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A NEW MODEL FOR ADDRESSING CONFLICTS OF INTEREST IN COLLABORATIVE CLINICAL TRIALS

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Abstract

The acceleration of technological change, public policy, economic forces, and increased collaboration between research institutions and industrial sponsors has dramatically increased potential conflicts of interest (COIs) in collaborative clinical trials (CCTs). This paper includes a short history of CCTs and describes the forces affecting public policy and increased collaboration and COIs. Current methods of identifying and addressing COIs will be described, as well as the shortcomings of these methods. Finally, a new, fully-transparent model for addressing COIs will be presented which protects human research subjects, end-users of technologies, and the scientific integrity in the clinical trials process.

Keywords: Clinical trials, human research subjects, conflicts of interest, collaboration

INTRODUCTION

How are new medications developed and brought to market in order to treat the pain and diseases of the public? The answer is longer than all of the bound volumes of books in your local library; in fact, we continue to spend vast resources on the search for new methods to understand the human body and the ailments it suffers. There are many philosophies, methods, and models used by academics and caregivers to treat patients. In the United States, one requirement in the process of making a new medicine available to the public is always the same -- at some point, the medicine must be tested on a human subject.

Testing on human subjects has proven to be dangerous not only physically, but ethically. In the quest for scientific progress, we have committed unethical experiments on human subjects without their informed consent. Positive outcomes did result, such as in the case of Edward Jenner's immunization experimentation on children (leading to the smallpox vaccination), and some experiments seem less dangerous, such as the Vipeholm experiments, in which mental patients in Sweden's Vipeholm Mental Hospital were fed large amounts of sweets to determine dental effects. These cases will never balance the scales on the side of good when contrasted with infamous and repugnant experimentation, such as Nazi sterilization experiments on Jewish and Gypsy prisoners. Lest U.S. readers believe that such experiments have only occurred on foreign soil, we must also recall U.S. experimentation with syphilis on poor minorities (the Tuskegee Syphilis Experiment) which continued through the 1970s, and the recently-revealed syphilis research performed by U.S. scientists on Guatemalan mental patients in the late 1940s.

It must give us hope that public scrutiny and public policy have determined that human subjects research must be performed under strict guidelines to protect the rights and safety of those subjects. A variety of codified legislation serves to protect and regulate human subjects research in the U.S., most notably 42 CFR Part 50 and 45 CFR Part 95, administered by the Department of Health and Human Services ("DHHS"). These regulations, passed in 1995,

require updating and revision now because of the increased incidence of conflicts of interest related to clinical trials.

The author notes that there are many other instances of human subjects research in the social sciences and other fields, but chooses to limit this paper to human subjects research in terms of clinical trials performed collaboratively between research institutions and industrial sponsors (referred to herein as "collaborative clinical trials" or "CCTs"), which involve a new drug or medical device ("technology") which is being tested on human subjects. There are many stakeholders involved in the CCT process: academic researchers, focused on learning about the drug, device, mechanism or mode of action, or the disease itself; the institution(s), focused on supporting life-changing research, increasing public opinion, financing further research or future students; the physicians and other caregivers, providing direct patient care and earning their wages; the patients themselves, many times having failed all other treatments and in end-stage terminal disease; and finally, pharmaceutical or biotechnology companies, often the sponsors of research and which carry much of the burden of cost in conducting CCT. Regulatory bodies involved in CCT include Institutional Review Boards ("IRBs"), specific to each organization having a part in the CCT and various federal agencies such as the Food and Drug Administration ("FDA"), DHHS, and other public and private sponsors. Finally, should the drug or medical device have been conceived by an employee at a public or nonprofit research institution, that institution's technology transfer office will be actively engaged in trying to commercialize the technology.

In an environment of constant collaboration, constant change, and conflicting values (i.e., valuing quick translation of a new technology to market versus valuing pedagogy or strict pursuit of basic science), it is not surprising that the regulations and codes of ethics governing human subjects research should be regularly tested in actual CCT practice. The acceleration of technological change, economic forces, and push for collaboration by public policy have dramatically increased potential conflicts of interest ("COIs"), a relatively nascent issue in CCTs which scholars, CCT participants, public policy advisors, and the public agree must be developed and institutionalized to protect human subjects in CCTs, end-users of technologies, and the integrity of scientific research.

