Lecture

Conflict of Interest in Research—The Clinician Scientist's Perspective

Nicole HY Kong, [1]*Bsc(Hons)*, Pierce KH Chow, [2,3,4]*MBBS, FRCSE, PhD*

Abstract

Conflict of interest (COI) in research represents situations that pose risks of undue influence on scientific objectivity and judgment because of secondary interests. This is complex but is inherent to biomedical research. The role of a clinician scientist can be conflicted when scientific objectivity is perceived to compete with scientific success (publications, grants), partiality to patients (clinical trials), obligations to colleagues (allowing poor scholarship to pass), research sponsors (industry), and financial gains (patents, royalties). While there are many ways which COIs can occur in research, COI mitigations remain reliable. Collaborations between investigators and industry are valuable to the development of novel therapies and undue discouragement of these relationships may inadvertently harm the advancement of healthcare. As a result, proper management of COI is fundamental and crucial to the maintenance of long-term, mutually beneficial relationships between industry and academia. The nature of COI in research and methods of mitigation are discussed from the perspective of a clinician scientist.

Ann Acad Med Singapore 2013;42:623-8

Key words: Academia, Disclosure, Industry

Introduction

Discussions of conflict of interest (COI) have been 'age-old' controversies since the involvement of industrial sponsorship in academic research begun. This topic is complex and entails numerous definitions, viewpoints, and confounding factors that are often non-quantifiable and difficult to objectify.

A detailed and encompassing definition set by the Institute of Medicine's (IOM) Committee has defined COIs as: "A set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest", identifying 3 main components of the definition: the primary interest; the secondary interest; and the conflict itself. As a matter of principle, the primary interest should take precedence over a secondary interest in any decision-making process.[1]

Conflict of interest is thus a set of circumstances that predisposes to an occurrence and not the occurrence itself. The occurrence itself would technically constitute a breach rather than a conflict. It is worthwhile to bear this in mind when considering conflicts of interest in research. Primary interests are generally described as the patient's interest, which includes integrity of research, welfare of patients, and quality of medical education. Secondary interests refer to the interest of the physician or researcher that may include financial gain, desire for career advancement, acknowledgment for personal achievement, and personal favours. The third component, the conflict itself, denotes any situation that basically risks the neglect of the primary interests as a result of the focus on the secondary. An individual recognised to have a COI does not imply the commitment of an unethical act, but that the situation generally poses an objectionable risk that decision-making may be unduly influenced by secondary considerations.[1]

[1]Department of General Surgery, Singapore General Hospital, Singapore
[2]Department of Surgical Oncology, National Cancer Centre, Singapore
[3]Department of HBP/Transplant Surgery, Singapore General Hospital, Singapore
[4]Office of Clinical Sciences, Duke-NUS Graduate Medical School, Singapore
Address for Correspondence: Professor Pierce KH Chow, Office of Clinical Sciences, Duke-NUS Graduate Medical School, Singapore, 8 College Road, Singapore 169857.
Email: pierce.chow@duke-nus.edu.sg

COIs can arise in any professions, but is of particular concern, and in full glare of the public eye in the area of biomedical research. The key to understanding this topic is to recognise that biomedical research is inherently conflicted. Perpetual contentions arise unavoidably from the differences in goals and expectations that stratify according to the different roles and professions in biomedical research. The Declaration of Helsinki summarises societal consensus that the primary purpose of biomedical research is to understand the causes, development, and effects of a disease, and to improve preventive, diagnostic, and therapeutic interventions through improved methods, procedures, and treatments.[2]

This purpose runs in line with what society expects of biomedical research, but the goals of institutions, researchers and sponsors involved in research may differ from this. Health Service institutions (and even Academic Medical Centres) work to establish corporate growth and diversification of research, or clinical services as their primary purpose. Decision-making processes from institutional grant applications to selecting flagship projects, and area of funding tend to be prejudiced by corporate bottom lines. Similarly, and even more so, industry sponsors target growth and profits, and efforts from government sponsors to diversify and encourage research is fundamentally intended to bring around economic prosperity, and in the final analysis, to win electoral support from their constituencies.

