

# Independent Institutional Review Boards

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Institutional Review Boards (“IRBs”) are committees charged by U.S. federal regulations<sup>1</sup> with protecting the rights and welfare of human subjects involved in research. One type of IRB is the independent IRB, which is separate from and unaffiliated with an institution conducting research activities. This article will provide a definition of independent IRBs, review the history of independent IRBs, and address the criticisms and advantages of independent IRBs.

## I. DEFINITION OF INDEPENDENT IRBS

There are several terms used to define independent IRBs, including “non-institutional,” “non-local,” “commercial,” “for profit,” “professional,” “multiple project,” and “central.” These terms tend to focus on one of three characteristics: the location of the IRB, the financial organization of the IRB, and the role of the IRB in multi-site research. The vast majority of IRBs in the United States are located within and supported by an institution at which research involving human subjects is conducted. Independent IRBs, in contrast, are not located within such an institution, instead standing alone as separate organizational entities. Thus, a useful definition of an independent IRB is one that is not located within nor supported by an institution engaged in the conduct of research. However, independent IRBs are established and supported by an organization, generally a corporation, and for the purpose of regulatory interpretation, this corporation is an institution. Defining independent IRBs as being neither located within nor supported by a research institution excludes IRBs that are created by and located within a pharmaceutical sponsor or a Contract Research Organization (“CRO”), a group of IRBs often designated with the term independent IRB. Some of these IRBs review research conducted

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<sup>1</sup> See, e.g., 21 C.F.R. § 50 (2002); 21 C.F.R. § 56 (2002); 45 C.F.R. § 46 (2002).

outside of the supporting sponsor or CRO, and to that extent, they function similarly to an independent IRB. In addition, some hospital-based IRBs have expanded their services to include the review of research conducted outside of the supporting institution.

Another set of definitions has focused on the financial status of the IRB, including the terms “commercial,” “for profit,” and “professional.” Traditionally, IRBs located in institutions have been supported by the institutions as administrative overhead, with no fee charged for their review of research. In contrast, independent IRBs have traditionally operated on a for-profit basis, although there is at least one long-standing independent IRB that operates on a non-profit basis. This distinction has been blurred in recent years, as many IRBs located in institutions now charge for the review of research funded by commercial sponsors. The advantage of charging for IRB review is that the financial support for the IRB grows at the same rate as the amount of research being reviewed by the IRB. A common problem faced by institutionally based IRBs is that their funding has not increased in proportion to the amount of research they review, and over time, this situation can lead to insufficient staff and resources to properly support the IRB. As discussed below, being paid to review and oversee research leads to a financial conflict of interest for IRBs. Another traditional financial distinction between independent and institutional IRBs is that institutional IRB members have traditionally participated on a volunteer basis, while independent IRBs members are paid for their participation. This is another distinction that is blurring, in that many institutions are now providing some compensation or reimbursement for IRB members, or have arranged for the IRB service to be taken into account by the department in which the member resides. Many institutions have also begun to compensate unaffiliated members for their time. When IRB members are paid for their services to an IRB, it is important that the payment be structured in such a manner that it does not create any incentive to approve the research. Common approaches are to pay members a flat fee per meeting regardless of the decision on any proposed research, or on a straight hourly basis.

Finally, independent IRBs are often characterized as being “multiple project” or “central.”<sup>2</sup> One of the more profound changes

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<sup>2</sup> Robert J. Levine, Louis Lasagna and Sanford Chodos, program co-chairs. Boston: Tufts Center for the Study of Drug Development, *DEMISTIFYING CENTRAL REVIEW BOARDS: CURRENT OPTIONS AND FUTURE DIRECTIONS: CENTRAL IRB REVIEW OF MULTI-SITE TRIALS* (Oct. 27-28, 1998) (summary report of outcomes from a conference held October 27-28, 1998, Arlington VA).

in the clinical research environment from 1981 to the present has been the growth of multi-site research studies. Whereas in the 1960's and 1970's research was generally conducted at a single site, much research today is conducted at dozens or even hundreds of individual sites. Often, a single independent IRB will serve as the IRB for those sites that are not located in an institution, while those sites located within institutions utilize their local IRBs. This role as a central IRB provides consistency in IRB decisions. The concept of central IRBs for multi-site research is gaining popularity, and there are several proposals and experiments under way for the use of central IRBs, whether independent or otherwise. For instance, the Pharmaceutical Research and Manufacturers of America ("PhRMA") has proposed a central IRB system that would allow, but would not require, an independent IRB to serve as a central IRB.<sup>3</sup> The National Cancer Institute ("NCI") has established a central IRB for the review of NCI-funded studies. In addition, in several locations, hospitals and universities have coordinated their IRB efforts to allow for any one of the institutions' IRBs to serve as a central IRB for the others, or have set up a single IRB to serve multiple institutions. Finally, many health organizations with more than one hospital have organized a single corporate IRB to review research. Some of these arrangements utilize independent IRBs, while others do not.

