

**The History, Function, and Future of
Independent Institutional Review Boards**

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The History, Function, and Future of Independent Institutional Review Boards

Executive Summary

The National Bioethics Advisory Commission ("NBAC") has requested information about the philosophical and practical issues related to the role of independent institutional review boards ("IRBs") in the current medical research community. This paper provides a working definition of independent IRBs. It describes their role within a broader framework of protections for human subjects. It addresses their history and development, and describes the strengths and weaknesses of independent IRBs.

As the term suggests, an "independent" IRB is a sub-set of a wider universe of IRBs; as such, it exists for the same purpose as all IRBs -- to review clinical research plans to ensure that adequate human subject protections have been incorporated. An independent IRB is subject to the same federal and state regulatory requirements applicable to all IRBs. Although it is difficult to produce a single definition of the term "independent IRB" due to the diversity of these entities, the following description is offered:

INDEPENDENT IRB: an IRB which reviews research for the purpose of assuring adequate protection of human subjects for entities that generally are not part of the same organizational structure as the IRB.

Beginning in 1966, the federal government established requirements for protection of human subjects in institutions receiving federal funding. Centers conducting research entered agreements called Multiple Project Assurances (MPAs) with DHEW through the Office of Protection from Research Risks (OPRR).^{*} That the system was decentralized and was institutionally-based is a reflection of the organization of research in that era. Academic Medical Centers were the locus of most research, research was predominantly single site and most sites acted independently and interacted rarely.

Over time, the research landscape has dramatically changed. In order to meet the demands of the new research environment, independent IRBs were born. The Food and Drug Administration's (FDA) recognition that IRBs need not be located in an institutional setting created the first gateway for the use of independent IRBs throughout the 1980's.

* OPRR was recently relocated and re-named the Office for Human Research Protection, OHRP.

In 1995, OPRR began granting Single Project Assurances ("SPAs") for projects reviewed by independent IRBs.

Although the greatest need for independent IRBs remains outside the academic and hospital setting, independent IRBs have been used in many institutional settings including: institutions that contract for outside review, institutional IRBs that accept the review of an independent IRB for multi-center studies, and institutions that use an independent IRB as a "bridge" to an improved internal review system.

The benefits of independent IRBs continue to emerge: (1) independent IRBs fill a void by providing review to centers that might not otherwise have adequate IRB review, (2) independent IRBs have provided significant advantages in reviewing multi-site research, (3) independent IRBs provide structured and efficient reviews, and (4.) their independence from the institution for which they provide reviews frees them from the conflicts of interest associated with the institution.

Several perceived weaknesses have been identified as inherent in the structure of independent IRBs: (1) conflict of interest, (2) the possibility of "shopping" for IRB approval and (3) lack of physical presence at the performance site. All of these concerns can be addressed through proper organizational structure and/or implementation of standard operating procedures.

Because Independent IRBs evolved out of a changing research environment, they are well suited to ensure that the needs of investigators, sponsors, and government regulators are met, while maintaining human subject protection.

INTRODUCTION

This report reflects the experiences of one person. I became involved in IRBs in late 1970 at the University of California, San Francisco, assisted in the writing of UCSF's second MPA in 1974, and co-wrote the first faculty guidance document. In 1984, I resigned from UCSF and, as no regional medical societies had answered the call for regional IRBs. I founded IRC Independent Review Consulting.

IRC, incorporated in 1994, currently specializes in review of medical device studies, use of biological specimens, biotechnology and social and behavioral studies. IRC has worked with several institutions as the IRB of record for their Single Project Assurance.

The thinking and opinions in this paper are mine and do not necessarily reflect those of other independent IRBs. I would like to offer appreciation for the many people who provided their editorial assistance, their time, and their kindness.

Erica Heath

I. Independent IRBs Defined

A. IRBs in General

Before discussing the definition of an independent IRB, a general review of the essentials of an "IRB" is offered along with a review of some of the elements that all IRBs share, and some elements that distinguish them.

- Every IRB is a committee.
- The membership composition of every IRB must meet certain regulatory standards.¹
- The function of every IRB is to review research plans to ensure that they contain adequate human subject protections.
- Such review includes both initial and continuing review.
- Every IRB is guided by federal and state laws and regulations, and ethical principles of human subject protection.
- Every IRB must have written policies and procedures.

