

## IF INSTITUTIONAL REVIEW BOARDS WERE DECLARED UNCONSTITUTIONAL, THEY WOULD HAVE TO BE REINVENTED

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### INTRODUCTION

As Chair of the Institutional Review Board of the Division of Biological Sciences at the University of Chicago for nearly a decade, I have had the opportunity to review more than 7000 clinical research protocols. I have done so in an era when zealous federal oversight and heightened public scrutiny of clinical research have given universities great concern. As one of the developers of a new class of drugs, I also know all too well the burden investigators face in negotiating complex institutional and federal regulations. Because I have had practical experience on both sides of the issue, I bring a unique perspective to this debate. From my perspective, many of the contributors to this symposium profoundly misunderstand the functions of an Institutional Review Board, perhaps because they have not had the opportunity to serve on one.

The “Art Bell”-like hypothesis<sup>1</sup> that an Institutional Review Board conspires to stifle academic freedom is a myth largely disseminated by individuals who have never been substantively involved with the process of drug development or Institutional Review Board approval. This misunderstanding is both factual and judgmental. For example, the temporal burden of approval is frequently cited as a reason to bypass Institutional Review Board approval. In our committees, full approval generally takes an average of twenty-five days from the time a protocol is considered. For survey studies, approval is granted only a few days after review at a meeting convened to verify survey modifications. I am sympathetic to the concept of streamlining the approval process, and my experience suggests that streamlining is possible. However, even absent streamlining, few important studies are abandoned solely because of rejection or delay by an Institutional Review Board.

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<sup>1</sup> Syndicated radio show host Art Bell is well known for his discussions of plots to cover up UFO sightings. See Art Bell: A Who2 Profile, <http://www.who2.com/artbell.html> (last visited on Apr. 8, 2007).

Beyond streamlining, evaluation of the legality of Institutional Review Boards is of academic interest only for two reasons. First, if review boards were abolished by legal action, necessity would force institutions to reinvent them. Second, the form of the reinvented board would probably be far less pleasing to its users than it is now. I will address each of these reasons in turn.

#### I. THE NECESSARY FUNCTIONS OF INSTITUTIONAL REVIEW BOARDS

To understand why Institutional Review Boards are necessary, one must understand the four important roles of an Institutional Review Board.<sup>2</sup> First among the functions of an Institutional Review Board is to ensure patient safety and equipoise, that is, balancing risk and benefit. A review by an independent board can improve the margin of safety for many clinical studies. Our institution has a number of scientific pre-screening boards for many of our protocols. All cancer protocols, for example, go through a scientific review board before the Institutional Review Board ever sees them. For most other studies, however, we provide the only scientific review that a protocol will receive.

Sometimes the danger posed to patients by a protocol does not involve the direct risk of a toxic drug. In 1998, the federal government enlarged the definition of risk to include risk to a patient's reputation and risk to a patient's insurability.<sup>3</sup> For example, sensitive medical records that document the course of a disease could influence a patient's insurability if they were divulged publicly. With the advent of the Health Insurance Portability and Accountability Act, Institutional Review Boards are further obligated to ensure the confidentiality of a patient's protected health information. Consider subjects with inflammatory bowel disease or those who carry the gene for breast cancer. Even questionnaire responses submitted by patients could potentially find their way into the public domain via the Internet or other means. Answers on questionnaires also might significantly affect insurability or employability. As one insurance executive commented to me, "I do not sell insurance for a house that is on fire." In sum, Institutional Review Boards serve the important function of protecting patients' health, reputations, and insurability by analyzing and balancing the risks posed by each protocol involving human subjects.

A second important function of an Institutional Review Board is protection of the investigator. Complaints about clinical studies are not rare events. Some complaints are legitimate; many are not. Because the Institu-

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<sup>2</sup> A collection of essays discussing the management and function of institutional review boards can be found in *INSTITUTIONAL REVIEW BOARD MANAGEMENT AND FUNCTION* (Elizabeth A. Bankert & Robert J. Amdur eds., 2d ed. 2006).

