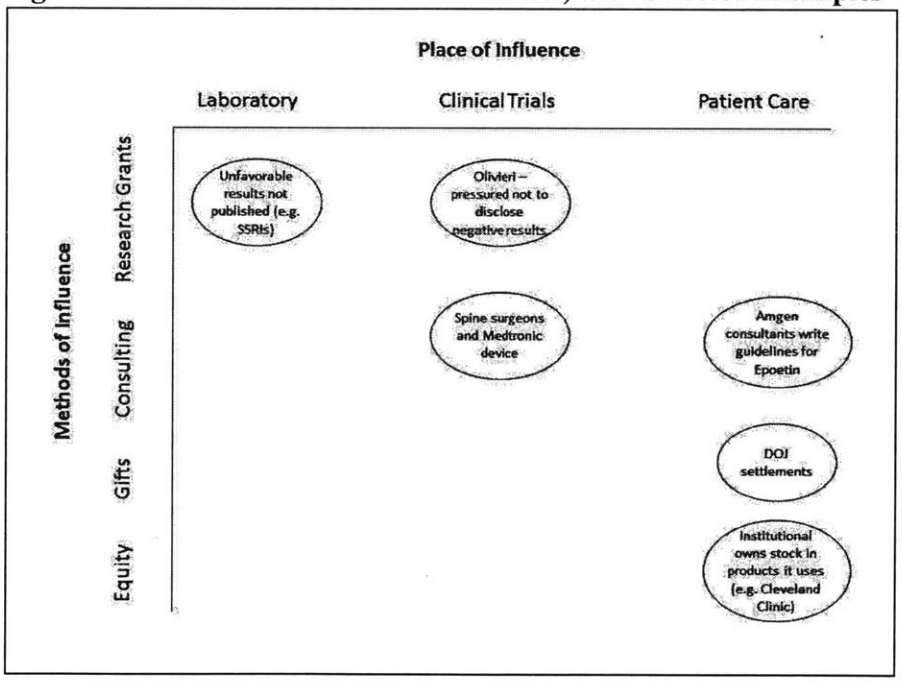
The National Research Council's Conflict of Interest in Medical Research, Education, and Practice lays out the following five forms of conflicts-of-interest:

- **Biomedical Research:** represent the dichotomy between academic openness and industrial secrets; e.g. researchers are discouraged from publishing results by industry sponsors, researchers are accredited to papers they don't spend sufficient time reviewing, or even ghostwrite, etc.
- **Medical Education:** occasions with industry gives gifts (e.g. free lunches) to medical students or continuing medical education, with the risk that physicians feel the need to reciprocate by prescribing their products.
- **Institutional Conflicts of Interest:** gifts given to a medical center by companies (e.g. related to the research conducted there), as well as personal conflicts of interest by senior officials in the administration.

- **Clinical Practice Guidelines:** physicians involved in drafting guidelines have financial ties to industry, perhaps as consultants
- **Patient Care:** legislation on the state level is most concerned with risks of industry involvement impacting patient care. This concern is that physicians will be motivated to prescribe products due to gifts or lucrative contracts.

However, it may be more helpful to conceptualize this as a continuum:

Figure 1: Continuum of Conflict of Interest, with Selected Examples



1.3 Conflict of Interest Regulation

There are many different ways and levels in which the conflicts-of-interest discussed above are regulated, including by industry, government bodies, state and federal legislation and academic medical centers.

Industry

Industry has sought to proactively self-regulate itself. In 2002, the Pharmaceutical Research and Manufacturers of America (PhRMA), which represents research-based pharmaceutical companies, created a Code on Interactions with Healthcare Professionals (to regulate interactions with marketed products and pre-launch activities), and Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results (for interactions with clinical investigators and researchers). The former code was updated and enhanced in 2009 (PhRMA). Likewise, the Medical Device Technology Association (Advamed) created a Code of Ethics on Interactions with Health Care Providers in 2004, and updated it in 2009 (Advamed).

Government Regulation

The National Institutes of Health provide important funding for researchers and clinicians. More stringent conflict-of-interest legislation has been passed by the NIH, requiring that investigators report financial interests over $5,000 to their institution and the institution describes the conflict of interest and how it is addressed to the NIH (Silverman 2011). According to the Office of Management and Budget, the new policy will cost 25% more than the 1995 regulations, and implementing the public disclosure will cost $350,000 (Ledford 2011).

In addition, state legislation of medical marketing began in 1992 in Minnesota, and by 2010 eight states and the District of Columbia have legislation. In addition to state legislation, national legislation was passed with the Affordable Care Act: the Physician Payment Sunshine Act requires that payments over $10 to physicians from manufacturers of pharmaceuticals or medical devices be reported. This collection was supposed to begin January 1, 2012 but has been delayed to at least January 1, 2013 as CMS prepares to implement this. (Sullivan 2012)

Academic Medical Centers

In addition, academic medical centers typically have conflict of interest policies. According to the American Medical Student Association (AMSA) which grades medical schools on their conflict-of-interest policies, as of March 7, 2012, 91% of medical schools have at least some conflict-of-interest policy, and 67% were rated as having model policy or good progress to model policies considering gifts, consulting relationships, speaking relationships, disclosure, pharmaceutical samples, formularies, industry sales reps, educational activities, compensation for travel, scholarships, and medical school curriculum. For example on the sales rep score, to receive a "model policy" score, industry sales representatives (pharmaceuticals and devices) must not be allowed to meet with faculty or market products in an academic medical center (AMSA).

Table 1: Timeline of Events Relevant to Conflict-of-Interest Policies (adapted from NRC)

1906	Pure Food and Drugs Act passed, prohibiting federal commerce in adulterated or misbranded food or drugs (precursor to FDA)	Patient Care
1972	The U.S. Congress passes the first antikickback statute (P.L. 92-603)	Patient Care
1980	Patent and Trademark Amendments of 1980 (P.L. 96-517) (Bayh-Dole Act) and Stevenson-Wydler Technology Innovation Act (P.L. 96-480) encourage the commercial development of federally developed or funded technologies	Biomedical Research
1981	Economic Recovery Tax Act of 1981 (P.L. 97-34) provides a 25 percent tax credit for 65 percent of private investments in universities for basic research	Biomedical Research
1987	U.S. Public Health Services (PHS) issues Grants Policy Statement, which states that grant recipients should have written guidelines on conflict of interest Accreditation Council for Continuing Medical Education (ACCME) adopts Guidelines for Commercial Support (revised and issued as standards in 1992)	Biomedical Research