This paper will give the reader a short history of CCTs over the past three decades, including the forces affecting public policy and increased collaboration in CCTs. Current methods of identifying and addressing COIs will be described, as well as the shortcomings of these methods. Proposed rule changes by DHHS and other scholars will be summarized, and finally, a new model incorporating many of these proposed changes and addressing many of the current shortcomings will be presented.

Background

Prior to 1980, intellectual property created by research funded by the federal government was owned by the federal government; however, this intellectual property languished in the hands of the government, and researchers were not incentivized to create new intellectual property. There were three main reasons that led to a change in public policy and the passage of the Bayh-Dole Act (P.L. 96-517, Patent and Trademark Act Amendments of 1980). First, as noted by Holbrook and Dahl (2004), "Congress recognized that the federal government could not oversee the daily commercial management of the intellectual property that was being created at universities as an outcome of federal investments in research" (pp. 89-90). In the decade or so leading up to the

passage of the Bayh-Dole Act, a lack of action by government workers (probably due to resource constraints) in commercializing technology funded by the government, as well as the lack of incentives for companies to spend large amounts on R&D without a guarantee of exclusivity such as is granted during the patent process.

Second, the federal government did, on occasion, grant the rights to some patent applications to research institutions, but the process of negotiating these transfers of rights was time consuming and cumbersome. According to Litan (2007), "Congress enacted the Bayh-Dole Act of 1980 largely to address this problem…" (p. 6); however, prior to enacting the Bayh-Dole Act, the National Institutes of Health had implemented a quasi-Bayh-Dole system called the Institutional Patent Agreement (IPA) program, in which the NIH granted some universities with technology transfer offices the right to commercialize some technologies; however, this was an agency program and not statutorily guaranteed, and so was halted in the late 1970s.

Finally, it was becoming apparent that the U.S. was having a decreased technological economic impact in comparison to the rest of world. Gatter (2003) notes, "federal policy makers were concerned that the United States was lagging behind Japan in transforming the results of scientific research into commercial products, and they blamed this shortcoming in part on the face that the results of publicly funded research were, at that time, public intellectual property" (p. 334). Industry, which recognized the risks and challenges of the process of commercializing nascent technology, had no incentive to spend vast resources developing an early-stage technology with no guarantee of exclusivity when the final product went to market.

The Bayh-Dole Act was enacted in 1980, and with this legislation, research institutions and their newly-created technology transfer offices filled the gaps left by a government unable and unwilling to commercialize intellectual property, and focused attention upon realizing economic benefit from the intellectual property developed by their faculty members. Specifically, the Act created a uniform public policy for the public agencies that funded research, which required that these agencies allow the recipients of these funds (nonprofits and small businesses) to retain title to inventions. In fact, the recipients of those funds are encouraged to file patents on those inventions, as well as to collaborate with commercial partners ("technology transfer").

Public policy since 1980 has encouraged industry-academic collaborations and industry funding, resulting in increased conflicts of interest. Along with the direct research institution-industry interactions necessitated by Bayh-Dole, the increased interaction between research institutions and industry is also a result of another public policy decision to decrease public funding of research institutions and allow private, industrial funding to take its place. Figure 1 below shows that trends in funding over the past thirty years have dramatically changed, making industry the majority funder of research and development.

The public policy success, measured in economic terms, of the Bayh-Dole Act is well-established. The Association of University Technology Managers estimates the royalties collected by universities during FY 2000 at over $1 billion, with 368 spin-off companies established that year alone (Duderstadt, 2004, p. 58). In an editorial piece written in 2002, popular magazine *The Economist* wrote, "[m]ore than anything, this single policy measure helped to reverse America's precipitous slide into industrial irrelevance" (2002). On the 30th anniversary of the Bayh-Dole Act, Senator Birch Bayh (with Joseph Allen and Howard Bremer) wrote, "[t]he Bayh-Dole Act works because it aligns the interest of the taxpaying public, the federal government, research universities…and private sector developers transforming government supported research into useable products" (2009, p. 1). Bayh, Allen, and Bremer also (2009) summarized the economic impact of the Bayh-Dole Act over the period of 1996

through 2007: a $187 billion impact on U.S. Gross Domestic Product, a $457 billion impact on U.S gross industrial output, and over 279,000 new jobs created (p.1).

Figure 1: Trends in research funding and licenses/options.

