The Credibility of Institutional Review Boards

Editor's Note: On occasion, we would like to present articles with commentaries in the newsletter to serve as a valuable educational tool for our readers. This article about Institutional Review Boards is accompanied by commentaries from Rev. Peter Clark, SJ, Ph.D., Jack Gallagher, Ph.D., Jenny Heyl, Ph.D., and Sr. Patricia Talone, RSM, Ph.D.

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Last year, in a congressional sting operation, the Government Accountability Office (GAO) created a fictitious company with a fictitious clinical study of a fictitious medical device, described as a surgical adhesive gel. (Alicia Mundy, "Sting Operation Exposes Gaps in Oversight of Human Experiments." *The Wall Street Journal*, March 26, 2009.)

It sent the protocol to three private or independent institutional review boards (IRBs), requesting approval to begin testing on human subjects.

One of the three IRBs approved the study, giving the fictitious company permission to test the gel on human subjects.

The IRB system of oversight of research involving human subjects has been in existence in the U.S. since the mid-1970s, initiated in an effort to prevent the kind of abuses that sometimes occurred in earlier research (the most well-known case in this country is the U.S. Public Health Service Tuskegee Syphilis Study).

IRBs, sometimes called research ethics committees or something similar, have the responsibility and the authority to protect the rights and welfare of human subjects. An IRB is a multidisciplinary committee that must approve any research study involving human subjects before it can be initiated and must exercise oversight of the study throughout its existence.

The GAO sting reinforced existing concerns about the quality and integrity of IRB review:

- The method devised to protect the ethical integrity of human subjects research may not be doing the job adequately.

- Without confidence in the quality of the review, it is difficult to have confidence in the ethical quality of the research itself.

Commercial IRBs

Traditionally, Institutional Review Boards were truly "institutional;" they were committees set up in academic and

medical institutions where the studies were being done, often with grant support from government or foundations.

Now much of the research is sponsored by industry and the studies are carried out in a wide variety of settings. Private or commercial IRBs conduct the ethical reviews outside of or independent of hospitals or universities.

Private IRBs are businesses, organized on a profit-making basis, different from the committee service model of hospitals and universities. While the traditional model of the IRB has its own credibility questions (see below), a significant amount of the concern about the work of IRBs is focused on the commercial model.

The responsibilities of all IRBs are the same, whether commercial or organizational, and the government regulations that they are to follow and to implement are the same.

While commercial IRBs are often referred to as "independent" IRBs, a major concern is whether they can really be independent, in the ethical sense of the word.

As Carl Elliott, the foremost critic of conflicts of interest in ethics-related work, has noted, "private IRBs have a direct financial interest in keeping their drug-company clients happy. If one for-profit IRB rejects a study as unethical, the pharmaceutical company sponsoring the study can simply send it somewhere else." (Carl Elliott and Trudo Lemmens, "Ethics for Sale: For–profit Ethical Review, Coming to a Clinical Trial Near You." *Slate*, December 13, 2005.)

Commercial IRBs are commonly used by researchers who are not associated with an institution in order to get approval to conduct clinical studies. They are also sometimes used by health care organizations that prefer to hire someone for this responsibility rather than manage an IRB themselves.

Commercial IRBs do high quality professional work much of the time (two of the three IRBs in the GAO sting did not approve the fictitious study).

The need to please customers, however, presents a constant pressure and a strong financial incentive to give customers the answers they want.

Even as she defends the ethical integrity of commercial IRBs, Lynn Meyer stresses the importance of a fast-turnaround time and a flexible schedule: "independent IRBs are businesses and, as such, must be cognizant of client expectations." (Lynn Meyer, "Ethical Integrity of Independent IRBs." *Applied Clinical Trials*, July, 2009.)

In order to protect their ability to do objective ethics reviews consistently in a customer-pleasing environment, commercial IRBs need to have effective measures in place to ensure that they investigate submissions thoroughly and adhere to subject protection requirements.

Hospital-Based IRBs

There are also questions and concerns raised about the work if IRBs located in health care organizations (university IRBs are not included in this discussion).

Among the quality and integrity challenges facing hospital-based IRBs, three are noted here.

1. When IRB membership is made up of internal staff (meeting part of their committee service expectation) and community members (serving on a volunteer basis), it may be hard to assure that all IRB members have the necessary expertise.

Effective IRB work requires experience and skill. Knowing what to look for in the review and knowing how to understand the ethically-significant issues in protocols are not skills that everyone develops easily.

Even if (and this is not always a given) all IRB members have a high level of commitment to the work and are provided opportunities for all necessary training, hospital IRBs are very likely to have some ineffective members.