1990	A U.S. House Committee on Government Operations report (*Are Scientific Misconduct and Conflicts of Interest Hazardous to Our Health*?) recommends the development of PHS regulations that "clearly restrict financial ties for researchers who conduct evaluations of a product or treatment in which they have a vested interest" Association of American Medical Colleges publishes *Guidelines for Dealing with Faculty Conflicts of Commitment and Conflicts of Interest in Research* American Medical Association (AMA) adopts statement on inappropriate gifts to physicians from industry American College of Physicians issues a position paper on physicians and the pharmaceutical industry.	Biomedical Research
1993	Minnesota law limits drug company gifts to physicians and requires company disclosure of payments to physicians (excluding drug samples and educational materials)	Patient Care
1995	U.S. Department of Health and Human Services Investigator Financial Disclosure Policy takes effect,"to help ensure the appropriate management of actual or potential conflicts". This require that institutions receive NSF and NIH funding maintain a policy on conflict-of-interest, which include financial disclosure and enforcement mechanisms. (NSF, Sullivan 2011)	Biomedical Research
1999	The death of Jesse Gelsinger in a gene transfer experiment provokes controversy after it is revealed that the principal investigator and his university had ownership interests in the company making the interventional product	Institutional; Biomedical Research
2001	ICMJE publishes new, more stringent policies on conflict of interest, requiring that authors on trials to sign a statement accepting full responsibility for the trial and describing the role taken by the sponsor as well as the author. (Davidoff)	Biomedical Research
	Vermont requires pharmaceutical companies to disclose payments to doctors and certain health care organizations related to marketing activities	Patient Care
	To promote adherence to its ethical guidelines, AMA, with funding from industry, initiates the campaign "What you should know about gifts to physicians from industry"	Patient Care
2004	The U.S. Congress questions NIH about the apparent failure of dozens of employees to disclose relationships with industry	Biomedical Research
	NIH issues stringent new policies for employees and later moderates them; HHS issues final guidance to institutional review boards on financial relationships in clinical trials	Biomedical Research; Patient Care
	Maine and West Virginia both require pharmaceutical companies to disclose advertising and marketing costs	Patient Care
2005	California passes Comprehensive Compliance Program, requiring pharmaceutical companies to specify a maximum	Patient Care

	marketing expenditure per physician, and disclose costs of all marketing activities.	
2007	The U.S. Department of Justice announces deferred prosecution or nonprosecution agreements that allow five orthopedic device companies to avoid criminal prosecution for providing financial inducements for surgeons to use their products.	Patient Care
	Nevada passes Marketing Code of Conduct Law, which requires pharmaceutical manufacturers to accept a Code of Conduct, including disclosure of marketing expenses.	Patient Care
2008	The Pharmaceutical Research and Manufacturers of America releases revised *Code on Interactions with Healthcare Professionals* and recommends an end to some gift-giving practices	Patient Care
	The Advanced Medical Technology Association issues revised *Code of Ethics*	Patient Care
	Massachusetts limits gifts and payments to physicians from pharmaceutical and device companies and requires companies to publicly disclose certain payments	Patient Care
	Washington DC requires pharmaceutical representatives to be licensed, and implements punishments for misleading marketing.	Patient Care
2009	Federal legislation proposed to require disclosure of company payments to physicians and others and reporting of physician ownership interests in health care facilities	Patient Care
	Vermont extended its previous disclosure legislation to include medical device manufacturers. In addition, it implemented a gift ban.	Patient Care
2010	Physician Payment Sunshine Act requires that payments over $10 to physicians from manufacturers of pharmaceuticals or medical devices be reported (beginning 2013)	Patient Care

2. Debate and Research Question

Conflict-of-interest regulations have lately been a hot topic of debate. Recent arguments have mostly focused around the risks of such relationships. However, there has also been evidence to suggest that such collaborations can create value.

2.1 Risks of Industry-Academic Relationships

The healthcare industry is a big business in the United States. In 2009, the US spent $300 billion on prescription drugs, and another $200 billion in medical devices (Weiss 2010). In addition, these costs have been rising. As the share of GDP devoted to healthcare spending increases, there is growing concern over industry's influence on decision making. In 2004, the pharmaceutical industry spent $7 billion on marketing to physicians (Cardelli 2006); A 2009 article estimated that drug and device manufacturers spent on average about $20,000 per doctor each year in marketing efforts (meals, gifts, travel, consulting fees and CME programs) (Weiss 2010). Consequently, it is not surprising that there is public concern about marketing to physicians. There are some common criticisms of these relationships, discussed in detail below.

Industry funding leads to non-disclosure of negative results:

Industry-sponsored trials are less likely to be published. For instance, Bourgeois found that they were also less likely to have been published within 24 months of study completion (32.4%, compared to 56.2% of nonprofit or nonfederal funded trials without industry collaborators) (Bourgeois 2010). This is a concern, as negative results should be relevant for treating patients. For example, one meta-analysis of SSRIs found them safe and effective; another one that took into account unpublished and published data concluded the opposite. One study found that seven industry-sponsored reviews recommended the experimental drug, while none of the Cochrane Collaboration reviews did. Another found that meta-analysis conducted by individuals with financial ties to a single company were not more likely than other individuals to

have results that favored the sponsor's drug; however, they were more likely to have favorable conclusions (NRC).

Industry-funded trials tend to be more likely to publish positive outcomes (Bourgeois 2010). A study of 332 randomized controlled trials published in 13 journals found that the industry funded trials were more likely to be associated with a pro-industry finding. Another analysis that focused solely on the journal *Spine* found that studies with industry funding were 1.6 times more likely to report positive results than studies with funding from other sources. (White 2007) 1998 study found a strong association between author's positions on calcium-channel antagonists and financial ties to industry. A more recent Canadian study found that "industry-funded trials are more likely to be associated with statistically significant pro-industry findings, both in medical trials and surgical intervention." This has been repeated by several other studies (Caulfield 2007).

In June 2011, The Spine Journal devoted a whole issue to a series of letters by spine specialists publically repudiating research by other experts that backed the use of a Medtronic bone growth product. At the heart of the issue were side effects that emerged in initial trials, which were considered by the FDA during review. However, researchers of studies sponsored by Medtronic after approval claimed these side effects were not seen in their patients (Meier and Wilson).

One famous case involved a company trying to suppress a principal investigator from disclosing negative side effects seen in a study. Dr. Olivieri, a hematologist at the Hospital for Sick Children, ran a clinical trial studying deferiprone for the treatment of thalassemia. After several years of clinical trials, in 1995, she became concerned the drug was not effective; later, she also became concerned that the drug might be causing liver fibrosis in patients. She reported

these concerns to Apotex Inc, the Canadian pharmaceutical manufacturer sponsoring the research, but Apotex disagreed with her conclusions, and felt there was no need to inform patients. Dr. Olivieri informed the Research Ethics Board, and was instructed to revise the existing protocols and consent forms to inform patients of the risk. When Apotex received the revised forms, they stopped the trial and informed Dr. Olivieri that she was not permitted to disclose any information about her trials, as it would violate confidentiality and would make her subject to legal action. This became a highly publicized controversy when it was revealed that Apotex was in discussions with the University of Toronto to make a multimillion dollar donation to the university for the construction of a new biomedical research center and to the teaching hospitals, the largest donation ever received by the university (Baylis). In 1998, Dr. Olivieri published in the New England Journal of Medicine that "deferiprone does not adequately control iron burden in patients with thalassemia and may worsen hepatic fibrosis" (Olivieri 1998).

This issue has continued to be highly controversial, with some arguing that her research was not scientifically sound and that the publicity surrounding it delayed the launch of the drug in the US, with the result of many children's deaths (Shuchman). Deferiprone was approved in August 1999 in Europe, but was not approved in the US until October 2011. The FDA review states that the original NDA was rejected because of issues with "clinical data, clinical pharmacology data, chemistry, manufacturing and control and a failed facility inspection" and recommended that the manufacturer conduct a prospective randomized controlled trial based on their recommendations. This additional multi-center study, along with data from clinical trials performed by independent investigators and peer-reviewed publications, was accepted. The reviewers also state that "The scientific issue of progression or development of hepatic fibrosis with deferiprone use was first raised in a New England Journal of Medicine article in 1998.