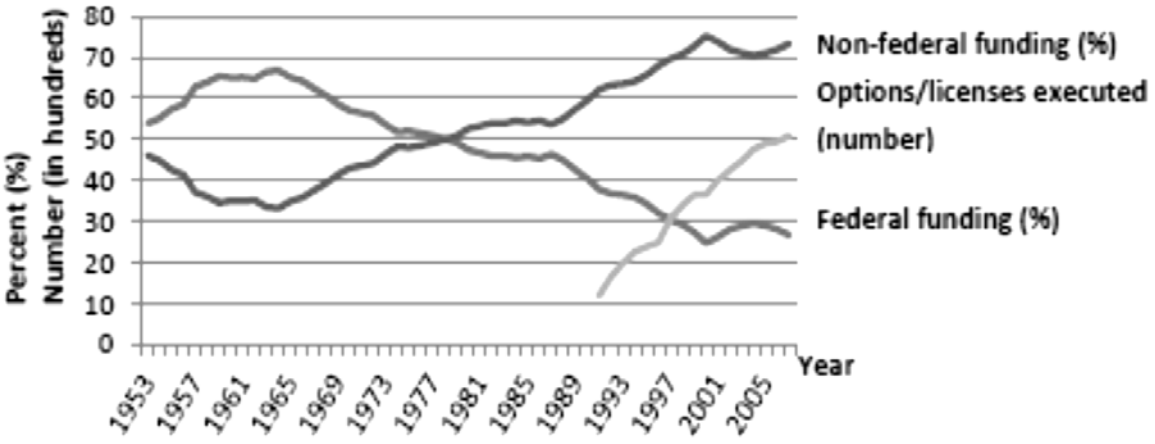


Figure shows executed by U.S. hospitals, research institutes, and universities. Sources. National Science Foundation, Division of Science Resources Statistics, AUTM STATT survey data. Trends in federal and nonfederal research and development expenditures are shown as a percentage of total research and development. Options/licenses executed are numbers in hundreds.

Many well-known medicines and medical devices were created and developed using the collaborative Bayh-Dole model, including coumarin (Coumadin™) and warfarin, widely prescribed blood thinners for treating cardiovascular diseases (Wisconsin Alumni Research Foundation), paricalcitol (Zemplar™) as treatment for bone diseases (WARF), cisplatin, a widely used chemotherapeutic agent (Michigan State University), and synthetic taxol, a first-line breast cancer treatment (Florida State University). The inventive process used to isolate human embryonic stem cells, which holds enormous potential for accelerating drug discovery, also came out of WARF, and the Hepatitis B vaccine (University of Rochester) and the prostate-specific antigen test (New York Health Department and Roswell Park Cancer Institute) were also generated from this university-industry collaborative model.

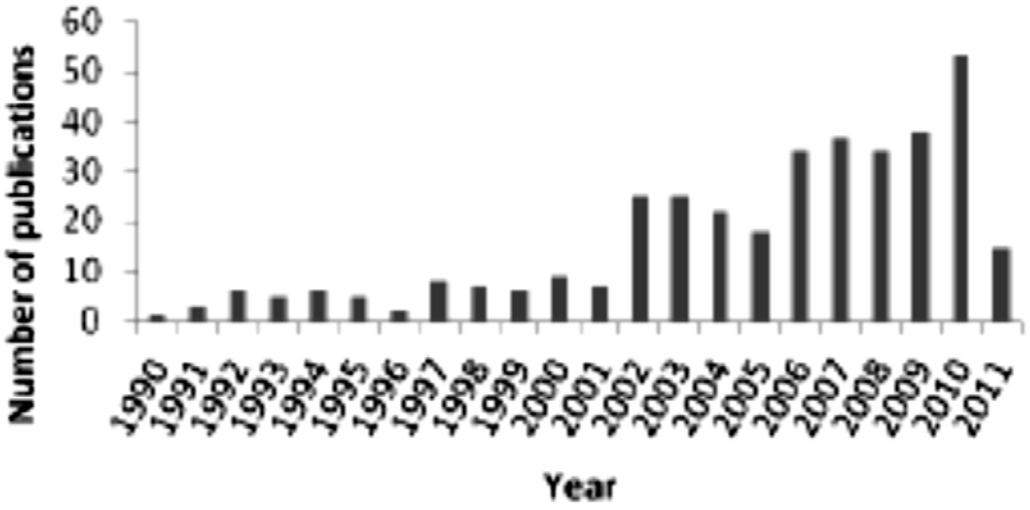
There can be no question that the public policy created by the Bayh-Dole Act and decreased federal funding for research has been invaluable in the advances in medical science, has caused economic growth, and perhaps has caused research to occur which has saved countless lives; however, the increased inter-relationship between industrial interests and academic interests, and the decreased intervention of public policy over the past thirty years caused a dramatic increase in COIs and potential harm to human subjects.