2. The IRB workload can often be a problem.

In organizations in which clinical research is common, the IRB often has a very heavy workload, requiring the review of hundreds of pages at each meeting. This takes time, if it is going to be done well, and not everyone can devote the necessary time. The result may be that the IRB members are poorly prepared and fail to identify issues or concerns.

Too small a workload can also be a problem. If a community hospital in which few clinical studies are done has its own IRB, committee members may not develop the necessary experience and expertise to do the job well. It is not unreasonable to wonder about the competence of an IRB that does not review many studies.

3. Though hospital-based IRBs are not profit-seeking businesses, they too may face expectations or pressures to approve proposed studies quickly.

The expectations and/or pressures can take different forms: hospital management may be eager to have a study approved for reasons of prestige and/or revenue; clinical investigators may expect that their "colleagues" will be "supportive" and "cooperative;" IRB members may be reluctant to place demands on individuals they know personally.

Research Oversight

As the number of research studies involving human subjects continues to grow, many of them sponsored by private interests, the need for careful ethical review before the studies proceed is as great as it has ever been. IRB review is the method in place to protect human subjects.

If we – health care professionals and the public – are going to have confidence in the work that IRBs are doing, ongoing attention to their quality and professionalism is required.

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Response One

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The protection of human subjects in the United States has evolved into a complex regulatory and legal environment involving 19 agencies in addition to the Food and Drug Administration (FDA) sharing oversight for the protection of study subjects. "This complex and crowded array of organizations has burdened Institutional Review Boards (IRBs) with substantial inconsistencies in ethics regulations and the challenge of complying with many different and potentially conflicting requirements."[1]. The result has been unnecessary delays in starting protocols, a waste of resources, and possibly, a less than optimal protection for research subjects.

After reviewing Leonard Weber's article, I wish to note a number of concerns that most bioethicists agree upon regarding the IRB system. First, there is an overrepresentation of Caucasians, researchers, and individuals affiliated with the home institution on IRBs. This could lead some to believe that the interests of the researchers and the research institution take priority over the interests of the research subjects. Second, the lack of staff support for many overburdened IRBs demonstrates that the administrators at the research institutions do not take the work of their IRBs seriously. Third, subjects often do not understand informed consent forms, in part because they are too complex. These forms often do not pass the IRB's own readability standard, namely, that they should be written at a 5th to 6th grade reading level. This could be rectified if researchers used Flesch-Kincaid Readability Tests that are designed to indicate comprehension difficulty when reading a passage of English. This program is found on most Word applications. Fourth, there is a lack of ethical training/certification for IRB members regarding issues such as research on protected populations, vulnerable subjects, ethical principles, conflicts of interest, etc. This could be corrected by having members participate in the Collaborative Institutional Training Initiative (CITI) for IRB members. In addition to these concerns, I would like to reflect upon three additional areas that need to be examined in order to improve the credibility of IRBs.

First is a concern about the use of multiple institutional IRB approvals for multi-site clinical studies. The current federal regulations regarding the protection of human subjects require IRBs

to examine initial research designs involving human subjects, to ensure that researchers provide subjects the opportunity to give informed consent and to make certain that subjects are not exposed to unreasonable risks as a consequence of their involvement in the study. Each institution engaged in the study, both in-country and out-of-country, will generally obtain individual IRB approval. These duplicative reviews have been shown to provide relatively few benefits, are time consuming administratively, and often delay the studies and increase the costs. Advocates for this process argue that having multiple IRBs examine a protocol would lead to the ethical improvement of the protocol and informed consent forms. Instead, it has been shown that "this practice seems to pose significant risk of diminishing studies' ethical integrity."[2]

A recommendation for streamlining and harmonizing the review process is the existence and use of a central IRB for multi-site studies. This central IRB would meet federal regulations, constrain duplication of review efforts, allow for consistency in interpreting regulatory requirements and keep the focus on ethical issues that are in the subject's best interest rather than on procedures and documentation. A central IRB could also cut the costs of operating institution-based IRBs. These costs include preparation of IRB materials, tracking IRB documents, storing documents, reconciling demands of multiple IRBs, overhead costs for housing and staffing IRB offices, running IRB panels, etc. Critics of a centralized IRB, like Weber, point out possible ethical concerns related to the independence of the IRB and possible financial conflicts of interest. However, with effective checks and balances in place these potential concerns and conflicts could be overcome so that the emphasis is on a thorough investigation of the study and the protection of all human subjects.