However, this finding has not been consistently observed in other published studies. Review of scientific literature reveals that hepatic fibrosis can be observed in the setting of thalassemia with iron overload and/or hepatitis C without use of deferiprone so determining causality in this patient population is difficult. Post-European Union approval, few cases of hepatoxicity have been reported" (FDA review). On the other hand, the Public Citizen's Health Research Group published a letter sent to the FDA on October 2011 (before the NDA was approved), stating that the data "were grossly insufficient and fail to demonstrate that deferiprone is safe and effective in the intended population" (Public Citizen).

Industry funding risks endangering patient care:

Non-disclosure of consulting agreements has raised concerns physicians are improperly prescribing medications due to financial incentives. There have been a number of recent scandals at academic medical centers.

For example, the 1999 death of Jesse Gelsinger at the University of Pennsylvania raised concerns, as the university had officials with financial interests in the company sponsoring the study (NRC). In 2005, the Cleveland Clinic was revealed to own 4.1% of AtriCure, the maker of equipment used in over 1,200 patients in the previous four years (Armstrong 2005). In 2008 a congressional investigation found that a child psychiatrist at Harvard had failed to disclose that he had received $1.6 million in consulting fees over a two-year period from a drug company that made an anti-psychotic he had been prescribing (O'Connor 2010). In the same year the chair of the Psychiatry Department at Emory University resigned after it was revealed that he failed to disclose substantial consulting payments from pharmaceutical companies, violating university

and federal rules (and exceeding university rules that he limit payments) (National Research Council).

Pharmaceutical companies often promote their products by having sales representatives visit physicians. In 2004, about $21 billion was spent on this. Some have argued that these interactions are unnecessary and that companies unduly influence physicians through visits and small gifts; however, others argue that vital information is exchanged. Recently, there has been concern that industry is unduly influencing physicians. In 1998, Roughead et al. stated that "The provision of gifts by sales personnel encourages an automatic response of indebtedness on the part of the receiver who will then look for ways to make repayment" (NRC). One study of 32 academic and community physicians in San Diego, Atlanta and Chicago found that physicians were influenced by sales representatives, and that conflict of interest is created (Chimonas, Brennan and Rothman, 2007 as cited in Chressanthis).

A number of recent scandals have been in the news inappropriate marketing of physician prescribing. Recent DOJ settlements have hit the billion mark.: GlaxoSmithKline agreed recently to pay $3 billion, Pfizer paid $2.3 billion to settle claims on Bextra, Abbott paid $1.5 million, Lilly paid $1.4 billion to settle sales of Zyprexa and Merck paid $950 million and pled guilty to illegally promoting Vioxx (Coffrey and Law, Whistleblower). Many smaller claims have also been in the news recently: Bayer $110 million for Yaz (2012); Warner-Lambert $430 million, for Neurontin (2004); J&J $158M for Risperdal (2012); Orphan Medical Inc. $20 million, for Xyrem (2007); and Merck and Co. Inc. $58 million Vioxx (2008) and $650 million for overcharging Medicaid for three popular drugs. The DOJ accused the companies of paying "consulting" fees, sponsoring "medical education", and providing "educational grants" all solely as marketing tools to increase prescribing. Medical device companies likewise have been in the

spotlight for inappropriate medical marketing: In 2006, Medtronic paid $40 million to settle charges with the DOJ, and in 2007 four major orthopedic device manufacturers (Zimmer, Dupuy, Biomet and Smith and Nephew) paid $311 million to settle allegations. All companies adopted integrity agreements as part of the settlement (NRC).

However, there is clearly information exchanged, which may be valuable for physicians. For example, Chressanthis et al. used an IMS database of 72 thousand physicians, looking at prescribing of a novel first-in-class pharmaceutical, an existing product that received negative clinical trials results, and an existing agent that received a black-box warning based on whether or not their institutions imposed restrictions on sales reps. The authors found that physicians with more restricted access were slower to prescribe the new drug, but were also slower to reduce prescribing of the drugs with new clinical information/a black box warning (Chressanthis). For medical devices, the picture is more complex. With complicated devices, sales people provide training, equipment calibration, and expertise and advice related to use of the device. For instance, the ACCULINK Carotid Stent System was only approved by the FDA with an appropriate training program (in which physicians would be trained by company representatives) (FDA PMA).

More recently, there has been concern about industry influence on clinical guidelines, thus impacting patient care. One study looking at clinical guidelines reported that 56 percent of 498 individuals surveyed had a conflict of interest, usually by being a consultant or advisor to a company in that therapeutic space (Mendelson 2011). One particularly famous case of this is with kidney dialysis guidelines. Amgen, the manufacturer of epoetin (which increases hemoglobin in dialysis patients) was the primary sponsor of the Kidney and Dialysis Outcomes Quality Initiative, which issued guidelines in 2006 recommending an increase in the target

hemoglobin levels (thus entailing higher doses of epoetin). Of the 16 people involved in drafting the requirements, 14 received some form of payment from a company potentially affected by the guidelines (Coyne 2007). In 2011, Medicare opted to disregard these guidelines, by removing a requirement that dialysis providers keep hemoglobin above the minimum (Reuters 2011). More recently, the FDA was urged to reconsider its decision to allow Yaz to remain on the market after it was revealed that four of the twenty-six members of the expert panel whose recommendation the FDA followed had ties to the pharmaceutical manufacturer – relevant because the panel had decided by a four-vote margin and all four had voted in favor (Yukhananov 2012).

"You can't have a panel with expertise in the area that doesn't have some kind of conflicts,"

--Dr. Denise Simons-Morton, responsible for assembling cardiovascular guideline group (Wilson)

2.2 Benefits of Industry-Academic Relationships

Collaboration between academic medical centers and companies can yield innovative new therapeutics. For example, collaborations led to a better understanding of the development of new classes of: drugs to treat HIV; a monoclonal antibody against the platelet glycoprotein IIb/IIIa; pulmonary surfactant which improves neonatal survival; rituximab, a monoclonal antibody effective against lymphomas; bortezomib, a protease inhibitor effective against multiple myeloma; and imatinib, a tyrosine kinase inhibitor effective against CML (NRC).

Historically, half of all biotechnology firms were founded by university scientists, most of whom retained academic appointments post-founding. In 2003, more than 70% of papers published by biotechnology firms were coauthored with a scientist in academia (Stuart 2007). One study found that more than half of papers referenced on drug patents between 1993 and 1994 belonged to academic researchers. (2-Campbell 2004). Another found that 27 percent of

new products commercialized by drug companies in the 1980s would have encountered long development delays without academic research. This was found to be true even though only 10-15 percent of drug discoveries are made at universities; the authors conclude that "academic research often results in findings that are necessary but not sufficient for the discovery or improvement of a drug. Industrial R&D must be carried out to extend, supplement and focus the findings of the academic R&D" (Mansfield 1991). When this research was repeated from 1986-1994, the percentage increased to 31 percent – the greatest out of all the industries studied (Mansfield 1998).

A 1994-1995 survey of over 2,000 life science faculty found that those with industry funding published more than faculty without industry funding (2-Campbell 2004). Furthermore, a 1996 survey found that faculty with industry funding were more likely to have applied for a patent, had a patent licensed, had a product under review or on the market, or started a company than those without funding (Blumenthal 1996). In a 2009 survey of 1663 researchers at academic medical centers, 51.9% had some relationship with industry and 40.7% said that this relationship contributed to their most important scientific work (Zinner 2009).

