The Crisis in Clinical Research: Research and Ethics: The Industrial-Institutional-Investigator Interface

Timothy Lipman, MD*†

Key Word: research

Thank you for this invitation, Dr. Buchman and the AFMR. I am honored to be here. Before I begin, I need to make a disclaimer: I work for the Department of Veterans Affairs at our local hospital, but anything I say are my own opinions and have nothing to do with the official VA policy.

Over the past week, Jews around the world have been celebrating Passover and, as part of the Seder, we repeat the Ten Plagues that God passed upon the Egyptians. Many Jews, at their Seders, will come up with 10 contemporary plagues and use these as a forum for discussion. So in thinking about this talk, I came up with 10 research ethical plagues: conflict of interest, bias, falsification of results, suppression of data, manipulation of data, misrepresentation of data, selective reporting of data, greed, acceptance of gifts, failure to consider the best interest of the research subject, and harmful results to patients for misinformation. This list evolved over a month as I thought about this topic. If I went through all of these topics in this list, Dr. Buchman would quickly hook me off the stage.

In thinking further about this topic, I recalled a classic Pogo cartoon. I think a major issue and a major theme is that we have met the enemy, and he is us. About a month ago, The New York Times published an article about ethical issues at Harvard Medical School involving a professor of pharmacology there. Recently, The Washington Post talked about a drug study that was silenced. The New York Times also published an article about another professor at Harvard University. All I can do is go by what I read: that if these investigators did these studies, they would gather the results that they wanted. In addition, congressional committees have recently been talking about oversight and the regulation of clinical trials. I want to focus on 3 topics, some of which other presenters have already addressed, but I will give these points greater emphasis: conflict of interest, bias, and institutional review boards (IRBs). These points all rotate around a triangle of participants: the clinical researchers, industry, and the academic institutions.

CONFLICT OF INTEREST

How do we define conflict of interest? Perhaps, the definition is like the US Supreme Court’s definition of pornography: We know it when we see it, yet it is difficult to define. To find definitions, I went to the Web and found multiple definitions, of which I picked several: “The entanglement of an individual’s private interest with professional obligations such that an independent observer might reasonably question whether the individual’s professional actions or decisions are improperly influenced by considerations of personal financial impact” and “Faculty, staff, or student, employees have significant financial or other personal considerations that may compromise or have the appearance of compromising the professional judgment or integrity in teaching, conducting, and reporting research.” These definitions contain 2 important elements: first, both address the financial conflicts of interest, and second, both address the appearance of conflict of interest. These 2 elements are integral in terms of conflict of interest.

Today, virtually all professional and society meetings have supporters—industry that sponsors these meetings. At these major meetings, for every presentation, speakers are supposed to talk about conflict of interest. While speakers follow the standard procedures for reporting conflict of interest, they are basically giving lip service to that standard. The concept is devoid of meaning, and we observe it because we reported it, but we ignore the spirit of what is meant or the overall implications. So the research ethics in the news that I addressed earlier really involve industry, they involve institutions, and they involve individual investigators. The problems revolve around money and various types of bias.

BIAS

What is bias? Bias is a subject that has interested me, as I have taught critical thinking to teach residents and GI fellows how to critically evaluate medical literature. Bias can be defined as a one-sided inclination of the mind. In study design and methodology, bias is a sampling or testing error caused by

The Conflict of Interest Triangle
systematically favoring some opinion over others or a combination of various design, data, analysis, and presentation factors that tend to produce research findings that should not be produced—something inherent within the study that generates a certain outcome. Bias in scientific studies does not mean prejudice, especially within the study design and methodology. Bias is a systematic influence that leads to different outcomes. It is often unintentional or subconscious. Many factors can influence an outcome that the study is measuring or a conclusion that is made within study design or methodology; bias can only be reduced by proper study design in execution and recognition of its actual or potential existence.

Studies of low quality have a high likelihood of bias, and high-quality studies have a low likelihood of bias. When we look at published studies and journal articles, I like to ask my students, residents, and fellows about bias: Does this study have a high likelihood of bias or a low likelihood of bias? What are the biases that are inherent in the design? Through bias, we are involved with a conflict of interest. Bias is created because the investigator has a hypothesis that he or she wants to prove. The investigator is also interested in professional advancement, and the study that proves a hypothesis is going to advance him or her further. Investigator, the industry, institutions are interested in the sales of a product. Bias is introduced by improper interpretation of results and by institutional conflicts of interest.

I would like to present 2 published examples of bias. The first is an article that was published about 6 years ago called “Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events.” The article is not easy to read. The investigators concluded that conclusions in trials funded by for-profit organizations (and usually, this translates as a euphemism for industry) may be more positive owing to biased interpretation of the trial results. The methodology may be sound, but the results are interpreted in a biased fashion. These authors concluded that the reader should carefully evaluate whether conclusions in randomized trials are supported by the data.