The professionals in the biomedical industry for example physicians, surgeons, researchers, and clinician scientists themselves tend to target increase funding, income, and higher academic status as immediate goals. As a result, they tend to be implicated with conflicts that value fiduciary influence and professional advancement over scientific judgement. A clinician scientist, defined here as a physician, surgeon, or clinician who also engages in clinical and translational research, plays a dual role that is contradictory at its very constitution, and as a result, bears the combination of potential COIs. While the first role, the role of a doctor is the immediate diagnosis and treatment of the patient (at the lowest practical cost to patient and best returns to institution), the second role, the role of the scientific researcher, while aligned to the first, can differ in details. The latter focuses on the endpoint of the study, as exemplified in clinical trials, where therapies will contribute to the improvement of treatment options for future patients.

In this paper, we examine the nature, consequences and recommendations of COIs from a clinician scientist's perspective. The topic of COI, medical and research ethics, and regulatory policies, discussed more extensively in the Western literature, has been found deficient in Asia. The significance of the topic will continue to grow with the rapid expansion of biomedical research in the local context.

Conflict of Interests and Relationships with Industry

The relationship of the clinician with industry is one of the most aggressively debated subjects in healthcare today.[3] Historically, academic researchers and Academic Medical Centres (AMCs) have full control of clinical trial management from study conception to published results. Today, academia continues to experience a power struggle with the industry. Pharmaceutical and device companies control study designs, data analyses, and make writing and publication decisions. Complex and extensive relationships formed through interdependence between academia and industrial partners including pharmaceutical and drug companies, CROs, and SMOs further complicate COI management.[4] Not all relationships represent true conflict. However, the potential for COIs can exist regardless of whether clinicians believe that the relationship affects their scientific judgement—conflict is relevant to all relationships to the industry. These relationships are ubiquitous, and may be overt, for example financial COIs, or less conspicuous, for example, personal, professional or intellectual.

Financial Relationships and Financial Conflict of Interests

From the 1970s, financial support from the industry has propelled academic research into the continual production of promising new products to enter industrial development. Results produced from interactions between academic research and industry support have been significantly positive, producing an increasing number of patents awarded to academic institutions, and growing government encouragement.[5] It must be recognised that the involvement of the industry is crucial to the development of new diagnostics and therapeutics that bring immense benefits to patients, without which biomedical research loses much of its meaning. To date, the number of clinical trials which the entire product's life cycle is funded by the pharmaceutical industry continues to increase. In the United States, financial support of medical research from the industry far exceeds the amount invested by the National Institutes of Health.[6] It is however, disconcerting to know that despite the efforts from regulatory authorities to put in place COI guidelines and policies, clinicians today have difficulty describing them.[7]

The growing relationship between academia and industry has inevitably led to suspicion that these collaborations increasingly focus on fiduciary benefits rather than patient care and medical advancement. Academics who have failed to protect their primary interests have crippled the trust of public in biomedical research.

Financial relationships with the industry have since been the focus of public, institutional, and regulatory scrutiny. It is relatively more measurable and objectifiable than non-

financial relationships. In this way, financial relationships can be more precisely monitored and therefore more effectively regulated.[1] Table 1 shows the types of financial conflict of interests (fCOIs).

Table 1. Financial and Non-financial Conflict of Interests (COIs) in Research

Financial COIs	Non-financial COIs
Research Incentives: • Incentives for patient recruitment. • Financial stakes in outcome of trial.	Professional: • Scientific advancement, recognition, and influence. • Undue interest to attain positive results, and pressure to publish. • Disregarding or under-reporting adverse effects.
Financial gains: • Travel, meals, lodging, personal expenses, and payment for professional services e.g. talks, sponsored consultancy, gifts, equity interest, personal funds.	Personal: • Nepotism—bias for family and friends. • Vigilante desire—recruitment of patients into trial for free medication/ treatment.
Intellectual Property: • Monetary benefits from patents and technology transfer, new venture formation, royalties.	Intellectual: • Any research participation i.e. grants and authorship directly related to topic of recommendation. • Prejudice against or towards certain therapy/drug due to any reasons not purely for patient benefits.

