The Controversy Surrounding Central Institutional Review Boards

Feature Editor Introduction: Kristi L. Kirschner, MD

For this column, we are tackling an issue that many in rehabilitation may not be familiar with—namely, central institutional review boards (CIRBs). As rehabilitation research continues to grow, particularly in collaboration with pharmaceutical and device manufacturers, CIRBs will probably play an increasingly prominent role.

Given the likely unfamiliarity of the issues posed by CIRBs, what follows is a brief commentary (by me, and my colleagues Teresa A. Savage, PhD, RN, and Debjani Mukherjee, PhD, of the Rehabilitation Institute of Chicago Donnelley Family Disability Ethics Program and Northwestern University Feinberg School of Medicine Medical Humanities and Bioethics Program) that lays out the issues, followed by expert commentaries and responses by Dr. John Whyte and Dr. Norman Harden. As always, we invite your comments and responses to this column!

INTRODUCTION

A debate has ensued about the use of central or commercial institutional review boards (CIRBs) for research. At the heart of the matter is research integrity, public trust, and, of course, protection of human subjects. The 2 quotes below exemplify the debate:

> At a time when commercial interests threaten the safety of research participants and the integrity of medical research, it is remarkable that North American regulatory agencies have not seen any problem with entrusting the rights and well-being of human research participants to a lightly regulated commercial enterprise. . ..The protection of research participants is a critically important public mandate, and it merits a truly independent regulatory structure [1].

> Making a distinction about the quality and merits of IRBs based on tax status is an antiquated piece of ideology reminiscent of Orwell's *Animal Farm*—"for-profit bad, not-for-profit good." The distinction obscures what we should care about and directly measure—the quality of IRB review of protocols and the monitoring of the safety of research participants [1].

In this column, we discuss the use of central or commercial (CIRBs) and summarize the historical context and debate. Throughout this feature, we welcome the reader to consider how the role of CIRBs may impact science and clinical care in the United States.

BACKGROUND

Investigative journalists have largely led the way in elucidating research projects gone awry. When we open a newspaper or read an online account, questions are raised about how the projects were approved, who was monitoring the safety and effects, and how conflicts of interest may have impacted the process. The IRB is a committee developed to oversee research that involves human subjects, with the charge of protecting the rights and welfare of research participants. The need for IRBs was recognized in the wake of egregious examples of abuse in research (eg, Nazi physicians during World War II [2], the Tuskegee Syphilis Study [3], and the Willowbrook hepatitis vaccine study [4]), and mandated by Title 45 CFR 46 (Code of Federal Regulations) Part 46. The requirements for IRBs are set forth by law and regulated by the Office of Human Research Protections within the U.S. Department of Health and Human Services.

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Historically, IRBs were set up by universities and medical institutions involved in human-subjects research. During the last 40 years, there has been the addition of for-profit or commercial IRBs, which are also subject to the same federal laws and regulations. [Although most CIRBs are commercial, there are a few exceptions, such as the National Cancer Institute IRB (http://www.ncicirb.org). For the purposes of this column, we are concentrating on for-profit, commercial (or central) IRBs and will refer to them as CIRBs.] CIRBs are being used increasingly for pharmaceutical and medical device clinical trials. From 2000 to 2006, clinical trials in the United States increased nearly 50% to 59,000 drug trials [5]. Research moved from academic medical centers to clinical research organizations or private physician offices. One of the oldest and most respected CIRBs, the Western IRB (WIRB) "reviews more than half of all trials of new drugs submitted for FDA approval. . ." and some academic medical centers are outsourcing their IRB work to CIRBs [5]. Cancer researchers have been the most vocal advocates for the use of CIRBs because they focus on the complexity of the trials, the duplication of reviews, and the ease of coordinating multisite, multi-investigator research. Although a growing number of academic and governmental institutions use CIRBs, some core ethical issues have been raised, including protection of human subjects, actual and perceived conflicts of interest, and balancing the specialized knowledge and speed of CIRBs, with the local knowledge and due process of local IRBs.