Second, IRB jurisdiction and authority is virtually never challenged or evaluated. Once the IRB renders its decision on a clinical trial protocol, it is rare that research investigators will question their recommendations and decisions or even challenge them. The fear is that, if they do, the research protocol will be put under greater scrutiny or it will not be approved. In multisite protocols, if the IRB questions the study design or a basic aspect of the protocol, often the investigators will withdraw the protocol from that site and will either find a new site or will increase recruitment of subjects at an already approved site. What the investigators do is just circumvent that particular IRB. "There is generally no change in the protocol—and therefore no reduction in the number of subjects exposed to whatever risks the IRB identified." (Menikoff, 1593)

Federal regulations allow for appeals if research investigators disagree with the IRB decision, but this rarely happens. One might wonder whether investigators even know that they can appeal a decision and whether they know the procedure for an appeal. Is the appeal directed to the home institution or to the federal

government? Consequently, if no one ever questions IRB decisions, how do IRBs ever measure their effectiveness? "There are no data measuring whether IRBs are doing their job in protecting study volunteers from unnecessary risk of harms. The IRB system, which evolved from an institution-based structure with little accountability or data collection, lacks even rudimentary metrics for measuring its own success" (Getz, 28).

The IRB system is in need of reform. IRBs are not reviewable. Information about the activities, meetings, and decisions of IRBs is not circulated because IRB administrators and university research administrators are very reluctant to share data, citing concerns about confidentiality. This has led numerous critics to complain about the shortage of data on how IRBs function.[3] To rectify this concern, a metrics for measuring the success of IRBs should be established.

Third, informed consent forms have to be more specific about potential financial conflict of interest. IRBs need to examine more closely the budgets of clinical trials and any financial information pertaining to the study must be disclosed in the patient consent form. With the increase in multi-site clinical trials it has become even more important that IRBs have a template for a standardized budget that each clinical trial can submit. There have been recent trials where conflicts of interest regarding the financial aspects of the trial have become evident. In most cases, the criticism has been leveled at the IRBs for not doing a better job in evaluating potential financial conflicts of interest. With multi-site trials, especially those in foreign countries, it is difficult to standardize a budget because costs can vary from site to site. However, a standardized format would give IRB members a better understanding of the legitimate costs of the particular trial and would allow them to better assess, review, and monitor the overhead costs by giving them a benchmark. This would help prevent any potential financial conflicts of interest.

In addition, disclosure of financial arrangements must be part of the informed consent form for the participants. Critics argue that informed consent forms are already too complex and too long and that this addition would only confuse participants and distract them from examining the more important risks and benefits of the clinical trial. This is a specious argument. Any conflict of interest has the potential to pose a threat to the scientific integrity of the clinical trial by introducing forms of bias that impact the enterprise of science itself. Research subjects have the right to know that the science behind the clinical trial is sound and that they are protected as research subjects. Therefore, individual investigators have the ethical responsibility to disclose financial interests that may affect the outcome of the clinical trial.

There have been substantive criticisms leveled at the present IRB system by subjects, researchers and the public in general. These criticisms question the basic credibility of our national IRB

system and the future of clinical research. Unless reforms are enacted immediately the basis of clinical research may be in jeopardy. We owe it to research subjects and to society as a whole to have an IRB system that protects all who volunteer to participate in research by maximizing benefits and minimizing harms.

[1] Kenneth Getz, "Frustration with IRB Bureaucracy and Despotism." *Applied Clinical Trials*, January 2011: 26-27

[2] Jerry Menikoff, "The Paradoxical Problem with Multiple-IRB Review." *The New England Journal of Medicine* 363, 2010: 1591-1593

[3] Carol Heimer and JuLeigh Petty, "Bureaucratic Ethics: IRBs and the Legal Regulation of Human Subjects Research," *Annual Review of Law and Social Science* 6, December 2010: 601-626

Response Two

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Len Weber's "The Credibility of Institutional Review Boards" has "hit the nail on the head." His concerns regarding commercial IRBs as well as the difficulty of managing an effective IRB in a community hospital are legitimate and should be a cause of concern to all of us in the Catholic health care ministry who sponsor research protocols. In my comments, I would simply like to highlight what I believe are risks to the mission of Catholic health care that can be associated with out-sourcing an IRB to a commercial entity.