<sup>3</sup> See Protection of Human Subjects: Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure, 63 Fed. Reg. 60,353, 60,364-67 (Nov. 9, 1998).

tional Review Board has reviewed and approved the study, we often intercede between the investigator and the complaining subject. Some complaints are as trivial as non-timely payment for volunteer studies. In other instances, the issue may be a perception of unwanted intrusion. No man wants to be called at home by an anonymous surveyor asking if he would be interested in participating in a study on prostate cancer. The man called presumes that the caller has had access to personal medical records. Unsolicited requests for study participation lead to complaints from patients to the investigator, institution, or even the federal agency supporting the study. Violations of the Health Insurance Portability and Accountability Act have criminal sanctions. After President Clinton's surgery, seventeen hospital employees were dismissed for attempting to access his records without approval.<sup>4</sup> In some cases patient complaints warrant a re-examination of one or more aspects of a research protocol. In the rare instances of improper conduct, an Institutional Review Board may ask the investigator to cease enrollment in the study. Without an Institutional Review Board, these investigative functions would have to be performed by another organization, one that, not appreciating the value of the study and its scientific context, would be less likely to protect the legitimate work of the investigator.

A third important function served by Institutional Review Boards is to protect the institutional interest. Although constitutional arguments about the validity of Institutional Review Boards may have theoretical merit, in practice these arguments are moot. Private universities are largely corporations. The respect for academic freedom within these corporations is desirable, but not indispensable. In a politically charged and racially sensitive environment, the purpose of many clinical trials can easily be misunderstood. For example, the selection of HIV-positive foster children in the early stages of HIV drug trials in New York received considerable adverse publicity.<sup>5</sup> The publicity centered on whether an appropriate third-party advocate had been appointed before enrollment of the children into trials of anti-retroviral therapy. The trials provided the only access to new drugs for the foster children, and Columbia University was acting no differently than dozens of other institutions in its enrollment procedures. Yet the racial implications of the foster-parent system subjected Columbia University and other institutions in New York to considerable negative publicity. There are numerous other potentially charged research issues including the use of prisoners in clinical trials, fetal research, research on communicable and sexually transmitted diseases, and even simple surveys.

One only has to look at how both Northwestern University and the University of Chicago treated two recent controversies to understand that

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<sup>4</sup> Jordan Lite, David Epstein & Celeste Katz, *Clinton File Snoopers Rapped*, N.Y. DAILY NEWS, Sept. 11, 2004, at 6, available at [www.nydailynews.com/news/local/story/230961p-198366c.html](http://www.nydailynews.com/news/local/story/230961p-198366c.html).

<sup>5</sup> Letter from Karena Cooper, Office of Human Research Protections, to Harvey Colten and Laura Forese (May 23, 2005), available at [http://www.hhs.gov/ohrp/detrm\\_lettrs/YR05/may05c.pdf](http://www.hhs.gov/ohrp/detrm_lettrs/YR05/may05c.pdf).

universities will do whatever is necessary to protect their reputations and corporate interests. Whether it is Arthur Butz, seeking to legitimize his revisionist views of the Holocaust by linking them to the Northwestern University Web site, or a student at the University of Chicago who was censured for placing the sign “Mo’ Mohammad, Mo’ Problems” on his door,<sup>6</sup> universities are sensitive to political influences that compromise their corporate interest. Institutional Review Boards can forestall the public image problems and protect the institution’s reputation by weeding out politically sensitive studies before they are approved.

Finally, the fourth function of the Institutional Review Board is to maintain the public trust in the conduct of science.<sup>7</sup> Conflict of interest must be avoided and the validity of a study must be assured to sustain the public trust. The subjects needed for scientific studies may be unwilling to participate if they distrust the science produced by institutions. As an example, consider the debates on the legal and moral obligations of the 1932 Tuskegee Study of Untreated Syphilis in the Negro Male. This celebrated case, which culminated in a presidential apology, is viewed by our local population as an example of the use of African-Americans as guinea pigs. Such a case leads many subjects to decline participation in clinical trials even when they might well benefit. Other more recent examples are the falsification of data in stem cell studies<sup>8</sup> and breast cancer trials.<sup>9</sup>

Although deliberate falsification or alteration of data is rare, when it is discovered, as in the recent example of the drug Vioxx,<sup>10</sup> the public becomes skeptical of research integrity.<sup>11</sup> In 2001, the death of a volunteer in a research study at Johns Hopkins University, a leading medical institution, led to a temporary suspension of all human research at that institution.<sup>12</sup> Because of its prominence, the study evoked considerable reaction in the scientific and public communities and an institutional commitment to re-

<sup>6</sup> Aaron Brown, *Prophet Cartoon on Door Prompts Action*, U. CHI. MAROON, Feb. 17, 2006, available at [http://maroon.uchicago.edu/online\\_edition/news/2006/02/17/prophet-cartoon-on-door-prompts-action](http://maroon.uchicago.edu/online_edition/news/2006/02/17/prophet-cartoon-on-door-prompts-action).

