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Role of conflict of interest in biomedical research

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Abstract
Scientific knowledge is often considered objective and absolute; however, history of science shows that it is contingent upon the existing knowledge systems and the process of evidence generation itself. Randomized Control Trials are the gold standard as far as clinical evidence is concerned. Processes are incorporated to minimize an investigator's bias towards obtaining a favorable outcome. As the role of big pharm becomes more prominent and rather pivotal in conducting modern clinical research, scientific community faces a new and overarching challenge: Conflict of Interest (Coif). This article will delve into the details of how Coif can potentially diminish the credibility of scientific research and how should consumers of scientific literature ascertain the reliability of industry sponsored clinical research.

Keywords: biomedical research, scientific knowledge, health, medicine

Introduction

We are a part of the neoliberal knowledge economy, where the knowledge produced ought to have an exchange value and has to be profitable. This knowledge economy has an ideological commitment and it is driven by a value system that extols efficiency and marketability of knowledge. Knowledge, like any other commodity is to be governed by the rules of demand and supply. As the resources for social sectors were withdrawn to be invested in more productive and profitable sectors, as per the conditions imposed by the Bretton Woods financial institutions, it had its impact on academic research as well. Unavailability of resources created an opportunity for 'for-profit' business organization to invest in academic research. And how would they get best returns on their investments; by creating a system of production and consumption of knowledge that can generate results as quickly as possible and as efficiently as possible. A delay in getting the trial results, or getting an approval for national use will diminish the returns on investment. However, finding answers to complex questions is time consuming and hence not a profitable proposition. Given this context the role of regulatory and decision-making agencies becomes more pronounced to balance the need for profit with the need for people's health. There are precedents to warn us that the haste to be done with the regulatory requirements leads to the process of research itself being compromised. Ethical guidelines then become nothing more than dispensable hindrances. Does this interconnectivity between institution and processes not raise the question of conflict of interests? Is it not indispensable for the National Technical Advisory Group on Immunization to look at the conflict-of-interest aspects before making its recommendations? Although conflict is obviously an intrinsic and often unavoidable feature of public health programmes, given the increasing partnerships of the industry with governments and academics, regulating agencies should always try to mitigate particularly blatant forms of conflict.

> "The case against science is straightforward: much of the scientific literature, perhaps half, may simply be untrue. Afflicted by studies with small sample sizes, tiny effects, invalid exploratory analyses, and flagrant conflicts of interest, together with an obsession for pursuing fashionable trends of dubious importance, science has taken a turn towards darkness…The apparent endemicity of bad research behaviour is alarming. In their quest for telling a compelling story, scientists too often sculpt data to fit their preferred theory of the world. Or they retrofit hypotheses to fit their data."
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> Richard Horton, Editor of The Lancet, 2015 [1].

These views were expressed by the Editor in Chief of The Lancet, a prominent medicine journal with an Impact Factor of 44·002 and currently ranked second out of 151 journals in the Medicine, General & Internal subject category [1]. Horton expressed his anguish on the state of affairs in the scientific research community after attending a symposium on the reproducibility and reliability of biomedical research in London in 2015, along with editors of some the most reputed medical journals in the world. This is a result of incentivizing productivity in research rather than its accuracy, Horton questions the benchmarks that have been set to evaluate to evaluate researchers. Issues raised by Horton stem from larger structural issues that modern biomedicine research faces, the issues of the paradigms of scientific epistemology itself. What is the nature of Science and how is scientific knowledge gathered? What are the assumptions being made and evidence collected to make a scientific proposition? And how can we test scientific knowledge? Scientists and philosophers have been grappling with these questions from ancient times and such is the nature of these enquiries that the debate still goes on. Modern scientific methods are inductive; basing general statements on accumulated observations of specific events, forming hypothesis based on such observations and testing those hypotheses. Although inductive methods have come to dominate and define scientific knowledge for centuries now, scientists and philosophers have simultaneously found

themselves at odds with the purported certainty that inductive methods lend to any hypothesis. Austrian philosopher Karl Popper argued that knowledge is both probable and contingent and the best way to prove a hypothesis is to try to disprove it. The real test of knowledge is not corroboration but falsification, attempting to disprove a theory is the best way to prove a theory (Magee 1973) [6].

Popper's theory of falsification is of great relevance in the pursuit of modern scientific knowledge, which is dominated by statistical confirmation. But the problem with statistical data is that it confesses if interrogated long enough [1]. We are bound to find corroborating evidence if we are looking for it, therefore as modern scientists how we scrutinize supporting evidence and deal with counter evidence is the test for scientific discernment. Rotavirus vaccine research is a microcosm of the problems facing modern day science and according to Popper, it is both probable and contingent on existing evidence and new assumptions.