One study, which looked at reports published between 1979 and 1983 in six top basic science journals, found that the "strongest predictor of moving to randomized [clinical] experimentation was industry involvement in the original basic science publication" (Ionnidis).

The importance of these collaborations is more profound for medical devices, which have a more continuous process of innovation that requires many innovations on the original prototype. Some examples of medical devices that have evolved from close academic and industry ties include implanted defibrillators, prosthetic heart valves, mechanical ventilators, pulse oximetry, and phototherapy (NRC). However, there is concern that consulting

arrangements that do not result in significant device rearrangement may simply be inducements for physicians to use their device.

It is rare to find officials who do not have some sort of relationship with a company, and that "it is likely that limiting the ability of senior officials to interact with industry would reduce the transfer of scientific resources to and from the commercial sector." Officials at top research centers felt that their commercial relationships supported the educational mission, despite the risks of conflicts of interest. In two of the four institutions in which a substantial amount of clinical research was conducted, the authors found no examples of conflicts of interest (Campbell 2004a).

2.3 Further Discussion

Medical marketing legislation seeks to restrict pharmaceutical and medical device companies from improperly influencing physicians (by avoiding and/or disclosing gifts and financial arrangements). Some argue that these are onerous on the companies, but will not impact innovation because most concept ideation occurs in a small minority of physicians, sometimes called "key thought leaders." However, conflict-of-interest regulation at universities is likely to impact this relationship.

For example, despite the share of academic patents increasing, in 2003 the share of faculty members from clinical departments who held patents was only 3.5% (Azoulay 2007). The top 20 universities obtain 83% of the aggregate net returns generated from licenses (Bulut and Moschini 2006). As part of the DOJ settlement, the medical device companies agreed to disclose the names of all physicians and the amounts paid to them. One key finding from this data is that the physicians that received payments in 2007 represent only about 4% of orthopedic surgeons (Steinbrook 2011).

Restrictions that makes collaborations more difficult could do so either directly (e.g. by being unduly burdensome for either physicians or companies) or indirectly (e.g. by stigmatizing physician relationships with funding). For instance, editors sometimes will not accept review articles by authors that disclose financial interests, out of concern of their being influenced by those interests. In addition, some studies suggest readers are less likely to consider research interesting and believable if they know that the author had financial ties to a company (NRC). In 1996, 30% of life science companies surveyed reported that conflict-of-interest rules were causing difficulty collaborating (Blumenthal 1996). This is likely higher today since stricter conflict of interest policies are continuously emerging.

2.4 Research Question

Research to-date that has sought to illustrate the negative impact of conflict-of-interest rules has primarily been survey-based. A more quantitative approach may provide greater support for the argument that there are benefits to less strict conflict-of-interest rules, and to better understand the impact of tightening rules. My approach focused on using clinical trial data to quantify the impact of conflict of interest rules on clinical trials performed.

3. Methods and Research Design

3.1 Approach

My approach to assessing the impact of COI restrictions is to use an econometric framework to estimate the impact of each school's change in restrictions by level of clinical trials (e.g. comparing the pre-and post-policy trial trends), compared to institutions that did not have a change in restriction-level.

This approach is based on a number of assumptions. First, I assume clinical trials are a measure of clinical translation. It may be argued that clinical trials are a poor proxy for this. In addition, it assumes that the trials are initiated at a specific point in time. For this analysis, I assume the impact of COI restrictions is felt in trials initiated in the following year. This may not be accurate. Next, I assume that institutional mechanisms determine how physician inventors transition research from the lab into the clinic. Finally, I assume that COI interventions that change the institutional environment for scientific research will be reflected in the ability to move compounds into the clinic, which will be captured by clinical trials. This analytical framework relies on the fact that institutional changes induce changes in the number of programs moved into the clinic relative to baseline levels.

3.2 Dataset Construction

I used the following data sources to construct my dataset: clinicaltrials.gov, the AMSA scoreboard, NIH funding (report.nih.gov), hospital discharges and gross patient revenue (ahd.com), and faculty number (usnews.com).

I used clinical trials as a measure of innovativeness, understanding that clinical trials are key to the successful transition of innovation from the bench to bedside. The US Government mandated that a database be created by the NIH for clinical trials with the 1997 FDA Modernization Act (McCray 2000, FDA). Registration with this database (clinicaltrials.gov) became widespread in 2005, because in September 2004, the members of the International Committee of Medical Journal Editors (ICMJE) stated it would only consider a trial for publication if it had been registered before the enrollment of the first patient (beginning July 1, 2005). Studies currently in progress at that time were allowed until September 2005 to register (De Angelis 2005). All trials began to be reported in 2007, since the US Public Law 110-85

(Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, passed on September 27, 2007, required that all clinical trials be registered on clinicaltrials.gov. Compliance with the law is necessary to achieve both NIH funding and FDA approval (NIH).

I used AMSA scoreboards as an independent assessment of the strict conflict-of-interest rules. To achieve this, the Association of American Medical Colleges (AAMC) and the Institute of Medicine published guidelines in 2008 and 2009. The American Medical Student Association began publishing "PharmFree Scorecards" in 2007, which graded medical schools on their COI policies. Over the years, this has been refined with help from The Pew Prescription Project. As part of this, each school's policy is rated based on criteria described in Appendix (AMSA). These scores were used to rate the severity of COI rules, with a score of A or B corresponding to a "high" level of restriction. Schools with C or lower were considered not high, or base. Since this was first published in 2007, I had to extrapolate scores for 2006.

My complete dataset included 566,811 sites included in 50,769 clinical trials. I identified the top 150 zipcodes by number of sites, and from these identified 80 AMCs (matching zipcode with an accredited medical school. If there was no AMC within 30 minute drive, I excluded that zipcode from the dataset). Many AMCs corresponded to multiple zipcodes; in this situation, all were included. A few zipcodes had multiple institutions within a 30 minute drive; when this occurred, I selected the closest AMC. See full list in Appendix.

For this analysis, I only used clinical trials at these 80 medical schools from 2006 to 2011.

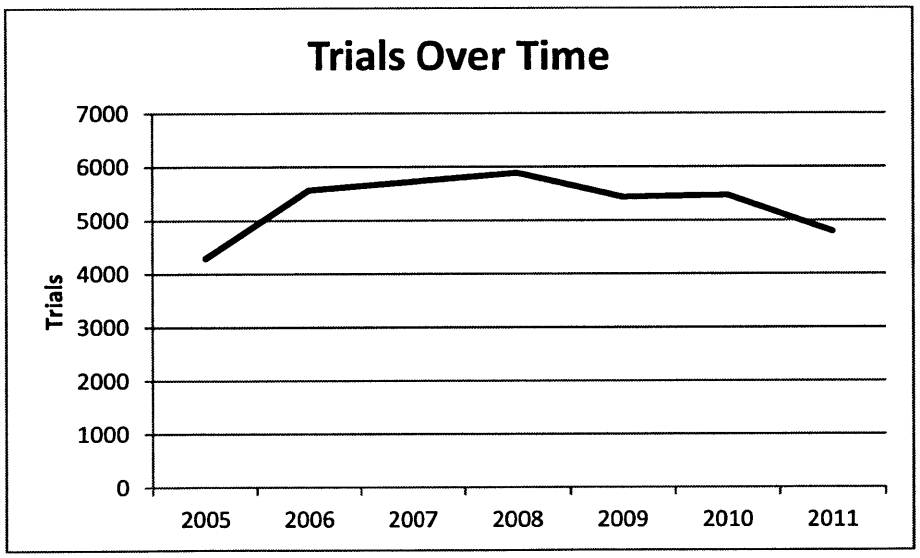
4. Results

4.1 Descriptive Statistics

There are two large trends in the data that are important to note. First, clinical trials increase from 2005 to 2008. Second, the share of AMCs with strict COI regulations increases over this time.