The most famous recent case of a COI resulting in harm to a human subject is the case of Jesse Gelsinger, an eighteen-year-old patient who died in 1999 while participating in a clinical trial at the University of Pennsylvania. Gatter (2003) finds "[t]he study's principle investigator and the University held equity positions worth millions of dollars in a company that owned exclusive commercial rights to the results of the research, and these financial interests allegedly caused the researcher and the institution to take unjustifiable risks with Mr. Gelsinger's life" (p. 330). Gatter (2003) also notes that "financial conflicts of interests are an outgrowth of federal technology transfer policy, which has successfully employed market incentives to make researchers and their

institutions more responsible the needs of corporations creating commercial medical products" (p. 334).

Not only have the incidences of COIs increased, but scrutiny of the issue has increased as well. The past fifteen years have seen an exponential increase in publications and studies of COIs, especially in relation to CCTs.

Figure 2. Trend in Web of Science Publications on Conflicts of Interest



Source. Thomson Innovation search using query syntax "TI=("conflict* of interest" or "conflict*-of-interest") AND (TF>=(1991) AND TF<=(2011)) AND ALL=(clinic* or medic*)," performed on April 18, 2011. Date limits were used to determine the total number of citations present each year from 1991 to the current date.

METHODOLOGY

This paper is based entirely upon a review of relevant literature, not on original empirical research. The relevant literature consisted of scholarly articles, books, editorial opinions, and popular articles. The author used Thomson Innovation to conduct a search of Web of Science articles over the period of 1991 through the present. The search syntax used was "TI=("conflict* of interest" or "conflict*-of-interest") AND (TF>=(1991) AND TF<=(2011)) AND ALL=(clinic* or medic*)." From the results of this search and the contents of some of the articles, the author retrieved further literature through Grand Valley State University's electronic article searching tool, Summit, available at http://gvsu.edu/library/. The author also used Google to direct her to original source material of U.S. government regulations, as well as resources made available through the Association of University Technology Managers at http://www.autm.net/. The scope of the literature review for this paper was preliminary and should only be used as the basis for further research. The author also notes that the new model proposed herein is a compilation of other scholar's proposals and further original, empirical research needs to be done to substantiate the suggestions made in each section of the new model.

Review of the Literature

"Conflict of interest" issues are those issues which have the potential for bias, or have could have the appearance of bias. Warner and Gluck's definition is simple and concise: a "conflict of

interest refers to a situation in which it appears that the researcher's financial or other personal interest could significantly affect the design, conduct, or reporting of research" (2003, p. 37). Thompson (1993) defines a conflict of interest as "a set of conditions in which professional judgment concerning a primary interest (such as a patient's welfare or the validity of the research) tends to be unduly influenced by a secondary interest (such as financial gain)" (p. 573). Although financial COIs are the most easily identifiable, other COIs may exist, such as those based on a power relationship (this could include situations in which a tenured researcher pressures an inexperienced technician to manipulate research results, or when a physician pressures a patient to participate in his or her research). Common scenarios (and this list is by no means limited to the following scenarios) in which an individual researcher might have a COI include when the researcher is paid as a consultant by an industry sponsor of his or her research in a CCT; when the researcher owns equity in an industry sponsor of the CCT, and when the researcher is an inventor of the technology being researched and thus will be a beneficiary of expected royalty payments from the sale of the technology. Research institutions also can have COIs, such as when they are the owners and beneficiaries of expected royalty payments from the sale of technology developed at the research institution, when they own equity in an industry sponsor, or when they are the potential recipient of media scrutiny as a result of CCTs.