There is a wide diversity of both form and function among traditional IRBs reflecting a continuum of purpose and practice. This diversity is reflected in the number of names used to describe them (see box). Many of these adjectives can apply to one IRB or to several. A few examples are:

- An IRB which limits its service to the single institution in which it is based,
- A "central" IRB serving within a regional health care system of multiple hospitals and clinics,
- A regional IRB serving one area – including its numerous hospitals and any private practices and clinics, who elect to use it.
- An IRB established by a physician solely to serve that physician's corporate practice,
- An IRB within the organizational structure of a contract research organization which also contracts for outside work,

Various adjectives, illustrative of the wide variety among IRB form and function, have been used to characterize IRBs.

Central
Collaborative
Commercial
Community-based
Contract
Dependent
For-profit
Free
Independent
Internal
Institutional
Local
Multiple Project
Non-local
Non-institutional
Professional
Remote

- A private international agency with an internal IRB to review its global studies.
- An IRB within a government agency.
- An IRB within a corporation.
- An IRB established to serve multiple functions including service as a bioethics committee, research committee and a medical staff advisory committee.

B. Similarities Among IRBs

The class of "independent" IRB is a sub-set within this general description of IRBs. Similarities exist between independent and institutional IRBs.

- They exist for the same purposes - protection of human subjects of research.
- They are guided by the same federal, and state legal and, ethical requirements including both the Dept of Health and Human Services (DHHS) and the FDA regulations, as applicable.
- They must have an organizational structure and written operating policies and procedures.
- Their membership composition must meet the same regulatory standards.
- They are subject to external audit by both FDA and OPRR (now OHRP) (for SPA approved work).

C. Differences Among IRBs

Although there is a splendid variety within both independent and institutional structures for IRBs, there are several key features that distinguish the Independent IRB

- The performance site is usually within an organizational entity different from that of the reviewing Independent IRB. (However, a traditional institutional IRB may offer courtesy review to investigators outside the institution.)
- The performance site is usually remote from the independent IRB reviewers. (However, a traditional institutional IRB may review remote work performed by its faculty elsewhere.)
- The members of the independent board are almost all external to its organization. (However, many traditional institutional boards that have had only one external member are increasing the percentage of external members.)
- The relationship between the independent IRB and the party seeking approval is through a contract or agreement rather than through institutional jurisdiction. (However, although the

relationship between a traditional IRB and its applicants is mandatory, the entity funding the study enters into a contract with the institution responsible for the IRB.)

Just as an institutional IRB is part of an institution, an Independent IRB is always a part of an organization that can be defined as an "institution" within the Common Rule.² As defined, institutions of either type may be large or small, for-profit or non-profit, professional or volunteer, professional medical practices, hospitals, non-profit foundations, or contract research organizations. The Independent IRB may also be part of a corporation unaffiliated with any other organization.

D. A Suggested Definition

The definition suggested here is intended to highlight both the similarities and differences. An Independent IRB is:

*an IRB...
which reviews research...
for the purpose of assuring adequate protection of human subjects...
for entities that generally are not part of the same organizational structure as the IRB.*

This definition suggests that an Independent IRB performs the same function as any IRB. It reviews research for the same purpose as other IRBs. The defining difference is that the institution conducting the research and the institution supporting the IRB are different organizational entities.³

II. An Environment Engendering Independent IRBs

The traditional institutional IRB was created in response to the research environment. When that environment changed it was necessary to create a legal and ethical alternative. The independent IRB arose to filled the need created by this change.

A. The Early Regulation of Medical Research and the Public Health Service Response

As long as man has been interested in scientific learning, people have conducted "experiments" to determine how the human mind and body respond to certain stimuli -- from machinery and electricity to sounds and chemicals. Gradually such "experiments" evolved from single anecdotal studies to more formal experiments, to "research" in which groups of subjects were studied in an organized manner to systematically answer a broader question.