Drug companies spend billions on marketing their products each year, primarily targeting doctors,[8] majority of whom are not involved in any form of research. It has been reported that physicians experience a sense of obligation to reciprocate gifts from pharmaceutical representatives, regardless of the price of the gift.[8,9] In a nationwide survey of physicians in the United States in 2007, 94% of them reported some form of relationship with industry.[10,11]

Physician–industry relationships can be grouped into 4 general categories. The first is free drug samples. The second category includes gifts, for example, food and beverages in the workplace, or free tickets to social events. Reimbursements for expenses, such as costs of travel, time, meals, lodging, and other personal expenses make up the third category. The fourth category comprises paid consultancies, service on scientific advisory boards, speaking at a conferences, or recruitment of patients in industry-sponsored clinical trials.[10-13] These relationships are not all directly related to biomedical research. In fact, the main target is the general body of doctors with prescribing powers.

In the case of clinical trials, patients' benefits and safety from participation are uncertain and dependent on the investigator. An investigator that holds a financial stake in the recruitment and outcome of the trial that they conduct has an ambiguous interest and may undermine trust.[14,15] The vulnerability of patients and trust placed on the investigator warrants that investigators do not have financial stakes in the outcome of the trial. Although the Declaration of Helsinki explicitly requires disclosure of funding sources to research subjects,[2] governmental or institutional requirements to disclose financial conflicts of interest to potential research participants are few, and if present, not extensive.[14]

Non-Financial Conflict of Interests

Non-financial COIs are typically harder to define and regulate. In this paper, we assemble them into 3 main groups: Personal, professional, and intellectual COIs (Table 1).

Most easily identified are personal COIs. By and large, researchers with authority in situations should not display preferential treatment for familial or personal relationships. Serving on review boards for grants and publications submitted by students, relatives or friends is an obvious example of a personal COI.[16] Allowing personal moral convictions or vigilante desire to influence a scientific opinion are other examples.

The pressure to produce positive results and high impact publications to advance in the academic world may lead to the committing of a professional COI. Unlike the rest which requires declaration for the public and authorities to judge, committing a professional COI equates to an undisputed violation of research ethics. This is very insidious and common but difficult to pinpoint and extends to poor or detrimental reviews of submitted publication or grant proposals of potential or actual professional and scientific rivals.

Intellectual COIs are defined as academic activities that create potential for attachment to a specific point of view that may unduly affect an individual's judgement about a specific recommendation.[17] These activities include receiving grants, participation in research, and authorship of original studies directly related to that recommendation, which a cognitive bias towards their area of expertise risks objectivity at a research question. Similarly, a potential conflict may not mean the researcher has compromised scientific objectivity, but indicates a need for disclosure when necessary, for the consideration of the public when judging the researcher's recommendation and statements.[17]

Conflicts of Interests in Clinical Trials

Majority of prominent clinical trials are co-sponsored by industry and a large portion of those trials tend to be solely funded by industry. These companies have research agendas that strongly focused on its products. An analysis of 577 randomised trials in 2010 showed that 82% (478/577) of them were sponsored by a single industry sponsor. A total of 88% (509/577) of the trials were either solely sponsored and evaluated only its own product, or if co-sponsored examined a single co-marketed product.[18]

There has also been extensive evidence that academic studies with industrial support are more likely to yield pro-industry conclusions.[19-24] A Cochrane analysis in 2012 including cross-sectional studies, cohort studies, systematic reviews and meta-analyses revealed that industry sponsored studies showed results that were more favourable but had less agreement with the conclusions, than in non-industry sponsored studies.[20]