Issues of Identification of COIs

Most research institutions have policies of self-disclosure by researchers who plan on engaging in research in which a conflict of interest may be present. For example, most research institutions require that researchers fill out conflict of interest disclosures annually, and update the disclosure within a specified time period if a new conflict arises. Titus, Wells, and Rhoades (2008) conducted a survey of investigators at research institutions to determine how often research misconduct was actually reported; the findings indicate significant under-reporting, and one cause is institutional culture. Although many institutions have conflict of interest policies, "leaders of institutions may also have concerns about handling research misconduct…because public image is important…some may try to minimize reporting and keep unfavorable information from reaching the [Office of Research Integrity] and the press" (Titus, Wells, & Rhoades, 2008, p. 981). Many conflict of interest situations could be mitigated by research institution policies, but often are not and the Office of Research Integrity (the federal agency charged with maintaining the integrity of institutions receiving federal funding from the Department of Health and Human Services) found in 2000 that "only 29% of institutional misconduct policies explicitly obligate members to report scientific misconduct" and an analysis of the institutional investigations reported by the Office of Research Integrity indicates that a very small proportion of research misconduct is actually reported (p. 982). Warner and Gluck (2003) conducted a meta-analysis of ten years of literature and find that "The rate of potential conflicts of interest for researchers appears to be at least 30% in some situations…and the rate of disclosure of conflicts of interest is as low as 2%," (p. 36). Ambiguity and lack of uniformity in standards for disclosure of conflicts of interest seriously undermines the effectiveness of COI policies, both individually and institutionally.

Bias in Designing, Reporting, and Publishing Clinical Trials

Increasingly, publication and reporting bias is suspected in medical and scientific literature. "Reporting bias" occurs when the nature of scientific results is reported in a skewed manner, and "publication bias" can occur when negative results are either not published or published after a considerable delay. Reporting and publication bias have the potential of harming end-product customers, which may be better informed if provided with all relevant information, instead of only the information required by the FDA for drug or device approval.

According to McGauran et al. (2010), reporting bias can be seen when "evidence tends to overestimate efficacy and underestimate safety risks," (p. 9), and publication bias. Many researchers studying incidences of reporting and publication bias have found empirical and anecdotal evidence to support this trend (McGauran, et al., 2010). Bekelman, Li, and Gross (2003) conducted a broad analysis of original, quantitative studies, and found "a significantly significant association between industry sponsorship and pro-industry conclusions" (p. 454). These pro-industry conclusions could be the result of inappropriate study designs, reporting bias, or publication bias (occurrence of positive experimental results being published more often than negative experimental results).

COIs have the potential to bias not only individual researchers and physicians directly, during interactions with patients, but indirectly, through bias in the process and performance of CCTs. Angell (2004) explains how clinical trials happen: "[b]ecause pharmaceutical companies do not have direct access to human subjects, they have traditionally contracted with academic researchers to conduct trials on patients in teaching hospitals…[t]here is now strong evidence that the studies themselves are biased by drug-company influence. Industry-supported research is far more likely to be favorable to the sponsors' products than is National Institutes of Health supported research" (pp. 127-128). Significant correlation exists between clinical trials conducted with pharmaceutical industry involvement and positive results (Peppercorn et al., 2007; Bekelman, Li, & Gross, 2003.) "Given the commercial interest that industry sponsors have in the outcome of the research they sponsor [Food and Drug Administration approval of pharmaceuticals, medical devices], their sponsorship can create a potential conflict of interest" (Gatter, 2003, p. 347).

Mitigating Bias Resulting from COIs

One of the primary methods to mitigate the risk of bias in research is through peer review; that is, publication in a peer-reviewed journal allows other researchers to replicate research in order to confirm or disprove the original researcher's findings. Peer review is central to the idea of research integrity, and critical to the issue of public trust. Most legal contracts between research institutions and industry will preserve a researcher's right to publish but in reality, Bodenheimer (2000) writes that some multicenter drug trials might have publication committees or industry funders which take over the writing of publications, shepherding such publications through the actual researchers to manipulate the actual information which finally gets published for peer review (p. 4).

While clinical trials (with the exception of Phase 1 drug trials) are required to be registered and published on ClinicalTrials.gov, only a small set of results are required to be published. Growing scrutiny upon unreported safety issues and efficacy data have recently caused pharmaceutical research and development companies, pharmaceutical industry organizations, and some

individual companies to commit to publishing their study results (McGauran et al., 2010, pp. 9-10).