## II. THE HISTORY OF INDEPENDENT IRBS

The human subject protection system in the United States has developed incrementally, often in response to cases of research abuse. The existence of independent IRBs originates from Food and Drug Administration ("FDA") policy issued in the preamble to its 1981 regulations on IRBs.<sup>4</sup> The use of IRBs in the United States, however, began in the National Institutes of Health ("NIH") in the 1960's. In 1966, Surgeon General William H. Stewart issued a memorandum requiring that an investigator obtain a review of research by "a committee of his institutional associates."<sup>5</sup> The policy applied to research funded by public health grants. In 1971, the Department of Health, Education, and Welfare issued a policy on the

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<sup>3</sup> FDA, *OHRP Express Support for PhRMA's Call for "Central" IRBs*, 7 FDA WEEK (July 20, 2001); *see also* PHRMA, *INSTITUTIONAL REVIEW BOARDS IN CLINICAL RESEARCH: PROPOSAL AND DISCUSSION* (1999).

<sup>4</sup> 21 C.F.R. § 56, at Preamble cmt.17 (2002); *see also* 46 Fed. Reg. 8958, 8962 (1981).

<sup>5</sup> Memorandum from Surgeon General William H. Stewart, to the Heads of Institutions Conducting Research with Public Health Grants (Feb. 8, 1966), *in* JAY KATZ, *EXPERIMENTATION WITH HUMAN BEINGS* (1972).

protection of human subjects.<sup>6</sup> In 1972, the NIH established the Office for Protection from Research Risk (“OPRR”) to ensure that there was consistent internal policy. In 1974, NIH enacted human subject protection regulations. The NIH also began to require that external institutions receiving NIH funding to perform research, usually universities and large hospitals, also establish IRBs to ensure the protection of human subjects at those institutions. Thus, NIH established, in its policy and regulations, that the institution was the responsible party for ensuring that human subjects were protected, and as a result, IRBs were appointed by the institutions receiving the federal funding to conduct research.

In 1974, Congress enacted the National Research Protection Act<sup>7</sup> in reaction to several cases of research abuse and misconduct. These cases included the PHS syphilis study, in which black men in Alabama were allowed to progress with untreated syphilis even after the availability of penicillin;<sup>8</sup> the Willowbrook state school hepatitis studies in which mentally disabled, institutionalized children were infected with hepatitis for research purposes;<sup>9</sup> and the Jewish Chronic Disease Hospital study in which patients were injected with live cancer cells to determine whether this would cause cancer.<sup>10</sup> In addition, Congress was concerned about the early phases of drug research being conducted in prisons and the use of fetal tissue for research purposes.<sup>11</sup> As part of the National Research Protection Act, Congress created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, and directed the Commission to issue a series of reports on specific issues involving human subject research. In 1981, based on these reports, the NIH revised its regulations on human subject protection,<sup>12</sup> and the FDA revised its regulations on informed consent,<sup>13</sup> and adopted a new regulation on IRBs.<sup>14</sup> Prior to 1981, FDA required research under its jurisdiction to be submitted to an IRB if the research was being conducted in an institution with an IRB, but FDA did not require research being conducted outside of an institution with an

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<sup>6</sup> DHEW Pub. No. (NIH) 72-102, Dec. 1, 1971.

<sup>7</sup> Pub. L. 93-348 (1974).

<sup>8</sup> See JAMES JONES, *BAD BLOOD* (1981); see also ALBERT JONSEN, *BIRTH OF BIOETHICS* 146-48 (1998).

<sup>9</sup> JONSEN, *supra* note 8, at 153-54.

<sup>10</sup> See KATZ, *supra* note 5, at 9-65.

<sup>11</sup> See JONSEN, *supra* note 8, at 94-98.

<sup>12</sup> 45 C.F.R. § 46 (2002).

<sup>13</sup> 21 C.F.R. § 50 (2002).

<sup>14</sup> 21 C.F.R. § 56 (2002).