Regardless of the type of IRB used, harm to research subjects has been documented, and regulations or mandates have been developed. For example, on January 15, 1994, then-President Clinton formed the Advisory Committee on Human Radiation Experiments. These experiments took place for 40+ years after World War II and the Cold War. The Advisory Committee on Human Radiation Experiments issued a detailed report of the multiple abuses that took place, including infringement of informed consent and the abuse of vulnerable populations [6].

In the more recent past, there are a number of questions raised about erosion of protections with current practices involving U.S. researchers who engage in clinical trials in developing countries [7]. Additionally, several high-profile deaths of research subjects have raised issues to consider. The deaths include Jesse Gelsinger at the University of Pennsylvania in 1999 [8], the death of a healthy volunteer Ellen Roche in an asthma study at Johns Hopkins in 2001 [9], and the death of Jolee Mohr, a 35-year-old woman in 2007 at the University of Chicago involved in a gene therapy study for rheumatoid arthritis [5]. Detailed reviews of these deaths revealed concerns about safety with the protocols, adherence to protocol, and the informed-consent processes.

Some evidence also exists that drugs and devices that are approved by the Food and Drug Administration (FDA) have a high incidence of postmarketing safety concerns. Examples of drugs that have been withdrawn from the market after FDA approval, sometimes years later, include rofecoxib, valdecoxib, trovafloxacin, mibefradil, terfenandine, troglitazone, cerviastatin, alosetron, and tegaserod. Other drugs have had black box warnings added after approval, such as selective serotonergic reuptake inhibitors (for suicide risk with adolescents) and rosiglitazone (for congestive heart failure and myocardial infarction risk). Some of the devices with postmarking safety concerns include drug-eluting stents, biventricular pacers, and implantable defibrillators. Since the passage of the Prescription Drug User Fee Act in 1992 (which allowed the pharmaceutical industry to pay a user fee to expedite the review of the drug), there has been marked increase in rates of postapproval safety problems in drugs that were approved in the 2 months before the approval deadline imposed by the Prescription Drug User Fee Act as compared with drugs approved in other months of the review cycle (odds ratio of 5.5 for drug withdrawals, black-box warning odds ratio 4.4, and discontinuation of at least one dosage from 3.3—all $P \leq .02$) [10].

In the analysis of many scholars who study the problems of drug safety in the United States, there have been substantial concerns raised about the undue influence of money in the erosion of protections of human subjects, particularly when pharmaceutical companies and device makers are involved [8,11-14]. The erosions of protections can occur in a number of ways, including: (1) independence of the researcher (financial ties, ownership of data, writing manuscripts, reporting harms); and (2) independence of the review bodies (eg, the IRB, FDA).

COMPLIANCE ISSUES

Federal regulations on the conduct of research apply to both local IRBs and CIRBs. In addition to protecting research participants, local IRBs also are motivated to uphold their high standards to protect the reputation of their institution. CIRBs also desire to protect their reputations, although any missteps or transgressions by the CIRB may not be public information, unlike for local IRBs. One needs only to search the Office of Human Research Protections Compliance Oversight webpage to find institutions that have been out of compliance. In the late 1990s and early 2000s, there were a number of university IRBs that had research activities suspended by the NIH Office for Protection from Research Risk (now Office for Human Research Protections). Duke University, Rush University, University of Rochester, and University of Illinois at Chicago are a few whose research was suspended and all active protocols had to be re-reviewed. There have been lawsuits against IRBs, such as in the melanoma vaccine case in Tulsa, Oklahoma, and the efalizumab (Raptiva) case, a psoriasis medication [15]. At the Medical College of Georgia, a psychiatrist stole more than $10 million of research money and allowed untrained employees to administer experimental drugs. The university IRB was unaware of the