Looking at all centers, the number of clinical trials increases from 4,290 in 2005 to peak at 5,887 in 2008, and then declines 19% to 4,791 in 2011.

Figure 2: Clinical Trials at Top 80 AMCs in the United States, from 2005-2011

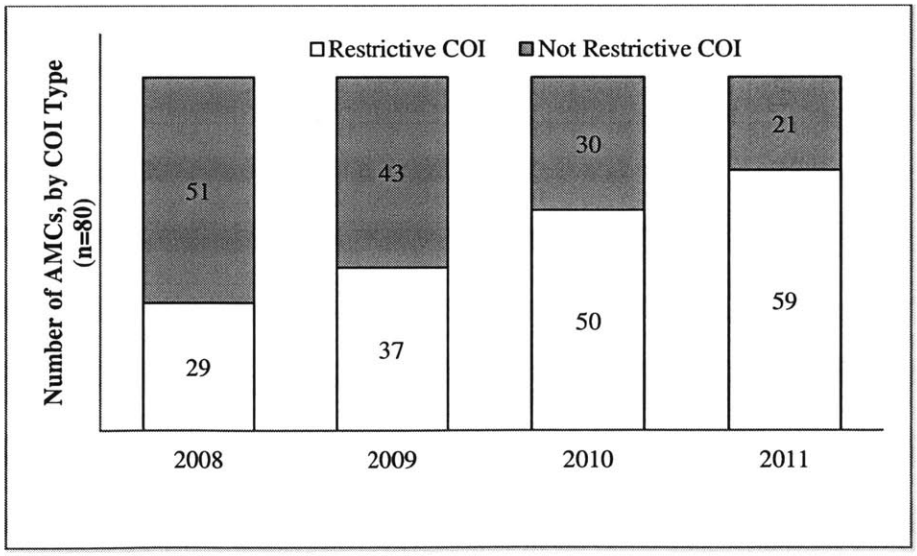


There are a few possible explanations for the decline of clinical trials overall. First, it may be the case that some trials were not included for 2011; however, the analysis was updated with the dataset in July 2012. Second, generic macroeconomic factors have influenced the pharmaceutical industry, with funding overall declining. Since trials have about a year lead-time, economic challenges in 2008 would be seen in 2009. In addition, the Affordable Care Act,

passed in March 2010, has created some uncertainty in the industry, and there have been a number of patent cliffs in 2010 at major companies that may have resulted in less funding for clinical development. In addition, there has been an overall trend towards moving clinical trials abroad, which may have accelerated in the last few years due to budget constraints. This would reflect fewer trials, as my analysis only considers US trials.

The share of AMCs with restrictive COI policies (defined as a C or below by AMSA) was initially 36.2% in 2008, when the first AMSA scoreboard was published. This increased to 73.8% in 2011. In other words, three years ago strict COI rules characterized a minority of institutions – today, it is the vast majority (nearly three-fourths).

Figure 3: Breakdown of Top 80 AMCs by COI Restrictiveness Level, from 2008-2011



Overall, AMCs with restrictive AMCs have higher numbers of clinical trials (77 vs. 62). This may be due to the fact that more prestigious/larger AMCs have both more clinical

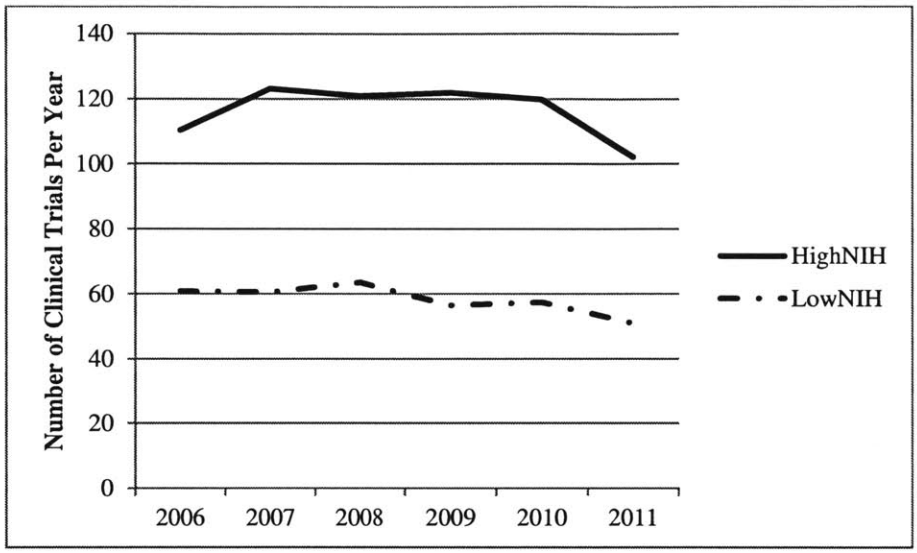
trials, and stricter COI rules. To examine this, I focused on 14 universities that received over $200 million in NIH funding in 2012.

Table 2: AMCs that Received Over $200M in NIH Funding in 2012

Rank	School	NIH Funding
1	Harvard	$ 434,745,756
2	Hopkins	$ 395,351,096
3	University of Washington	$ 307,035,131
4	UCSF	$ 303,909,201
5	University of Pennsylvania	$ 299,842,143
6	University of Michigan	$ 286,139,603
7	University of Pittsburgh	$ 271,239,804
8	UCSD	$ 270,348,537
9	Yale	$ 252,343,786
10	Washington University	$ 251,319,322
11	UCLA	$ 245,485,802
12	Duke	$ 232,793,621
13	Columbia	$ 208,724,131
14	Stanford	$ 203,463,786

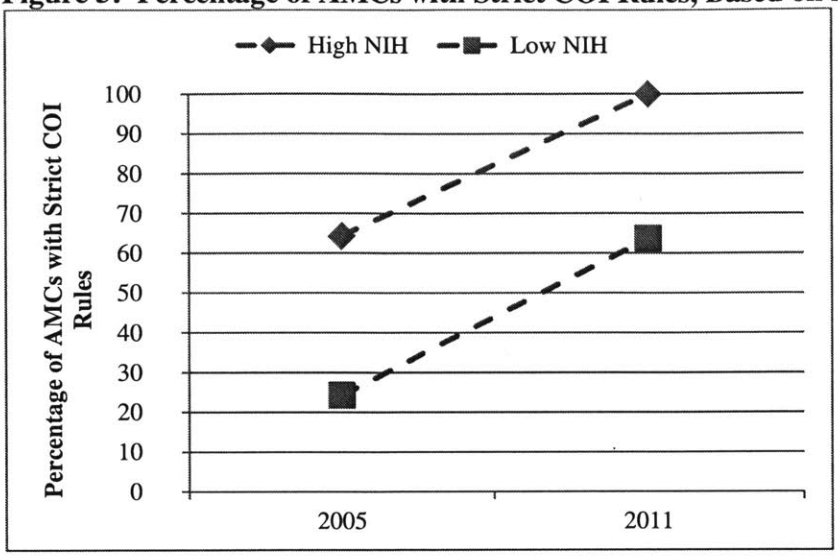
These universities had, on average, about twice as many clinical trials as those with less NIH funding (116, vs. 58 in 2011), and this was consistent over time.