Pro-industry Bias in Medical Publishing

Pro-industry bias has also been identified in medical publishing.[25-27] A study involving 6 major medical journals demonstrated that industry-supported trials were more regularly cited than trials with other types of support, and omitting them decreased journal impact factors up to 15% for the New England Journal of Medicine (NEJM) in 2007. Income from the sales of reprints made 41% of the Lancet's total income in 2005 to 2006.[28] In addition, a significant association between self-reported COIs of editorial authors and favourable editorial opinion has been reported. This analysis of phase III clinical trials of 4 major oncology journals also revealed 43% of these editorials to report at least one COI, with the most frequent being consultancy fees.[29]

Conflict of Interest Management

Conflict of Interest Policies

The design, implementation, and maintenance of COI policies are time-consuming processes, necessitating large amounts of administrative manpower, and continually effective supervision. COI policies should include the basic elements of financial relationships disclosure, prohibition of conflicted relationships, and how to manage conflicts that have been identified.[30] Because there can be substantial diversity in COI policies between institutions and different the roles in medical research, the institution must devise its own disclosure form and determine reporting thresholds.[31] Academics belonging to more than one affiliation will have to work within the governance of different COI policies. A clinician scientist for example, will need to understand policies that range from those of medical schools, hospitals, medical journals, professional societies, and advisory committees. The challenge facing AMCs, hospitals and educational institutes remains—the ability to conceive COI policies that reduce unnecessary relationships and remove undue influence, whilst designing collaborative models that encourage beneficial academic—industry collaborations.

Disclosure

Disclosure is the most commonly prescribed remedy for this pervasive and ambiguous topic. The evaluation of a COI is only possible if such conflicts are disclosed in the first place.[29] Although disclosure does not provide a comprehensive solution, it acknowledges potential conflicts, is low-cost, easily implemented, and requires minimal regulation.[32,33]

Many disclosure polices have been put in place to regulate conflict. Invited speakers at national and international conferences are required to disclose financial ties with industry. Similarly, submissions to international journal publications mandate the completion of the International Committee of Medical Journal Editors (ICMJE) conflict of interest reporting form[34] and failure to do so may lead to penalties. Some journal mete out severe penalties, for example, Environmental Health Perspectives imposes a 3-year ban on investigators who failed to disclose competing financial interests,[35] and the Mayo Clinic enforces internal investigations and participation in remedial activities for incomplete disclosures.[36]

COI disclosure aims to promote informed decision-making, establish trust, and protect welfare of research participants by deterring investigators from troubling financial relationships, and minimising the risk of legal liability.[32] Disclosure should provide adequate information about the type, scope, length, and amount of money involved in relationships to allow the public, patients, and institutions to assess the risk that secondary interests may influence primary objectives.[30]

The Role of AMCs and Physician Leaders

AMCs are where potentially conflicted relationships are concentrated, and therefore play a central role in upholding the integrity of its research. Because they are positioned to lead academic medical research, the AMC's institutional culture and requirements, for example, public access, peer review, and transparency, coupled with cautious monitoring, can minimise the likelihood of undue influence on the investigator.[8] At the same time, it is imperative that COI management can be carried out without preventing beneficial collaborations with the industry, particularly those that will benefit large groups of patients. AMCs should serve as an intermediary at the institutional level and act as the grant

holder to receive grants and financial support provided by the industry.

The significance of academic medicine leaders taking the lead in exemplifying COI management too, cannot be repudiated.[30] Physicians themselves tend to be more sensitive to unintended consequences that may surface from policy enforcement, and will hence be able to contribute an inside view to the development of stronger COI policies usually implemented by legislators. Leading by example will reinforce the importance self-regulation and management of COIs, and can greatly improve collaborative culture in the institute.

Importance of COI management in Asia

The increasing number of clinical trials and research run in Asia underscores the importance of good COI management. Introduction of proper systems for COI declaration presents accountability and will reduce potential conflict. When more academic research institutes, healthcare professionals, and researchers work in line to improve COI management, academic research is encouraged whilst breeding appropriate research values. Scientific research will be able to advance rapidly and evolve healthily, moving in line with Asia's vision of becoming the next medical research centre of gravity.

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