<sup>7</sup> Steven Peckman, *A Shared Responsibility for Protecting Human Subjects*, in INSTITUTIONAL REVIEW BOARD MANAGEMENT AND FUNCTION, *supra* note 2, chs. 1–4.

<sup>8</sup> Gretchen Vogel, *Picking Up the Pieces after Hwang*, 312 SCIENCE 516 (2006).

<sup>9</sup> Marcia Angell & Jerome Kassirer, *Setting the Record Straight in the Breast-Cancer Trial*, 330 NEW ENG. J. MED. 1448 (1994).

<sup>10</sup> Gregory Curfman, Stephen Morrissey & Jeffrey Drazen, *Expression of Concern*, 354 NEW ENG. J. MED. 638 (2006).

<sup>11</sup> Eve E. Slater, *Today’s FDA*, 352 NEW ENG. J. MED. 293, 295 (2005).

<sup>12</sup> Letter from Patrick J. McNeilly & Michael Carome, Department of Health & Human Services, to Edward D. Miller, Chi Van Dang & Gregory F. Schaffer, Johns Hopkins University (July 19, 2001), available at [http://www.hhs.gov/ohrp/detrm\\_lettrs/jul01a.pdf](http://www.hhs.gov/ohrp/detrm_lettrs/jul01a.pdf); see also Hopkins Responds to OHRP Suspension of Research, <http://www.hopkinsmedicine.org/press/2001/JULY/010719.htm> (last visited Dec. 3, 2006).

vamp the Institutional Review Board.<sup>13</sup> Institutional Review Boards help the scientific community preserve the public faith in science by serving as a visible sign of an institution's commitment to well-regulated and rigorous scientific study.

Because Institutional Review Boards protect patient safety, protect investigators from false claims, protect an institution's interests in maintaining its public image, and protect the public trust in science thereby ensuring the supply of study subjects, it is unlikely that they would be eradicated even if they were unconstitutional in theory. The practical value of Institutional Review Boards is so great that it is more likely that review boards would merely be recreated in another, possibly less benign, form.

## II. THE INFERIOR ALTERNATIVE TO INSTITUTIONAL REVIEW BOARDS

From my perspective as Chair of an Institutional Review Board and an active investigator, I see real threats to academic freedom, but not from Institutional Review Boards. If one accepts the premise that universities would establish other oversight boards to replace Institutional Review Boards were they declared unconstitutional, it may be instructive to imagine how the new oversight boards might function under the aegis of local institutions.

In each of our institutions, there already exist oversight mechanisms that regulate research. The most important of these models include increasingly restrictive conflict-of-interest policies to regulate research. These policies are based on local rules without standardized national norms. Even in renowned universities, conflict-of-interest regulations and bureaucracy often go far beyond federal mandate and sometimes beyond common sense. Absent national norms, there is no appeal from conflict-of-interest rulings.

Although there is a deeply rooted public perception that conflicts of interest affect the reporting of results in clinical trials, this perception is largely without foundation. In a recent article in the *New England Journal of Medicine*, Dr. Thomas Stossel argued that research misconduct, bias in reporting, and profit from new discoveries are not fostered by collaboration between academia and industry:

Relentless pressure from prominent authorities claiming that medicine and medical sciences are deteriorating in a morass of commercialism has influenced policy. The rhetoric of such authorities is harsh as they accuse scholars entangled with industry of being engaged in "unholy alliances", "losing their balance of values" as if in "the grip of the python," and of being in a crisis in which the "compromises engendered by the lure of profit are potentially devastating." Articulating these concerns are university presidents, heads of academic health centers and professional organizations, and editors of prestigious

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<sup>13</sup> Gina Kolata, *Johns Hopkins Admits Fault in Fatal Experiment*, N.Y. TIMES, July 17, 2001, at A16.

medical journals. The press, looking to such leaders as news sources, ignores opposing views and amplifies these messages.<sup>14</sup>

Overly zealous implementation of conflict-of-interest regulations can and will discourage participation from the very investigators who should be engaged. While the validation by an oversight board can be reassuring to an institution and to the public, the attempt to restrict the development of knowledge can impact both the inventor and society at large.<sup>15</sup>