Figure 4: Clinical Trials Conducted at High NIH Funding AMCs (>$200M) vs. Low NIH, 2006-2011



High-NIH AMCs were more likely than to have strict rules in 2005. This trend consisted over time, with 64% of high-NIH AMCs having strict COI rules in 2005, increasing to 100% in 2011; in contrast, 24% of low-NIH AMCs had strict COI rules in 2005, increasing to 64% in 2011. Both groups tightened COI rules over time.

Figure 5: Percentage of AMCs with Strict COI Rules, Based on NIH Funding



Consequently, the number of clinical trials was positively correlated to stricter COI rules. However, it is important to note that more prestigious AMCs (as suggested by greater NIH funding) have both stricter COIs and more clinical trials.

4.2 Economic evaluation of impact of COI regulation

I began by estimated the relationship between AMC and number of trials using an Ordinary Least Square Regression.

The empirical model takes the form

$$T = \beta_0 + \beta_1 COI\_high + \beta_2 Start + \beta_3 NIH + \beta_4 faculty + \varepsilon$$

Where trials at each AMC, T, is linearly related to:

- COI_high: A dummy variable, 1 if high level of restriction, 0 if not
- Start: the number of trials conducted in 2005, the year before my analysis begins, to control for the significant differences in size of institutions
- NIH funding: another control variable, which represents both the size and level of scientific and clinical research the institution engages in, and indirectly may measure prestige
- Faculty: the number of faculty at each institution, which reflects the size

With this regression, the coefficients are in the expected direction, except for faculty (which has an extremely small negative impact). Start and NIH both have expected positive coefficients, with significance. Restrictive COI policies have a negative coefficient, but no significance.

Table 3: Impact of Variables on Number of Trials, Linear Regression

Variable	Coefficient	Sign.
COI_high	-1.25819	
start	1.201969	***
nih	3.14E-08	***
faculty	-0.00121	**

Coefficients are significant at the 10-percent level (*), the 5-percent level (**), or the 1-percent level (***).

Seeing the large impact of the starting number of trials in the regression, a logarithmic model seemed more accurate than a linear one:

$$\log (T) = \beta_0 + \beta_1 COI\_high + \beta_2 \log(start) + \beta_3 \log(NIH) + \beta_4 \log(faculty) + \varepsilon$$

With this model, the coefficients are directional and significance is achieved for all variables except faculty. Based on this analysis, restrictive vs. non-restrictive COI rules results in 9.4% less clinical trials. This impact was slightly greater with high-NIH institutes or 11.5% less. In 2011, the average number of clinical trials conducted was 116, so this suggests that by having highly restrictive COI rules the institution conducted 13 less clinical trials

Table 4: Impact of Variables on Number of Trials, Logarithmic Regression

	All AMCs		High-NIH AMCs		Low-NIH AMCs	
Variable	Coefficient	Sign.	Coefficient	Sign.	Coefficient	Sign.
COI_high	-0.0984	***	-0.12221	*	-0.10219	**
log_start	0.9290	***	1.039227	***	0.910163	***
log_nih	0.0734	***	-0.21895		0.090357	***
log_faculty	-0.0305		-0.04029		-0.03645	

Coefficients are significant at the 10-percent level (*), the 5-percent level (**), or the 1-percent level (***).

Next, I added to this equation fixed effects by year. The year impact is, unsurprisingly, quite large, with a greater impact than COI. This makes sense, since we see in aggregate that the overall number of trials has been declining. However, the coefficient and significance on COI_low persists even with these year fixed effects.

Table 5: Impact of Variables on Number of Trials, Logarithmic Regression

Variable	Coefficient	Sign.
COI_high	-0.05322	*
log_start	0.926317	***
log_nih	0.06937	***
log_faculty	-0.03172	*
y06	0.17438	***
y07	0.189568	***
y08	0.250349	***
y09	0.110308	**
y10	0.15142	***

Coefficients are significant at the 10-percent level (*), the 5-percent level (**), or the 1-percent level (***).

Finally, I added in fixed effects by AMC. Control variables are excluded, as fixed effects per institution already achieve these controls. The coefficients are directional, and significance is

achieved. Shifting from high to low levels of restriction decreases the number of trials by 13.2% on a per-institution level.

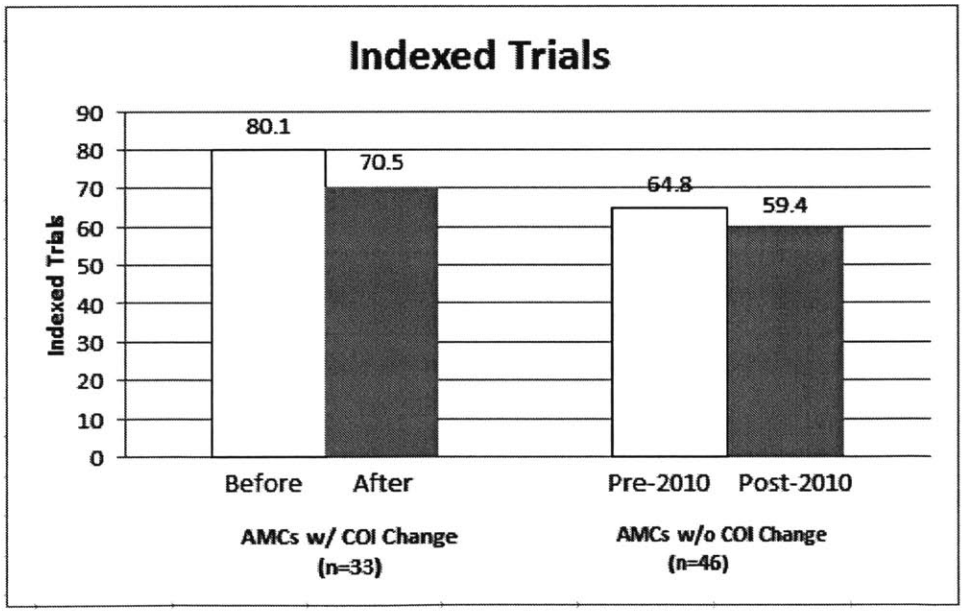
Table 6: Impact of COI change on a Per-institution Level, Log Function

Variable	Coefficient	Sign.
COI_high	-.1417292	***

Coefficients are significant at the 10-percent level (*), the 5-percent level (**), or the 1-percent level (***).

Even though all AMCs had a decrease in trials overall, the decrease for AMCs with COI change was on average 12% vs. 8% for AMCs that did not tighten AMCs.

Table 7: Impact of COI Change in Aggregate



However, when I also added in fixed effects per year the impact disappears. The year impact drowns out the COI impact, so it no longer achieves significance.

Table 8: Impact of Variables on Number of Trials, Logarithmic Regression

Variable	Coefficient	Sign.
COI_high	-0.0093	
y06	0.1945	***
y07	0.2069	***
y08	0.2705	***
y09	0.1313	***
y10	0.1574	***

Coefficients are significant at the 10-percent level (*), the 5-percent level (**), or the 1-percent level (***).