The second study came out last year and is titled, “Reporting bias in drug trial submitted to the Food and Drug Administration: a review of publication and presentation.” If the first study was difficult to read, this article is even worse. The investigators concluded that many trials have not been published 5 years after the Food and Drug Administration (FDA) has approved the findings. The new drug or the study is submitted to the FDA, the FDA approves it, but the investigators still do not publish the results from their trials. Considering the discrepancies between new drug applicants and published reports, the authors find that published reports tended to be more favorable than the new drug applications. They concluded that the information available in the scientific literature is incomplete and potentially biased.

We have conflicting objectives: the physician scientist, as a pure physician scientist or the medical scientist, is interested in advancing knowledge in patient care, but he or she is also interested (as I mentioned) in personal and professional advancement; and the industry is interested in selling the product, making profits, and creating returns for investors. We also must consider the institution: one member of this triangle that is interested in bringing income to the institution, supporting its staff, and also developing a reputation as an outstanding institution.

INSTITUTIONAL REVIEW BOARDS (IRBS)

The primary purpose of IRBs is to protect the study participant, both the participant’s safety and privacy. I recently spoke with the chair of our IRB and one of my mentors. He said that IRBs are generally given a defective product. Most submissions, other than the proposals that are going to the National Institutes of Health, have not undergone critical scientific review. Therefore, the IRBs must consider the science of the study in addition to or in lieu of the ethics of the study. If an investigator begins with poor science, that investigator will finish with poor ethics, because if we ask subjects to participate in trials that are not well designed, we create ethical issues.

Institutional review boards face a variety of impediments to their functions. First, investigators may have conflicts of interests. The IRB members are peers of the investigator, and no one wants to damage the reputation or career of a colleague. The IRB’s institution wants to bring in the money and is therefore funding the protocols. The IRB exists to protect participants; however, human-research protection is based on case reports and research oversight, such as the Nuremberg cases or the Tuskegee Syphilis Trials, so that the worst example governs what happens in the IRB. Institutional review boards do not follow a specific standard and have become an increasing burden, particularly because of all the paperwork.

Are IRBs too paternalistic? Are we too concerned with protecting the patient? Every time a regulating agency sees an ethical lapse, the members create more regulation. Have we gone too far? One major concern is the development of non-academic, for-profit, usually pharmaceutical industry–driven trial sites, which usually are private practices that develop a sideline of revenue generation to perform clinical trials. They then use for-profit IRBs, and we must determine if for-profit IRBs create a conflict of interest. In the same way, we can ask if a physician taking care of a study participant has a conflict of interest because that physician is monitoring that patient in a clinical trial.

CONCLUSION

Research costs money, and our potential funding sources are the federal government, academic institutions, industry, and third-party payers who should support research but do not. The federal government and industry funnel most of their funds to various institutions, so their funds are difficult to obtain. We do not have enough money for research, for education, or for reimbursement to keep and support investigators. Our investigators are also required to complete too much paperwork. We may have too many restrictions. And we certainly have ongoing ethical conflicts. I have a few ideas for discussion. We could solve our issues by establishing oversight by noninterested organization; we need to train experts in methodology, at least for clinical trials, so investigators design valid studies; and we should consider unrestricted grants—unrelated to the product—for funding possibilities. These solutions are ideal.

In conclusion, to ensure that we research ethically, we as investigators probably should not do anything that does not feel “right.” We do not want to see our names in The Washington Post.

In Sum: The Problems

• Not enough money
  – For research
  – For education
  – For reimbursement
• Too much paperwork
• Too many restrictions?
• Ethical Conflicts!

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The New York Times or coming up in a congressional hearing. Also, to ensure that we are ethical, in all educational programs, research endeavors should include contrarians. Unfortunately, contrarians are rare, but somebody needs to say, “Whoa, what is going on?” In regard to funds for research, the third-party payers need to be pressured to contribute to clinical research. These people benefit from research; therefore, they should be taxed or contribute voluntarily. More regulation is not the answer; ultimately, we all have to remember Pogo: “we have met the enemy and he is us.” (Walt Kelly, 1971).

Lastly, let me quote an article (“When science is a siren song”) that appeared about a month ago in The Washington Post: “Ultimately, it is up to each of us to develop a more skeptical ear, to approach received wisdom cautiously and to pay more attention to data than to narrative. Only by discovering our inner scientist can we fully delight in the hope of new research without being seduced by its charms.” We must pay attention to the facts of the case rather than conclusions and to avoid conflicts of interest and bias.

REFERENCES