Regulatory Oversight for COIs

The FDA, which has oversight over clinical trials for medicines and medical devices tested on human patients, has specific regulations for clinical trials on human subjects. While the sponsor(s) of the trial (usually industry) must collect information on financial relationships from research investigators before the trial begins, the FDA does not review the financial relationship information until after the trial ends and often does not enforce its own regulations, (Office of the Inspector General, 2009, p. 3).

Current DHHS regulations, which apply *only* to institutions that accept federal funding for research, "require institutions to include precautions against conflicts of interest on the part of those involved in the inquiry or investigation" itself (Department of Health and Human Services, 2005). Institutions are not required to identify all potential conflicts of interest, however. The current *de minimus* threshold for disclosure of significant financial interests is $10,000, and many exclusions can apply. Identified conflicts of interested are not regulated by DHHS; the research institution must only assure the DHHS that the conflict is being managed. According to Johns (2003), "no laws or regulations directly govern the financial conflicts of interest of institutions or institutional decision makers" (p. 742). Some sectors of research have been legislated, such as the Public Health Service and the Food and Drug Administration, but there is no overarching set of laws. According to Gatter, current conflict of interest guidelines by the federal government are "heavy on procedure, light on substance" (2003, p. 349). Huang and Hadian also conclude that uniformity in standards, interpretation, and application are needed to better protect human subjects (2006, p. 1).

For these reasons, DHHS has published major proposed changes to its financial conflict of interest regulations in May of 2010 (Federal Register, FR Doc. 2010–11885). These regulations are both heavier on procedure and heavier in substance:

- The *de minimus* threshold for significant financial interests is lowered to $5,000 and there are fewer exclusions.
- The research institution is required to publically disclose identified potential conflicts of interest (presumably, this is to give the public the visibility to see the source of funding so that they may judge whether the research is biased).
- The research institution is required to create a specific management plan for dealing with identified conflicts of interest (and report elements of the plan to the Public Health Service).

While changes to the Public Health Services' conflict of interest policies will be useful in managing recipients of federal funds, they still assign research institutions the responsibility of management and enforcement.

Other Methods Used and Proposed for Managing COIs

In the context of promoting transparency for professional medical associations, Rothman et al. (2009) recommend publishing the amount or portion of their operating budget that comes from industry (pp.1368-69), and proposes that "research funds from industry…should go to a

[professional medical association's] central repository or committee…" (p. 1370). While these ideas are intriguing, they may be too drastic a change to the current infrastructure and process by which research institutions operate.

Holmes et al. (2004) notes that some committees might manage COIs "by building firewalls between the inventor and any research involving his or her device or compound;" among other methods of managing COIs (p. 230). Holmes also recommends that "written policies must provide guidelines for disclosure or recusal from decision-making processes for individuals who are conflicted" (p. 232), and to either "preclude clinical research with potential conflict from occurring at the institution," or have "clear firewalls between investment decision making committees, technology transfer, and the research arm of the institution" (p. 232). While most institutions now have written COI policies and may use firewalls as a method of managing COIs, without constant reminder of COI policies, public enforcement actions, or publication of management plans, various stakeholders can either "fall under the radar" or may not have access to information that is relevant to evaluating CCTs.

Because the potential for COIs at the institutional level may be even more harmful to the public, whether by creating an institutional culture wherein individual conflicts are tolerated or through lack of management of specific conflict of interest situations, self-regulation by research institutions is inherently unwise. As far as the author knows, the only mechanism to counteract these problems is to exclude members of a COI-regulating body which are likely to be more biased than others. Unfortunately, if all members and alternate members of that body are affiliated with a research institution, and the research institution stands to benefit from a financial relationship, it becomes hard to characterize any management plan as unbiased. In the case of IRBs, federal regulations require an unaffiliated layperson to be a member of each IRB, which may mitigate some of the risk of this situation.