5. Conclusion

This paper presented a detailed analysis of the impact of conflict-of-interest regulation at academic medical centers. My results suggest a decline of clinical trials at institutions that implemented strict COI regulations, relative to universities that have less strict regulations. This decline persisted despite controls based on initial number of trials, number of faculty, NIH funding, and patient revenues.

It is important to note that clinical trials is a poor proxy for innovation and scientific translation. However, seeing an impact on such a high level suggests that this impact would be even more noteworthy if a more nuanced proxy was evaluated instead.

This analysis provides the first econometric assessment of the highly controversial COI policies that have been implemented. This evaluation of this changing policy environment addresses and clarifies a series of debates among policy-makers. While there is a clear need to protect students and patients, such conflict-of-interest legislation is associated with lower number of clinical trials, and perhaps poorer translation of scientific innovations into the clinic and hopefully ultimately to patients.

There is a key question that should be addressed by future research: whether trials merely shifted to institutions with less restrictive policies (suggesting they were initiated by external parties, such as industry) or whether they failed to take place (suggesting that endogenous physician-scientists were crucial catalysts). Due to the importance of physician-inventors in scientific innovation, and partnerships with industry to drive research from the lab into the clinic and eventually to patients, this is important to understand further.

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Appendix

Trial information

All Trials

Variable	Obs	Mean	St Dev	Min	Max
trials	480	68.46	90.88189	4.00E+00	560
start	480	53.625	73.91832	5	428
nih	480	1.01E+08	1.00E+08	0	4.35E+08
faculty	480	1849.875	1559.188	39	11817
COI_high	480	0.414583	0.493164	0	1

AMCs with NIH > 200M

Variable	Obs	Mean	St Dev	Min	Max
trials	84	116.3333	106.7849	8.00E+00	453
start	84	90.78571	83.62842	9	341
nih	84	2.83E+08	6.30E+07	203000000	4.35E+08
faculty	84	3046.786	2637.192	853	11817
COI_high	84	0.738095	0.442312	0	1

AMCSs with NIH <200M

Variable	Obs	Mean	St Dev	Min	Max
trials	396	58.30556	83.83996	4.00E+00	560
start	396	45.74242	69.28451	5	428
nih	396	6.22E+07	5.34E+07	0	1.96E+08
faculty	396	1595.985	1057.068	39	4705
COI_high	396	0.34596	0.476282	0	1

AMSA Scorecard

Policies are rated on each of the domains listed below, using the following general format.

3 = Model policy
2 = Good progress toward model policy
1 = Policy is absent or unlikely to have a substantial effect on behavior
0 = Institutions that do not respond to requests for policies or decline to participate will receive scores of zero in every category.

1. Gifts and individual financial relationships with industry

1A. Gifts (including meals)

Background: Numerous published studies demonstrate that small and large gifts play a role in influencing prescribing decisions, which directly affect patients. Medical personnel consistently underestimate the extent to which they personally are influenced. Industry-sponsored meals are a form of gifting.

3 = All gifts and on-site meals funded by industry are prohibited, regardless of nature or value.

2 = Less stringent limitation on industry-funded gifts (e.g., gifts prohibited above $50/year – or gifts prohibited but meals allowed)

1 = No policy, or policy that would not substantially reduce gifting (e.g., gifts are allowed but discouraged, or limited in a non-specific way to "appropriate," or primarily for the benefit of patients).

1B. Consulting relationships (excluding scientific research and speaking)

3 = Consulting relationships with industry must be subjected to institutional review or approval. Additionally, they must either be described in a formal contract, or payment for services must be commensurate to the task.

2 = As above, without the institutional review or approval requirement.

1 = No policy, or policy that would allow consulting relationships to occur without institutional scrutiny or that would allow relationships in which payments are not commensurate with work.

1C. Industry-funded speaking relationships

Background: Research relationships with industry may entail beneficial public presentations and speeches by individual researchers. However, industry also uses academic physicians to support marketing goals by identifying and cultivating speakers who give a positive message about the drug in question. Such ongoing relationships, sometimes called "speakers bureaus," are unnecessary and detrimental.

3 = Speaking relationships are prevented from functioning as de facto gifts or marketing. An effective policy must not implicitly permit (a) long-term speaking agreements or (b) industry to have a role in determining presentation content. (Some effective policies may explicitly prohibit participation in a speakers bureau. Other effective policies contain elements such as limits on compensation and reimbursement and a requirement to ensure the scientific integrity of information presented.)

2 = Industry-funded speaking relationships are regulated, but with less stringent limits on longevity, content or compensation.

1 = No policy, or policy that does not define the limits on longevity, content or compensation.

1D. Disclosure

3 = Personnel are required to disclose past and present financial ties with industry (e.g., consulting and speaking agreements, research grants) on a publicly-available website and/or disclose such relationships to patients when such a relationship might represent an apparent conflict of interest.

2 = Universally-required, internal disclosure to the medical school or hospital administration. (Policies requiring disclosure only when presenting or publishing do not meet this criterion.)

1 = No policy.

2. Pharmaceutical Samples

Background: The U.S. pharmaceutical industry distributes some $18 billion per year in drug samples. Published studies show that a substantial proportion of these samples are used by physicians, staff and their families. Such use is a clear financial conflict of interest that confers no possible benefit on patients.

When sample medications are accepted and dispensed in the clinic setting, the usual standards of inventory control, drug interaction and dosage screening, labeling and documentation may be bypassed (contravening Joint Commission standards for hospital accreditation). Distribution of non-formulary drug samples has the potential to undermine the intent and function of the formulary.

Furthermore, the distribution of samples has been shown to lead physicians to prescribe drugs that differ from their preferred drug choice, reducing their prescribing of unadvertised drugs in favor of advertised drugs and decreasing their use of first-line (relative to second-line) therapies. This implies that the direct distribution of samples to physicians may, in aggregate, increase costs while reducing the safety and effectiveness of prescribing.

3 = Industry samples are prohibited, except under certain narrow circumstances approved by the institution that protect the interests of patients and prevent the use of samples as a marketing tool (e.g., policies that allow samples under limited circumstances with the approval of the Pharmacy and Therapeutics (P&T) Committee or policies that incorporate samples into a larger program designed to ensure the availability of brand-name and generic

medications to under-insured patients; if the circumstances of the specific program are not defined, the policy should define the approvals process). Where there is a specific program in place, the policy must prevent samples from being given directly to physicians by pharmaceutical sales representatives.

2 = Samples or vouchers for medications may be provided, but with significant limitations (e.g., samples may not be given directly to physicians, samples must be dispensed or controlled by the pharmacy department).

1 = No policy, or a policy that does not substantially limit the use of samples (e.g., samples limited to formulary items, or samples not for personal use).

3. Purchasing & Formularies

Background: Individuals with financial conflicts of interest should not make institutional purchasing decisions. Decisions influenced by personal conflicts have the potential to adversely affect institutional costs and the quality of patient care. Pharmacy and Therapeutics (P&T) Committees typically decide which drugs will be on the hospital's "preferred list," known as a formulary. Other committees may make other purchasing decisions.

3 = Formulary committees and committees overseeing purchases of medical devices should exclude those who have financial relationships with drug or device manufacturers. Exclusion may be specific to participation in particular decisions for which the staff member has a conflict of interest. This policy does not prevent expert clinicians from advising a committee, provided that potential conflicts are disclosed. (Note: this standard is not intended to prohibit indirect financial interests, such as investments in mutual funds that may own pharmaceutical company shares).