Many research studies have lead to ground-breaking discoveries that have benefited humankind as a whole. The public has known, however, that these research projects also have the capacity to damage the human participants and may present unacceptable risks to society as a whole. This negative side is evidenced by the horrific "experiments" conducted during World War II, or by the later revelations concerning American studies such as those performed at the Jewish Chronic Disease Hospital⁴ or at Willowbrook State Hospital.⁵ In 1966, an article by Henry

Beecher⁶ brought prominent attention to human research abuses in medical schools and hospitals, citing 22 cases involving highly questionable ethics.

In recognition of the potential risks to human subjects inherent in scientific research, and knowing that the U.S. Government was actively funding such research, U.S. Surgeon General William Stewart issued an important policy statement on February 8, 1966⁷ related to the administration of federal grants and contracts supporting research, development, and related activities involving human subjects. Key elements of this policy were:

- A decentralized system delegating responsibility from the federal funding agency to the recipient institution,
- Centering responsibility for protection of human subjects at the institutional level.
- Review by a "committee of peers" at the funded institution,
- Use of an assurance statement from, officials at the funded institution to the funding agency within the Public Health Service

The first assurances, issued in 1966, were very short and dealt only with fundamental issues. Later assurances have become complex and reflect many subsequent interpretations of the initial basic premises.

The concepts outlined in Surgeon General Stewart's policy statement were refined over the next few years, and by 1971, had made their way into the "Grants Administration Manual" of the Department of Health, Education and Welfare ("HEW"). The concepts were made available to the newly formed reviewing committees through distribution of a pamphlet readers called "The Little Yellow Book"⁸. This pamphlet instructed that studies involving human subjects needed committee review. The review was to address three concerns: (1) whether benefits of the study exceeded risks, (2) whether the rights, safety and welfare of subjects were protected and (3) whether adequate provisions were made to obtain informed consent. Human subjects were persons placed "at risk" by their participation. (Interestingly, if an investigator decided that his subjects were not "at risk," review was not required.)

In May 1974, the first regulations requiring IRB review for protection of human subjects were issued as Title 45 of the Code of Federal Regulations ("CFR"), Part 46. For the first time the committees conducting research reviews became known as "institutional review boards."⁹ The new regulations provided revised definitions of research, human subject, and assurance, and provided criteria for IRB review and expanded the elements of informed consent.

- "Research" was defined as a type of activity that was prospective and would lead to generalizable knowledge.
- A "human subject" was defined as the living subject of that activity regardless of the level of risk.

- An "assurance" meant a document in which the institution agreed that it would comply with human subject protection requirements, and in which it described the review and implementation of procedures undertaken to do so.
- The three review criteria were expanded to seven.
- Informed consent was further described, and additional elements of information required for informed consent were listed.

In June of 1974, the National Research Act (Public Law 93-348) was signed into law, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research ("National Commission"). The National Commission was charged with making recommendations particularly about inclusion of various vulnerable populations in research. Their best remembered report dealt with the "ethical problems" precepts underlying Western research. The National Commission's work resulted in the Belmont Report and in an affirmation of the basic requirements of the IRB system.

Over time, the regulatory system evolved to include more types of research, and to increase the importance of IRBs and the amount of work they were asked to perform. Social and behavioral research funded by the Public Health Service (PHS) was brought within the jurisdiction of the regulation and IRB review.

Critically, an increasing number of assurances contained a statement that *all* research conducted within the institution must be reviewed using the single standard set forth in 45 CFR 46. This meant that, in an institution with a Multiple Project Assurance ("MPA"), all studies were reviewed under 45 CFR 46 regardless of the source of funding or other regulatory controls.

Other federal agencies were actively developing human subject protection programs, most of which adopted the same basic requirements involving IRB review and informed consent. However, each agency had slightly different requirements. For instance, the Dept. of the Navy required signatures of all, IRB members on approval letters, while the Dept. of Energy had other elements of consent. The FDA requirements were more voluntary and did not require consent if the doctor determined it was not in the subject's best interest. This conflicting hodge-podge of regulations caused substantial confusion.