A NEW MODEL FOR ADDRESSING COIs IN COLLABORATIVE CLINIAL TRIALS

We must look at this issue as the result of and a problem for public policy. About thirty years ago, the federal government decided to accelerate the commercialization of basic and applied research by taking a hands-off approach and letting public and nonprofit research organizations interact directly with industry. This public policy decision worked, but had the unintended consequence of dramatically increasing financial conflicts of interest, thus endangering public trust in research integrity, which is essential for maintaining the pace of acceleration without returning to the staleness of the pre-1980s. An underlying issue which has not been addressed on the national policy level is the reliance of research institutions on industry funding. Specific prohibitions or management plans for specific financial conflicts of interest do not "address the financial conflict of interest that could be created when researchers and their institutions rely on private industry to fund a significant portion of their human subjects research" (Gatter, 2003, p. 367). National policy could influence this issue by issuing advice, a guideline threshold, or substantive help in reducing the portion of industry funding individual institutions rely upon to fund their research programs. The following model is collaborative, but it would need publication and guidance on a national policy level. The first step is creating a uniform national policy, from which dialogue between the stakeholders can begin. For this reason, the author advocates using the proposed DHHS rules as a standard for all organizations involved in CCTs.

Standardization of COI guidelines

Perhaps the most disquieting aspect of the discussion of COIs and clinical trials is that there are so many different guidelines for identifying and managing them. It seems worrisome, as a prospective clinical trial subject, that a researcher at one institution must disclose a $4,000 honorarium from his industrial sponsor, while a researcher at another institution does not need to disclose the same honorarium because it does not exceed an arbitrary threshold for a "significant" financial transaction.

Because the PHS required all recipients of federal research funding to have written COI policies, there are thousands of different policies in existence. The first step toward standardizing and having a true dialogue on "significant" financial or other interests must be to start with a single policy document which may be modified as public and scholarly debate progress over time. To that end, the proposed rulemaking by the DHHS of 42 CFR Part 50 and 45 CFR Part 94 should be adopted and incorporated into existing institutional COI policies. According to the PHS *Analysis of Impacts,* (Federal Register, Vol. 75, No. 98, may 21, 2010/Proposed Rules, p. 28700-701), approximately 5,000 institutions would be affected by the proposed changes. Inasmuch as many clinical trials are conducted in academic-medical centers and the proposed rules incorporate a provision for institutions conducting PHS-funded research to establish a legally-enforceable written agreement with any sub-recipient, contractor, or collaborator, to comply with PHS regulations or the institution's policy(s). Adoption of the same substantive guidelines by the FDA would ensure that clinical trials and non-clinical trials research would be subject to the same general definitions and policies, thus reducing confusion and conflicting standards.

As described above, self-disclosure by researchers is a problem at most institutions for three main reasons: 1) researchers do not believe a potential conflict will cause bias in their research, 2) institutional culture does not embrace full disclosure for publicity-related reasons, and 3) varying monetary thresholds and types of conflicts are not standardized across institutions, public agencies, or industry. In this proposed model, yearly COI disclosures should ask all employees to list all organizations from which the employee receives a W-2 or Form 1099 (or any other IRS tax form denoting an income source). This method would not only standardize the monetary amount across institutions, but it would simplify employee disclosures for employees since they could be timed to coincide with tax season, when all tax forms are readily available for input onto a COI disclosure. This standard approach, which must be enforced by all research organizations, will institutionalize this yearly disclosure and make the practice rote. This may also enable cross-checking with IRS databases for auditing purposes.

Universal Publication of COI Management Plans, Clinical Trial Designs and Results on Clinicaltrials.gov

The recent Patient Protection and Affordable Care Act includes the Physician Payment Sunshine Act" (PL 111-148) which requires drug and medical device manufacturers to disclose payments to physicians in a publicly-available Internet resource managed by the Secretary of Health and Human Services. The author suggests that the same standard should be used for payments to researchers in CCTs, possibly using the existing government-maintained database of clinical trials information, http://www.clinicaltrials.gov. This would enable any member of the public to access a specific clinical trial and view any related COI management plans (both

institutional and individual), resulting in a transparent and consistent disclosure to the public of every clinical trial.

In addition to the publication of COI management plans on the Clinicaltrials.gov database, legislation should be introduced which requires the *complete* study design of all clinical trials to be disclosed on the database and requires the complete study results to be posted on the database, whether the trial was completed, changed during the course of the trial, or not completed. This transparency in research design and reporting will ensure that peer scientists can evaluate the results of clinical trials based on scientific merit, incorporating knowledge of good scientific study design and the influences upon the stakeholders in the clinical trial.

Use of Existing Infrastructure

As any research administrator or researcher knows, each passing year brings more regulations and more burdensome administrative requirements, and each passing year brings less funding for meeting these requirements. Thus, any new model to address conflicts of interest must be cost-effective and not put a greater financial burden on already overtaxed research administration systems. For this reason, this new model will use the IRB system already in place in all organizations conducting human subjects research to eliminate the necessity of creating another administrative department and institutional infrastructure for COI disclosures and management.