2 = Less stringent policies that do not prohibit individuals with conflicts from participating in purchasing decisions (e.g., policies that require members of committees overseeing purchases merely to disclose potential conflicts of interest).

1 = No policy, or policy that merely cautions against conflicts of interest.

4. Industry Sales Representatives

Background: Industry sales representatives are employed to increase the sales of their company's drugs. Permitting their access to medical staff is not in the interests of patients or staff.

3 = Pharmaceutical and device representatives are not allowed to meet with faculty regardless of location, or are not permitted to market their products anywhere inside the

medical center and associated clinics and offices. (Exceptions may be made for non-marketing purposes, such as training on devices or equipment.)

2 = Pharmaceutical representatives are permitted to meet with faculty, but with significant limitations (e.g., only in non-patient care areas or only by appointment). Exceptions as above.

1 = No policy, or policy that does not substantially limit access.

5. Education

Background: It is essential that financial support not influence the content of educational activities. Where financial support from industry assists in the delivery of educational activities, it must not be linked to an individual company's interest in promoting specific products. Therefore, a firewall should separate the donor from those developing the educational activity.

Educational activities take place both "on-site" (that is, within the medical school or hospital campus) and "off-site" (at outside facilities, including professional conferences). Many policies distinguish between on-site and off-site activities.

5A. On-site Educational Activities

3 = Industry is not permitted to provide direct financial support for educational activities, including Continuing Medical Education (CME), directly or through a subsidiary agency. (However, companies may contribute unrestricted funds to a central fund or oversight body at the academic medical center, which, in turn, would pool and disburse funds for programs that are independent of any industry input or control.)

2 = Less stringent limitations to ensure independence of educational content (e.g., standards to establish freedom from industry influence of content, such as review and approval of presentations; language that prevents industry from selecting the speaker; a requirement that programs adhere to ACCME* standards; or language such as: industry funding may be allocated for a particular topic, but must be provided directly to the department, not to individuals). *Note: ACCME is a non-governmental oversight organization that establishes accreditation standards for CME activities.

1 = No policy, or a policy that would not substantially limit industry influence over educational activities (e.g., industry funding must be disclosed).

5B. Compensation for Travel or Attendance at Off-site Lectures & Meetings

3 = Personnel may not accept payment, gifts or financial support from industry to attend lectures and meetings. (An exception may be made for modest meals, if part of a larger program.) Travel support may only be accepted if it is subject to institutional approval or industry is prevented from selecting ("earmarking") the recipients. Note: speaking and consulting relationships are evaluated separately in domain 1.

2 = Less stringent limitations.

1 = No policy, or a policy that would not substantially limit participation in industry-funded events and meetings.

5C. Industry Support for Scholarships & Funds for Trainees

3 = The policy must either prevent industry from earmarking or awarding funds to support the training of particular individuals (recipients must be chosen by the school or department), or the policy must mandate institutional review of the giving of funds. (This does not preclude grants that fund a specific research project.)

2 = Less stringent limitations.

1 = No policy, or a policy that would not substantially regulate industry funding of scholarships and funds for trainees.

5D. Medical school curriculum (or other documentation of educational objectives/course content)

3 = Students are trained to understand institutional conflict-of-interest policies and recognize how industry promotion can influence clinical judgment.

2 = Curriculum addresses conflict of interest in a more limited way (e.g., training on policies only).

1 = No policy (not addressed in curriculum or elsewhere).

6. Enforcement

A. Is it clear that there is a party responsible for general oversight to ensure compliance? (Y/N)

B. Is it clear there are sanctions for noncompliance? (Y/N)

AMCs by ZipCode and Trials

#	Zipcode	# Trials	Name
1	78229/77030	5,564	Baylor
2	02115/02114	3,817	Harvard
3	30322/30342/30033/30308/30060/30309	3,461	Emory
4	60611/60612/60614	2,951	Northwestern
5	92123/92103/92037/92108/92120	2,751	UCSD
6	90048/90027/90211/90404/91505/90502	2,427	UCLA
7	63141/63110	2,396	Washington University
8	94305/94609/94304	2,282	Stanford
9	19104	1,843	University of Pennsylvania
10	46202/46260	1,817	Indiana University--Indianapolis
11	33143/33021/33136	1,762	University of Miami
12	21205/21231/21205/21224	1,681	Hopkins
13	92868/92801/92708	1,653	University of California--Irvine
14	98109/98104/98105/98101	1,650	University Washington
15	32224/85259/32207/32216	1,584	Mayo
16	75246/75231/75230/75235	1,569	Utexas Southwestern
17	48202/48201	1,561	Wayne State University
18	15232/15213		University of Pittsburgh

		1,544	
19	94115/93720/94110	1,449	UCSF
20	10032	1,338	Columbia
21	60637	1,230	Uchicago
22	44106/44122	1,181	Case
23	48109	1,093	Umich
24	80218/80220	1,049	University of Colorado
25	55455/55404	1,031	University of Minnesota
26	95817/95661	988	University of California--Davis
27	72205	974	University of Arkansas for Medical Sciences
28	21201	941	University Maryland
29	45229/45219	939	University of Cincinnati
30	43210	923	OSU
31	33612/33613	899	University of South Florida
32	10029	885	MT. Sinai
33	52242	803	Iowa
34	10016	782	NYU
35	32806	768	University of Florida
36	20010	740	Uniformed Services University of the Health Sciences / VA Medical Center
37	10467/10461	709	Einstein
38	90033	697	USC
39	40202	695	University of Louisville
40	19107	686	Jefferson Medical College

41	35209/35233	677	Alabama Birghamham
42	50309/50314	633	Des Moines University
43	85006/85712	599	University of Arizona
44	73104	593	Oklahoma State University
45	37203	579	Vanderbilt
46	27103	548	Wake Forest
47	91010	546	Western University of Health Sciences
48	2118	493	Boston University
49	20007	482	Georgetown University
50	53226	472	Medical College of Wisconsin
51	27705	437	Duke
52	67214	417	University of Kansas Medical Center
53	60153	407	Loyola University
54	13210	401	SUNY--Syracuse
55	96813	398	University of Hawaii--Manoa (Burns)
56	2111	394	Tufts University
57	23298	376	Virginia Commonwealth University
58	7601	370	University of Medicine and Dentistry of New Jersey--Newark
59	70112	358	Tulane University
60	36608	351	University of South Alabama
61	38105	347	University of Tennessee Health Science Center
62	64108	334	University of Missouri--Kansas City
63	49503		Michigan State University

		332	
64	2903	327	Brown
65	19111	321	Drexel University
66	97210	316	Oregon Health and Science University
67	68131	313	University of Nebraska Medical Center
68	78705	310	Texas A&M Health Science Center
69	92354	308	Loma Linda University
70	85013	302	Midwestern /Arizona College of Osteopathic Medicine
71	39216	296	University of Mississippi
72	12208	295	Albany Medical College
73	80204	290	Ucolorado
74	6510	286	Yale
75	68114	283	Creighton University
76	23507	277	Eastern Virginia Medical School
77	76104	275	University of North Texas Health Science Center
78	94598	252	Touro University California
79	73112	244	University of Oklahoma
80	33308	242	Nova Southeastern University