In 1978, the National Commission concluded that IRBs should be governed by uniform federal regulations¹⁰ This very well received recommendation eventually resulted first in the 1981 regulation which harmonized FDA with DHHS and then in the 1991 issuance of the Common Rule.¹¹

The National Commission also recognized that flexibility must be maintained in creating IRBs. For example, the National Commission explained that an IRB may be located in the institution where the research is being conducted or outside of it, and may review research for one institution only or for several institutions.¹²

B. The Food and Drug Administration (FDA) response

Although the FDA was an agency within the DHEW and later the DHHS, its history with regard to human subject protection, developed independently of its sister agency, the National Institutes of Health. The FDA regulations developed in response to other incidents, Congressional actions, and its own regulatory responsibility.

The FDA's history of regulation of human subjects research started in 1962 with the Kefauver Amendment to the Food, Drug and Cosmetic Act. This act included the requirement that informed consent should be required unless it "was deemed not to be feasible," or it was "contrary to the best interests of such human beings."¹³

In 1971, the FDA required IRB review if the study was to be conducted with institutionalized subjects or in an institution with an IRB; for sites with no IRB, IRB review was not required.¹⁴

FDA regulations requiring IRB review for FDA regulated products were first published on January 27, 1981. They closely resembled the DHEW regulations in the description of an IRB and in the review criteria used.

Recognizing that many products were tested at sites without an IRB, FDA nevertheless required IRB review for all studies. In the preamble to the 1981 regulations, FDA recognized the gap in coverage by IRBs and suggested that local governments, medical societies or the sponsor itself might form IRBs for these studies.

FDA accepted the Common Rule on June 18, 1991 -- although the agency published deviations from the Common Rule for purposes of meeting its statutory mandate to regulate health-related products.¹⁵ While the regulations presumed that clinical investigators were affiliated with medical institutions that had an IRB, the FDA recognized that there may be circumstances for which there was no IRB available and that contracting with an IRB might be possible.

"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 IRBs. 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 the regulations or by submitting the research proposal to an IRE 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 or an IRB created by the sponsor."

46 Fed. Reg- 8962 (Jan. 27, 1981). *Preamble comment #17*

C. The Changing World of Medical Research

When *Dr. Stewart* issued his policy statement in 1966, research was conducted typically by a single investigator working in an academic medical center on a federally-funded project, with a small number of human subjects. Most exceptions to single site studies were federally funded cancer studies carried out by groups such as the Eastern Oncology Group or the Pediatric Oncology Group which conducted multi-center studies centered in academic centers. The world of research was poised for change. Several events transformed the face of research in the United States.

First, Medicare's introduction of Disease Related Groups ("DRGs") as a basis for reimbursement led to a decreasing number of hospital admissions, shortened hospital stays, and a resulting lower hospital census. This led to a corresponding increased need for delivery of ambulatory care axed, thus for research in that setting.

Second, federal legislation imposed the requirement that sponsors provide evidence that their pharmaceutical products were "effective" - evidence that would be provided primarily through human research studies.¹⁶ The number of human subjects needed to show efficacy grew quickly. Large multi-center trials became more standard. This led to discontent with the inconsistency associated with review of one protocol by many IRBs under the decentralized IRB system.

A third change was environmental. Specialty equipment and medical and scientific expertise could increasingly be found in community settings. Lab tests could be performed quickly and efficiently in-house. Magnetic resonance imaging ("MRI") and other diagnostic tests became available at for-profit diagnostic centers. Other business tools such as courier services, fax and modem transmission, and affordable computers, allowed the placement of research studies in smaller, less costly, more responsive community medical centers.

Fourth, academic institutions oriented to research covered by government grants were often not attuned to the needs of the pharmaceutical industry for timely and validated study data. Some institutions were more intrigued with basic research than in conducting the directed work necessary to support a drug sponsor's protocol. Pharmaceutical sponsors, wishing to achieve speedy reviews of proposed studies and uniformity among many study sites, often perceived the academic community as impractical in producing data.

Gradually, more pharmaceutical studies were placed in secondary care hospitals and, eventually, in private medical practices. It was no longer considered mandatory, or even wise, to test a pain reliever, a metered-dose inhaler, or a vaccine in expensive, large academic medical centers -- especially if the eventual users would be treated in ambulatory settings.