It is important to note that this model only uses the IRB mechanism for identification and management of individual COIs, and identification but not for management of institutional COIs. Institutional Review Boards are not immune to the conflicts of interest and numerous studies have found that faculty members of IRBs have industry affiliations and indirect pressure to facilitate human subjects research which could benefit their institutions (Huang & Hadian, 2006, p. 2).

In Cases of Identified COIs, an External IRB or Ethics Consultation Service Should be Used to Prepare a Conflict Management Plan and Manage the Plan

Another aspect of this new model to mitigate the shortcomings of institutional COI management is the use of an external COI management body or independent committee to manage any identified institutional COI. Following the strategy of using existing infrastructure, this author would suggest expanding the service offerings of Western IRB and other independent IRB service providers to encompass COI management in such instances. Cho et al. (2008) performed a pilot program of an ethics consultation service at Stanford University, one of the goals of which was to "integrate ethical considerations into the early phases of research planning" (2008, p. 1).

Technological Integration of Conflict-Checking Software

Because the effectiveness of self-disclosure is largely dependent upon the potentially conflicted researcher or an individual whistleblower, research institutions should research other methods of learning about potential financial conflicts of interest. There are a variety of business software solutions which integrate virtually all facets of a corporate environment in order to maintain effective systems and enforce compliance. For example, legal firms have utilized both stand-alone and integrated conflict-checking software for many years; this software can monitor all

parties to a lawsuit, attorneys, family members, vendors, employees, and clients. Integrating a research institution's human resources systems with its financial systems and either adding an existing conflict-of-interest software product or customizing software to fit institutional needs would greatly enhance the knowledge available to the IRB assigned to identify COIs. It would also make COI identification scalable in large organizations, where multiple IRBs are used for different research areas and no single committee can possibly know all of the potential COIs on a given CCT.

Areas for Further Research and Exploration

The legal field has recognized the importance of avoiding COIs for many years, and has voluminous materials and resources available for identifying and managing conflicts. The most basic of methods to manage a conflict is a "firewall," in which individuals identified as having a conflict are excluded from knowledge of or decision-making ability in a specific situation (depending on the scope of the conflict). In some situations, lawyers, judges, and even whole law firms voluntarily withdraw from or are excluded from participating in cases. Financial systems, especially lending and securities industries, are also engaged in constant dialogue about the identification and management of conflicts of interest.

As noted above, this proposed model has not been the subject of original research, although it is supported by literature in the field. Each aspect of the new model should be tested empirically for effectiveness, and the cost in terms of time, personnel, and money needed to implement such a system should be defined. Finally, the most difficult aspect of seriously evaluating this new system will be to engage the stakeholders in CCTs, policymakers, and the public to create a unified effort and a new cultural norm: full transparency in all aspects of collaborative clinical trials.

CONCLUSION

The tide is already turning as the public, policymakers, associations, and research institutions recognize that a lack of oversight and inability to enforce potential conflicts of interest is eroding public trust in research integrity. Gatter (2003) writes, "one person's financial conflict of interest is another's example of efficient technology transfer" (p. 341). Public policy makers must weigh the trade-offs between efficiency and safety for human subjects. Currently, the scales are tilted toward efficiency: effective market incentives for technology transfer have made CCTs an economic commodity, and now externalities in the form of potential or real harm to human subjects have increased to the point that the public wishes to regulate trade in this commodity.

If we study all of the stakeholders, influences, values, and norms in a collaborative clinical trial, we will never fail to identify conflicts of interest; however, as a society we are collectively committed to protecting human research subjects, end-users of technologies, and the scientific integrity. The new model proposed in this paper is fully transparent, and whether individual components of the model are judged to address the current issues in CCTs or not, a holistic vision of full transparency of researchers, industry, and universities will enable human subjects to make informed decisions to participate in clinical trials. Full transparency will enable members of the public and legislators to understand the forces affecting collaborative clinical trials and to maintain control over ethical boundaries. Finally, institutionalization of a new cultural norm - transparency in all aspects of collaborative clinical trials - will enable scientists to

evaluate the content of those CCTs with a full knowledge of all factors – enabling peer review in its most candid form and ensuring the integrity of scientific research.

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