IRB to receive IRB review.<sup>15</sup> Starting in 1981, with the adoption of the new regulations, FDA required all research under its oversight to receive IRB review. In preamble commentary to the new regulations, FDA stated:

Physicians who practice in their offices and who wish to conduct clinical investigations for a sponsor or as sponsor-investigators are required to comply with these regulations to obtain a research permit. The agency recognizes, however, that in some instances such physicians (and other health professionals who would otherwise qualify for a research permit) may not be affiliated with an institution or have direct access to an IRB. In those instances, FDA advises that several options are available to the physician. A sponsor-investigator who is unaffiliated with an institution with an IRB can comply with this requirement by obtaining review at an institution whose IRB conforms with these regulations or by submitting the research proposal to an IRB created under the auspices of a local or State government health agency, a community hospital, a private or public medical school, a county or State medical society, the State medical licensing board, an independent nonprofit group—such as a foundation or society interested in a particular health concern, e.g., kidney disease or family planning, or an organization involved in intergroup communications, e.g., the American Arbitration Association. A private physician who wants to conduct clinical research for a sponsor, in addition to these options, may use an IRB created by the sponsor.<sup>16</sup>

Based on this preamble comment, a market was created for independent IRBs to provide oversight to investigators doing FDA-regulated research in their offices or in institutions too small to support an IRB. Thus, independent IRBs served as an interstitial means of providing oversight when a traditional institutionally-based IRB was not available.

Although FDA created this new niche market, the NIH did not agree with FDA's policy for many years. OPRR did not allow independent IRBs to review federally-funded research until 1996, based on the regulatory interpretation that research institutions should establish and oversee internal IRBs, as well as unease with the for-profit structure of independent IRBs and the resulting financial conflict of interest. In 1996, OPRR changed its policy and began to

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<sup>15</sup> 21 C.F.R. § 312(a)(2), at 10C (1975); *see also* FDA, COMPLIANCE PROGRAM GUIDANCE MANUAL (1977), *cited in* Erica Heath, *The History, Function, and Future of Independent Institutional Review Boards* (Aug. 2001), available at <http://bioethics.georgetown.edu/nbac/human/overvol2.html> (last visited Apr. 11, 2002).

<sup>16</sup> 46 Fed. Reg. at 8962 (1981).

allow independent IRBs to review federally-funded research. In 2000, OPRR was moved from its location in NIH up to the office of the Assistant Secretary for Health at the Department of Health and Human Services (“DHHS”) and renamed the Office for Human Research Protections (“OHRP”). This new office has revised the process by which an institution may designate an IRB, making it easier for institutions to use an independent IRB as an IRB of record, and also has opened up voluntary registration of all IRBs, whether or not it is located within an institution. As a result of this revised policy, some research institutions have contracted with independent IRBs to provide either complete IRB services or services for a designated subset of research, such as FDA-regulated studies.

### III. CRITICISMS OF INDEPENDENT IRBS

There have been three main criticisms of independent IRBs over the years: (1) that they have a substantial financial conflict of interest; (2) that they are usually not located where the research is being conducted, and therefore cannot properly assess local attitudes; and (3) that the existence of independent IRBs allows and even promotes IRB shopping. The conflict of interest faced by independent IRBs is real and substantial. Independent IRBs are paid by sponsors and investigators to protect subjects who are participating in research conducted by those sponsors and investigators. A conflict of interest can be defined as a situation in which individual A’s duties to individual B conflict with either A’s duties to third parties and/or to A’s self interest, thus causing a potential for improper bias in the fulfillment of A’s duties to B. Independent IRBs have a primary duty to protect the rights and welfare of research subjects, but they are also engaged in a business relationship with their clients, the investigators, and sponsors. There are three main methods to address conflicts of interest once they exist: (1) disclosure of the conflict of interest to the affected parties; (2) controls to minimize the likelihood of bias from the conflict of interest; or (3) elimination of the situation leading to the conflict of interest. Disclosure is a common approach in several fields, including government, the legal profession, and academia. Disclosure is an awkward approach for independent IRBs, in that the relevant party to disclose the conflict to is the subject, through the consent process. However, there is FDA guidance stating:

FDA also believes that an explicit statement that an IRB has approved solicitation of subjects to participate in research could mislead or unduly induce subjects. Subjects might think that, because the IRB had approved the research, there is no need to

evaluate the study for themselves to determine whether or not they should participate.<sup>17</sup>

As a result of this guidance, any disclosure of the conflict of interest faced by the IRB should also be careful not to state that the IRB has approved the study or to disclose the purpose of the IRB. The result would be a cryptic disclosure to the subject of a conflict of interest of an undefined group.