Industry Involvement and Credibility of Research

The partnership of science with business has also shown to give rise to practices ranging from ghostwriting and ghost-managing to producing favorable results (Sismondo 2007) [9]. Business interests in scientific research have now been known to influence the scientific rigor and the results of a study. Studies have reported that authors whose findings favored the safety of a drug, were found to have frequent financial relationships with the drugs' manufacturers than the authors whose work did not and that the results favoring a new therapy over a traditional one was more likely to be reported if the study was funded by the new therapy's manufacturer (Stelfox *et al*. 1998) [10]. Another systematic review demonstrated that articles from symposiums sponsored by a single drug company were more likely to have outcomes favorable to the sponsor's drugs than articles without company support (Cho and Bero 1996) [2]. A health policy report prepared by Bodenheimer to discuss some of the problems raised by pharmaceutical industry funding of drug trials had interviewed six clinical investigators and the respondents cited instances when publication of articles was stopped or whose content was altered by the funding company to suit its ends (Bodenheimer 2000) [1]. Frank Davidoff and others in their joint editorial publication of 2001 questioned the objectivity of industry led clinical trials. They noted Public discourse about this published evidence of efficacy and safety rests on the assumption that clinical-trials data have been gathered and are presented in an objective and dispassionate manner. This discourse is vital to the scientific practice of medicine because it shapes treatment decisions made by physicians, and drives public and private health-care policy (Davidoff *et al* 2001) [3].

Another review of 44 research articles to analyze the industry conflict of interest in the clinical trial of oncology drugs found that 5 percent of industry sponsored scientific studies of cancer drugs reached an unfavorable conclusion about the company's products vis-à-vis 38 percent of studies arriving at adverse conclusion with nonprofit funding. The study further reported that a number of cases have shown that investigators who publish or communicate results contrary to the expectations of their sponsors face intimidation and efforts are made to discredit them professionally including threats of legal action (Friedberg 1999) [4].

But it is not only business interests that have compromised the sanctity of research in science, scientists themselves have been held responsible for numerous unethical and sometimes illegal practices in the name of science. History of clinical trials is marred with many such instances when scientists have violated scientific and ethical principles either for personal gain or to benefit governments and institutions. Unfortunately, it has taken many tragedies for the scientific community to come up with a code of ethics and principles that must govern research, especially ones involving clinical trials. The Nuremberg Code was the first set of such guidelines that was part of a judicial order condemning the atrocities of Nazi physicians, it focused on the need for consent and a favorable risk to benefit ratio. But it fell short of dealing with what is now understood as a norm for clinical research i.e., fair subject selection and independent review. The gaps in the Nuremberg code were attempted to be filled by the Helsinki Declaration of 1964. The declaration has been revised many times since then; adding guidelines on protocols of studies, informed consent from legally incompetents and minors, rights of participants and publishing of outcomes (WHO 2001). The latest modifications in the declaration were ratified by World Medical Association in 2013 and it iterates the importance of disclosure of trial related information.

"Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports" (Masic *et al*. 2014) [1]

Jonathan Quick, director of the essential drugs and medicine policy of WHO in 2001 wrote in the editorial of Bulletin of the World Health Organization expressed his concerns on the validity and reliability of clinical trial results by observing that clinical trials are at the core of effective research and development, but the reliability of these trails is currently under threat by three major flaws:

- Investigator's conflict of interest,
- Inappropriate involvement of sponsor institutions in study design and management,
- Bias in publishing and disseminating results (Quick 2001) [8].

There is enough evidence to prove that some of the most credible voices in global public health have been expressing their concerns on the authenticity and accountability of clinical trial findings for quite some time now. Business involvement has the potential to affect the processes as well as the results of a clinical trial.

Collaboration of business and academic interests in designing and conducting a scientific study is a rising global phenomena. The infusion of industry funds into clinical trials has improved clinical practice, yet the medical literature contains many articles expressing concern about industrial funding of clinical research. Academic research is more time intensive because academicians and scientists have multiple obligations to fulfill. The delay in getting an institutional approval, designing and conducting the study means that the subsequent approval is delayed. The time cost translates into financial loss for the manufacturers and hence the speed of the trial becomes of paramount importance for the manufacturers (Bodenheimer 2000) [1]. This has also given rise to the phenomena of Contract

research Organizations (CRO) and Site Management Organizations (SMO). These professional organizations can be contracted with the responsibilities ranging from study design to completion of the entire research process. The Commonwealth Fund Task Force on Academic Health Centers found that academic research is slower and more expensive than the research conducted by commercial and professional institutions like CROs and SMOs (Their 2000) [11].