First, a commercial IRB functions in lieu of the hospital it represents. The IRB becomes the agent of the hospital that employs it. The commercial IRB can conduct the review that leads to the endorsement of a research protocol, can monitor the course of the research project and ultimately close the study. In each of the steps in a research project the commercial IRB functions as the agent of the hospital. This leads to at least two questions. First, does the IRB know the mission of the hospital well enough to ensure that there is compatibility between the research and the organization's mission? Every research project begins with an expected unknown. The safety and efficacy of a new medication even at stage three of a research protocol remain somewhat unknown. If it were known with scientific certitude, there would be no need for the research. Since virtually all trials conducted in community hospitals are stage three trials their outcomes are expected. Nevertheless does a commercial IRB know the level of risk the hospital is willing to ask its patients to accept? Will the IRB monitor the consent to ensure patients are not induced into a trial with unrealistic expectations of a medical benefit? We ought to keep in mind that some trials of new forms of chemotherapy are conducted on patients who have not responded favorably to current treatment modalities. They are vulnerable

Second, do Catholic hospitals that contract with a commercial IRB have an assurance from that IRB that it is sufficiently familiar with the *Ethical and*

Religious Directives? What is important in this context is not just a factual awareness of the Directives that can come from reading them, but rather the competency and wisdom that comes from interpreting and applying the Directives in concrete circumstances over time. The easy example to refer to is the language used in cancer research that requires subjects to avoid pregnancy and getting a partner pregnant while on the protocol. But there are, I believe, much more significant issues. When a patient signs on to a research protocol their clinical status as patient is changed to that of a subject. The physician becomes a researcher. This change in nomenclature is not just a verbal game; it is a shift in language which accompanies what is really an ontological change. The researcher's goal is verifiable data. The subject is the source of such data. The physician-client relationship depicted in Part III of the Directives has been substantially altered. Is the patient/subject sufficiently aware of this altered relationship? The patient/subject lying on an examination table or a gurney is responding to the same physician in a white coat with a stethoscope draped around his or her neck who yesterday was the patient/subject's physician but who now is a reseacher. But why is this physician engaged with this person? To benefit him or her? To gather data? Or some combination of the two? This blurring and confusion of roles can happen too easily in community hospitals where physicians frequently have long-standing relationships with patients who in the course of a complex illness can become subjects.

Medical research is best conducted in large teaching hospitals that have the expertise to carry out the complex work of an IRB as well as the research itself. This is, I believe, a much more daunting task in community hospitals.

Response Three

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Reading Leonard Weber's article on the credibility of IRBs prompted reflection upon my nine-year experience on an IRB. This reflection raises more questions than it answers, but perhaps can promote further dialogue among those who participate on IRBs. As the full-time ethicist at a large tertiary-care community medical center, it was a given that I would sit on the IRB. Although I had a good understanding of the historical abuses of human subjects and an advanced degree in philosophy with a concentration in ethics, in retrospect, I was not prepared for the amount and scope of the work required on the IRB.

In my early days, all the paperwork to be reviewed for the IRB meeting scheduled ten days hence was delivered to my office in a heavy-duty canvas bag by the IRB coordinator. (Fortunately we have now moved to a web-based system; I fear the new reusable grocery bags would not hold the material for one meeting.) I mention this because the weight of the bag was both literal and figurative. I felt obligated

to read every page of every document. I quickly learned that I was not going to be able to read nor, as a non-scientist, be able to understand every page of the protocol and I began to skim that document and focus only on the ethical elements it contained. I constantly fought the feeling of being overwhelmed and inadequate to the responsibility of the role.

While getting acculturated to the committee and the monthly process, I began to focus on the one area where I had some level of confidence and expertise – the consent form. I could thoroughly scrub the document for the 'required elements,' and check that the vocabulary and syntax were at a 7th grade reading level. But there were bigger issues in the consent form. For example, now that clinical trials were more likely to be multi-site trials, how can we ensure that subjects understand when they are a *subject* in a clinical trial and when they are a *patient,* when in each case they are visiting the same physician? Could boilerplate language adequately address this conceptual confusion? And then there is the language regarding potential or known risks to fetuses and the related requirements for subjects' participation. How could we adequately relay the risk while allowing participants who assiduously practice the birth planning methods acceptable within the teachings of the church to be accepted into the trial? This was a great deal to expect from a lengthy document written at the 7th grade level. And here's the rub, the consent form cannot do it all, but the consent form is one aspect over which the committee has most control. We know that 'informed consent' is a process and not just a piece of paper; and yet it's often easier to focus on what's within our control than address larger issues not amenable to consensus. Ezekiel Emanuel, et.al, in a 2004 article identifying problems of IRB said, "IRBs devote substantial time to the informed consent forms at the expense of serious consideration of other important ethical issues."[1] Furthermore, a study published in the *British Journal of Clinical Pharmacology* in 2009 demonstrated that improvements to informed consent documents do not increase patients' comprehension in biomedical research.[2] Illustrative of this, I recall a story conveyed by a colleague on our committee. She attended a conference where a family member of a subject who had died as a result of participation in a clinical trial was a featured speaker. During Q&A the speaker was asked, "What could we, as members of an IRB, have done to better inform you and your family of the risks?" The speaker replied, "Nothing, we trusted our physician and thought this was going to help our son."