The second approach to conflicts of interest is to control them with the goal of minimizing the likelihood of improperly biased decision making. There are several methods that an independent IRB can implement to control its conflict of interest. First, the majority, and preferably all, of the IRB members should be independent of the corporation that supports the IRB, so that the members' only affiliation with the corporation is being an IRB member. As part of this independence, none of the IRB members should "have an equity interest (e.g., partnership, stocks, or profit-sharing) in the organization providing IRB review."<sup>18</sup> Third, there should be a "firewall" policy by which business interests, such as billing issues, are not disclosed to, nor discussed with, board members. This policy should be continually emphasized during both IRB member and IRB staff training. Fourth, IRB members should be paid for their services in a manner that will not influence their vote on any particular item, such as a flat fee per meeting regardless of the actions taken by the Board. No member should be paid "more than reasonable compensation for IRB services."<sup>19</sup>

The third approach to conflicts of interest is to eliminate the situation leading to the conflict. Under this approach, the use of independent IRBs is prohibited. The College of Physicians and Surgeons of the province of Alberta, Canada, has adopted this position, and requires that all research conducted in Alberta be reviewed by one of four designated IRBs.<sup>20</sup> The stated goal of this approach was a concern about public safety based on the use of

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<sup>17</sup> FDA, *FDA Approval of Studies*, available at <http://www.fda.gov/oc/ohrt/irbs/informedconsent.html#approval> (Sept. 1998).

<sup>18</sup> OHRP, *Subject: Update - Suitability of a Designated Institutional Review Board (IRB)*, available at <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/ind-irb.htm> (Feb. 1997) (on file with author).

<sup>19</sup> *Id.*

<sup>20</sup> College of Physicians and Surgeons, Province of Alberta, 58 *THE MESSENGER* 3, (1997), available at <http://www.cpsa.ab.ca/messenger/Messenger%2058.pdf>; see also College of Physicians and Surgeons, *Research Ethics Review Committee (RERC): Information and Application Package*, available at <http://www.cpsa.ab.ca/research.htm> (last visited Apr. 11, 2002) (on file with author).

“privately operated research ethics boards” to review research.<sup>21</sup>

A second common criticism of independent IRBs is that they often review research that is performed non-locally, often across the country and even internationally. The Common Rule and FDA regulations require that “[t]he IRB shall be sufficiently qualified through the experience and expertise of its members and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.”<sup>22</sup> Both FDA and OHRP have issued guidance on non-local IRB review of research and the appropriate knowledge of community attitudes.<sup>23</sup> Concern about knowledge of local conditions falls into two general categories: knowledge of the conditions surrounding the conduct of the research, and knowledge of the attitudes of the subject population towards given research projects. A non-local IRB can gain knowledge about the local conditions surrounding the conduct of the research by inquiring about factors such as the number of studies being conducted, the number of research staff, and on-site emergency procedures, by having local representation in the IRB meetings, and by conducting site visits. Information about community attitudes can be obtained through questions to investigators during initial and continuing review, the use of local representatives and IRB members, interviews with local residents, site visits, and searches of the internet and other media. The attitudes of distinct cultural communities can be obtained through appropriate board member participation or consultant expertise, or through representation from the community, but the attitudes of general geographically-defined communities are often difficult to assess based on the variety of opinions individuals hold towards research based on their own experiences. When local media reports on problems with research, such as the suspension of an institution’s assurance with OHRP, subjects often ask their physicians about the conduct and oversight of research, generating local and generally transient, negative attitudes towards research. It is worth noting that knowledge of community attitudes is not an issue restricted to independent IRBs. Many institutionally-based IRBs

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<sup>21</sup> *Id.*

<sup>22</sup> 21 C.F.R. § 56.107(a) (2002); 45 C.F.R. § 46.107(a) (2002).

<sup>23</sup> FDA, *Non-Local IRB Review*, available at <http://www.fda.gov/oc/ohrt/irbs/nonlocalreview.html> (Sept. 1998) (last visited Apr. 10, 2002); see also OHRP, *IRB Knowledge of Local Research Context*, (Aug. 1998) [Updated July 21, 2000], available at <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/local.html> (last visited Apr. 10, 2002).



review research conducted in non-local settings, including international settings.