Furthermore, conflict-of-interest regulation of research is easily misapplied to invalidate legitimate studies. A fundamental misunderstanding of the invention process by those who regulate research can promote faulty reasoning. The process of drug and medical device discovery often involves a collaborative effort between academic inventors and industry which can be misconstrued as a conflict of interest. The costs of invention and development are extraordinary. Only 1 in 100,000 potential new compounds reaches commercialization. It is, therefore, inevitable that large drug trials reported in major medical journals will be sponsored by drug companies. Given the rigor of the screening process before drug companies will invest in new drug research, it is doubtful that large companies will invest in drug trials likely to fail. It is a tautology, therefore, to suspect a relation between industry sponsorship and positive outcome in clinical trials.<sup>16</sup>

Stringent regulation of corporate-sponsored research and continuing medical education has also been suggested.<sup>17</sup> Acceptance of such a radical solution, in which corporate entities would surrender their products to academia, would no doubt signal the end of academic research as we know it. As noted by Stossel in a commentary<sup>18</sup> on such a solution, it has the intellectual substrate of the infamous book *Malleus Maleficarum*, commissioned by Pope Innocent VIII, which served as a principal reference for the discovery of witches. I contend that full disclosure of conflict is usually adequate to inform subjects of conflicted investigators. Because conflict-of-interest policies are not rooted in federal mandates or even specifically enumerated

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<sup>14</sup> Thomas Stossel, *Regulating Academic–Industrial Research Relationships—Resolving Problems or Stifling Progress?*, 353 NEW ENG. J. MED. 1060, 1063 (2005) (citations omitted).

<sup>15</sup> It is embarrassing to report that at our own institution a physician who invented a new device was recently advised that “to prevent even the appearance of direct involvement, he would not be permitted to be more than an author on any publication in which the University of Chicago Hospital patients participated.” Fax from a representative of the University of Chicago to a physician at the University of Chicago (Feb. 22, 2006, 19:29 CST) (on file with author). This decision was overturned only upon faculty and provost review.

<sup>16</sup> See Justin Bekelman, Yan Li & Cary Gross, *Scope and Impact of Financial Conflicts of Interest in Biomedical Research*, 289 J. AM. MED. ASS’N 454 (2003) (finding in a review of 37 studies of quantitative data on the financial relationships among scientific industry, academic institutions, and investigators that financial relationships were not widespread).

<sup>17</sup> Troyen Brennan et al., *Health Industry Practices That Create Conflicts of Interest*, 295 J. AM. MED. ASS’N 429, 430–32 (2006).

<sup>18</sup> Thomas Stossel, *Witch Hunt*, WALL ST. J., Feb. 21 2006, at A18.

in university regulations, they are often highly arbitrary and without basis for appeal.

In addition to the chilling effect on scholarship, there are very real consequences to the public interest by oversight of clinical studies through the blunt tool of conflict-of-interest regulations. Brian Druker, the discoverer of Gleevec, a miracle drug for leukemia, received money from Novartis for research support and published the article that detailed the drug's development in a prominent medical journal.<sup>19</sup> Although thousands of lives were saved by the early use of this drug, Professor Druker would have violated conflict-of-interest regulations had he been on our faculty. If evolution had been designed with this upside-down logic of punishing success, we would all be single-celled organisms. Institutional Review Boards, acting within national norms for conflict of interest, are a far better model for providing oversight functions than ad hoc institutional committees. If Institutional Review Boards were abolished, the unfortunate situation produced by conflict-of-interest oversight would likely be extended to all clinical research.

### III. CONCLUSION

In conclusion, I believe that there are compelling arguments in favor of Institutional Review Boards or something very much like them. I believe there are institutional threats to academic freedom, but Institutional Review Boards are near the bottom of the threats list. While Institutional Review Boards can, and in all likelihood do, slow and somewhat impede research, few worthwhile proposed studies are abandoned because of them. Should Institutional Review Boards be found unconstitutional, my experience with institutionally mandated issues such as conflict of interest suggests that whatever replaces them may not be substantially better and might in fact be far more limiting.

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<sup>19</sup> Brian Druker et al., *Efficacy and Safety of a Specific Inhibitor of the BCR-ABL Tyrosine Kinase in Chronic Myeloid Leukemia*, 344 NEW ENG. J. MED. 1031, 1036 (2001).