I cannot end without saying how extremely fortunate I've been to work with highly qualified and motivated colleagues, each of whom brings an area of expertise to our IRB. My reflection includes only one aspect of the IRB's responsibility and has brought into sharper focus that I have perhaps squandered time that might have been better spent addressing some of the larger unresolved ethical issues mentioned by Weber and others. I owe better to the potential subjects in our trials as well as my colleagues on the IRB.

[1] Ezekiel J Emanuel, MD, Ph.D.; Ann Wood, MA; Alan Fleischman, MD, et.al. "Oversight of Human Participants Research: Identifying Problems to Evaluate Reform Proposals," *Annals of Internal Medicine*. 2004; 141:282-291.

[2] Adeline Paris, Christian Brandt, Catherine Cornu, et.al. "Informed Consent Document Improvement Does Not Increase Patients' Comprehension In Biomedical Research," *British Journal of Clinical Pharmacology*. 2009; 69:3; 231-237.

Response Four

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The egregious violation of human dignity, autonomy, informed consent and patient beneficence that occasioned the 1974 Belmont Report was conducted in Macon County, Alabama, near the town of Tuskegee, a primarily rural community mid-way between Columbus, Georgia and Montgomery, Alabama. Even today, driving to Tuskegee from either of those cities, one quickly realizes the poverty of the region. Tuskegee University Bioethics Center, in response to the infamous 40-year public health experiment, dedicates itself to exploring the moral issues that underlie research and medical treatment of African Americans and other underserved people. The human subjects—poor, rural, African-American men—were led to believe that they were receiving free health care from the government, even after it had been discovered that penicillin would cure their syphilis. Even the local professionals involved with the study were far removed from decision-making regarding treatment of these human subjects.

The Belmont Report determined that medical research must first undergo rigorous study and approval from a multi-disciplinary Institutional Review Board, consisting of at least five members. Key to the Belmont Report's stipulations is that at least one of the IRB members should be someone "from the community, "that is, someone unaffiliated with the university, medical center or other entity conducting the research. Furthermore, the members must be diverse in race, gender and cultural background and be sensitive to local community issues. The inference is that local persons are the best ones to determine what is in the best interest of their neighbors.

This specific Belmont Report criterion is precisely what makes the growth of commercial IRBs so troubling. How might a commercial entity situated on the West coast, for example, reflect the diversity of Native American peoples in rural, northern Minnesota? Do they understand the historical and cultural challenges experienced by the 50,000 members of the Bosnian Community in eastern Missouri? Do IRB members understand the cultural background of the medical subjects they purport to assist? Do they know and embrace the history and philosophy of the hospital or organization serving these people?

From its inception, Catholic health care in the United States has prided itself upon its

commitment to serve vulnerable populations. Catholic hospitals operate in urban, suburban and rural areas, embracing persons of all religions, ethnicities and economic backgrounds. Directive #3 of the United States Conference of Catholic Bishops' *Ethical and Religious Directives for Catholic Health Care Services* asserts that "Catholic health care should distinguish itself by service to and advocacy for those people whose social condition puts them at the margins of our society and makes them particularly vulnerable to discrimination...." Because Catholic health care takes this instruction seriously, many of its institutions exist in areas that the scientific community denotes as "subject rich." Therefore, many Catholic facilities draw researchers.

An institution might desire to outsource their IRB review for several reasons. Commercial IRB members do not volunteer for their work; they are paid. Because their work is not an "add-on" they often reply to the principal investigator more quickly than do the more taxed institution-based IRBs. Furthermore, small community hospitals, not to mention critical access hospitals, often do not possess the human capital to conduct the lengthy and rigorous protocol review process. However, while commercial IRBs often respond to research protocols more quickly than those that are system or institution-based, the directive of the Belmont Report to incorporate members of the community into the ethical review process seems sorely lacking.

Catholic health organizations have an opportunity to evaluate their IRB processes in order to insure that the vulnerable persons they serve are not further victimized by a process that neither understands them nor fully respects their human dignity. Catholic facilities, often contained within larger systems, must seek ways to maximize their resources within and across systems, always recognizing the professional and moral obligation they hold.