Another criticism of independent IRBs is that their existence promotes “IRB shopping,” the practice of submitting a research proposal disapproved by one IRB to a second IRB to see if the outcome is more favorable. IRBs located within an institution traditionally establish sole jurisdiction over the review of research to be conducted within that institution. Therefore, if an investigator is not approved by that IRB, there is no opportunity to send the research to another IRB. In contrast, if an investigator is conducting research in her office or at an institution without an IRB, she can then submit a disapproved research study to subsequent independent IRBs. However, research institutions and even university systems can also be “shopped.” A Genentech representative stated at a Congressional hearing:

When somebody brings us a list of 50 potential sites for clinical investigations, one of the things that goes into the equation of whether or not to use them is . . . the difficulties of getting things through the IRB. For instance, the University of California is really . . . difficult, whereas I could do things at the Mayo Clinic or in Utah or Texas where it's much easier. That's time and money, and it ultimately turns into quality science.<sup>24</sup>

There are several means to address the problem of inappropriate IRB shopping. IRBs can ask about prior IRB disapprovals on their application form. In addition, IRB members and staff often communicate informally regarding research, and disapprovals by one IRB are often disclosed to other IRBs in this manner. A preferable solution is through regulatory disclosure requirements. Presently, the only regulation that requires disclosure of IRB disapprovals to other IRBs is the FDA regulation allowing an exception from informed consent requirements for emergency research.<sup>25</sup> However, FDA is currently seeking commentary on whether it should amend its regulations to require sponsors and investigators to inform IRBs about any prior IRB review decisions.<sup>26</sup> A similar provision is included in a current bill before Congress entitled the “Human Research Subject Protection Act of 2000.”<sup>27</sup> While

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<sup>24</sup> THE PINK SHEET, May 3, 1999, at 27 (quoting John Curd, *Genentech VP of Clinical Development*).

<sup>25</sup> 21 C.F.R. § 50.24(e) (2002).

<sup>26</sup> 67 Fed. Reg. 44 (Mar. 6, 2002), available at [http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=2002\\_register&docid=02-5247-filed](http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=2002_register&docid=02-5247-filed) (last visited Apr. 10, 2002).

<sup>27</sup> 106 H.R. 4605, 96th Cong. (2000).

investigators and sponsors can IRB shop for inappropriate reasons, it should be noted that there are also legitimate reasons for IRB shopping, such as timeliness, quality, and cost.

#### IV. ADVANTAGES OF INDEPENDENT IRBS

The existence of independent IRBs provides several advantages. They have traditionally played an interstitial role in providing IRB review for FDA-regulated research being conducted by physicians in offices and clinics that are not large enough to support an internal IRB. As many drugs and devices are investigated and eventually used in this environment, this provides a valuable service. Independent IRBs also provide the possibility of IRB review for research that is not required by regulation to undergo IRB review, such as non-federally funded *in vitro* fertilization research that does not involve an FDA-regulated test article. Independent IRBs also provide consistency of review for multi-site clinical trials, which “eliminates the complications that result from multiple, local IRB reviews of a sponsor’s research plan. It also facilitates analysis of adverse-event reports submitted from individual sites and, in so doing, can enhance protections for human subjects.”<sup>28</sup> Independent IRBs are usually well-funded and well-staffed based on the fee-for-service financial base, and as a result can provide a timely review. Independent IRBs are also largely free of the conflicts of interest that arise from the location of an IRB within an institution, such as IRB members reviewing research conducted by friends, colleagues, and supervisors. As discussed above, however, independent IRBs do face financial conflicts of interest. Finally, independent IRBs can provide support services for institutions that are overburdened, have compliance problems, or wish to outsource IRB review for financial reasons.

#### CONCLUSION

Independent IRBs traditionally played an interstitial role by providing IRB review for investigators conducting FDA-regulated research in settings without an IRB. In recent years, however, the role of independent IRBs has been changing, as has the IRB system and the research environment in general. The traditional distinctions between independent IRBs and institutional IRBs have blurred, and independent IRBs have taken on additional roles. Many institutionally-based IRBs now charge for the review of research and

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<sup>28</sup> Office of the Inspector General, *Institutional Review Boards: The Emergence of Independent Boards*, June 1998, at 6.

compensate their IRB members. Some have also begun to review research conducted outside of the institution on a fee-for-service basis. Independent IRBs now review federally funded research, and often review research conducted at large research institutions, serving as IRBs of record for those institutions. Central IRB functions, which traditionally were limited to independent IRBs reviewing FDA-regulated research, are now often structured in other ways. As these roles continue to blur, it will be important to ensure that the advantages of independent IRBs are maintained, while the disadvantages are properly controlled and addressed.