As the rise of these organizations is a new phenomenon, their role, functions and even their definition has not been promulgated. Only available resource is the Guidelines for Good Clinical Practice, published in 1996 by The International Council for Harmonization (ICH). It was created in 1990 after a meeting of representatives of the regulatory agencies and industry associations of Europe, Japan and the US. The ICH defines a CRO as;

"A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions." (ICH 1996) [5]

Defining what responsibilities, a CRO can handle, the report further specifies that the trial sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO and the CRO is expected to implement quality assurance and quality control (Ibid).

Size and Potential of the Global and Indian Vaccine Market

Vaccines are neither consumer goods nor are they like any other pharmaceutical product. They are administered to a cohort of healthy children, and in India the size of this cohort is more than quarter of a billion. Sheer size of this group and the lucrative business opportunity it provides to a manufacturer, has made the Indian vaccine market much coveted. Once a vaccine is introduced in the country's UIP the manufacturer gets a 25 million large captive market without any need to market or push for the product. This research attempts to explore if the business interests have outweighed the epidemiological needs of the country.

Global vaccine market is a booming business sector, but the real opportunity lies in the developing countries that share 83% of the world's population but only 18% of the vaccine sales. Clearly, the future of vaccines relies on the global south. The size of global vaccine market was estimated to be USD 24 billion in 2013 and is expected to reach USD 100 billion by 2025. A growth rate of 10-15% is twice as much as the growth rate of the pharmaceutical markets and the size of the vaccine industry has trebled in a period of just eight years from 2000-08 (WHO 2009). This kind of growth is extraordinary and is buoyed by a global push for vaccination lead by UN agencies, transnational partnerships and foundations. Indian market is expected to grow at a higher rate than the global vaccine market at a rate of 20% and is estimated to reach USD1.65 billion by 2020 (OPPI 2012). The Indian vaccine market has tremendous size as well as growth potential, to put the volume of Indian market in perspective; the volume of vaccines Indian government purchases for a vaccine in the UIP is more than the volume of purchase of sixty rich countries. That is the scale of the market the new rotavirus vaccine is going to have. Interestingly, the future of this immense market is shaped not by a global health agency or national governments, but by a few of the world's largest private and non-governmental institutions.

An important reason for the burgeoning growth is the nature of the product itself, new product developments of vaccines are driven by technology-push innovation than demand-pull innovation. Markets in developing countries are perfect places for this top-down technology push, as soon as the requirement for a vaccine starts getting saturated in developed countries, its growing needs in developing countries is suddenly being realized. If a vaccine is included in a national immunization programme, it gains a captive market, which only grows with the growing population every year. Even if a vaccine is not under any NIP, mechanisms like pre-qualified orders from WHO and UNICEF and Advance Market Commitment by governments and GAVI ensure a steady flow of vaccines in the market.

However, market projections did not include a deciding variable that changed the course of the global vaccine market; and that variable is the COVID19 disease. The biggest health crisis of the century has drastically increased the size and demographical spread of the global vaccine market. The market initially more or less limited to childhood immunization has now incorporated every adult on the face of the world as a potential consumer. In the absence of a safe and effective treatment option, vaccines against the new coronavirus disease. Billions of dollars have been invested in the COVID-19 vaccine research, both by governments as well as by pharma companies. As immunization has gained prominence on the global health agenda, the markets are only going to be more lucrative. It is no surprise that industry is showing greater interest and putting in higher investments in manufacturing and marketing new vaccines. Strengthening industry-academic research complex brings many advantages like unhindered flow of funds and an efficient research process, but it has its own pitfalls, which will be discussed in the subsequent sections. However, before doing that, it is also important to look at the regulatory-policy framework that governs this research process and the eventual marketing of the vaccine.

Discussion

There is a growing concern among the scientific community on the endemic lack of rigour in research. Researchers often selectively use data to fit their narrative, compromise on research design and allow their conflict of interest to affect their findings. It calls for scientists, scholars and policy makers who use and reproduce these studies in their own works to be more vigilant while dealing with scientific research. A part of maintaining rigour in secondary research should now include ensuring that the research articles used and analyzed are reliable and present valid findings. Role of scientific studies is critical in evidence-based policy making where the evidence has to be critically examined before decisions are made. Credibility of evidence becomes especially important in case of translational research as it could have long term and serious impact on a country's health systems. Whenever research translates into policy, rigour has to be sacrosanct and a strong evidence base should inform policy decisions.

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