In 1991, with most federal agencies adopting the Common Rule, the Food and Drug Administration ("FDA") adopted similar regulations under Title 21 CFR, Parts 50 and 56 to provide protections for human subjects participating in commercially funded research. Although FDA adopted most of the Common Rule's research review requirements, FDA also crafted carefully designed provisions that deviated from the Common Rule. These deviations from the Common Rule created regulations that would better fit FDA's mission to protect the public health in reviewing and approving new pharmaceuticals, medical devices, and related technologies. The deviations accommodated diverse medical settings, regulated through control of the product rather than study funding, and were particularly suited to research intended to support product marketing applications.

With all of these changes, new means of addressing research review requirements were necessary. Investigators who were asked to conduct studies in community settings found little infrastructure available. Services available in an academic environment were non-existent outside of that environment. There was no investigator training, little information on accounting

or budgeting issues, little available liability insurance, and few trained coordinators. There were few resources sufficient to create or manage an internal IRB. Moreover, institutionally-based IRBs generally were unwilling or unable to review clinical studies outside of their particular institution. The chronic problem of under resourced IRBs combined with liability concerns led to "courtesy" reviews being offered only rarely by institutional boards to community centered studies.

As previously stated, the FDA acknowledged this problem in 1981 when it promulgated regulations on the protection of human subjects in research. It anticipated that medical societies and medical boards would step forward to create regional boards but acknowledged that other solutions were possible.¹⁷ In reaction to the changes in the medical research environment, the community of independent IRBs was born.

III. The Development of Independent IRBs

Between the late sixties and today, many independent IRBs were established¹⁸ to meet the needs of the changing research environment. They developed in response to different environments. They served a broad range of needs, from the review of food ingredient proposals, to psychological studies, to physiological and surgical protocols. Each was unique.

Although no accurate count is currently possible due to differing definitions and the lack of any central counting method for IRBs, a list of some independent IRBs that review FDA regulated studies is attached. (Appendix A).

The FDA's recognition that IRBs need not be located in an institutional setting created the first gateway for the use of Independent IRBs. Thus, between 1981 and 1995, independent IRBs primarily were used to review FDA-regulated clinical studies in small clinics, community hospitals and private practices.

Today, Independent IRBs are responsible for review of a wide variety of studies conducted in a wide variety of settings.

For many reasons, including the increase in regulatory requirements for pre-market clinical testing and the market "exclusivity" granted to drug sponsors for such tests, the number of research studies funded both by public and private sources has increased dramatically.¹⁹ As a result, multi-site studies involving thousands of human subjects have become much more common. Because independent IRBs are not limited in their review to a single site, they have proven their value in the area of multi-center or national trials.

The greatest need for independent IRB review remains outside the academic and hospital setting. However, some hospitals that conduct little research and are too small to support their own IRB

Founding Dates
1988 Western IRS
1981 St. David's
1983 Biomed
1983 Schulman Associates IRB
1984 <i>IRC Independent Review Consulting</i>
1985 Essex IRB
1985 RCRC
1986 Ethical Review Board
1999 New England
1991 Quorum.
1993 Chesapeake
1996 Copernicus
1999 IntegReview
2000 Goodwyn.com

engage the services of Independent IRBs. Additionally, Independent IRBs are now serving as IRBs for some institutions where the IRBs connected with the institutions have chosen not to review some or all the research conducted at their institution. Further, Independent IRBs also provide their review services to investigators performing research not subject to federal regulation. While not federally-regulated, such research may be funded or conducted by foundations or private institutions that require IRB review.

OPRR (now OHRP), was the federal entity responsible for regulating the conduct of research funded by the Department of Health and Human Services, ("HHS") and for signing assurance agreements. For a long time the OPRR did not sign any assurances for institutions that wished to contract with independent IRBs as review bodies for HHS-funded research. However, in 1995 the OPRR began accepting Single Project Assurances ("SPAs") for projects that involved review by "a separate institution with an IRB."²⁰ The OPRR's acceptance of independent IRB reviews was based on the IRB's commitment to stay well-informed about local sites and community opinions and to comply with all applicable OPRR requirements.²¹ Many Independent IRBs now review projects subject to SPAs - often for small companies or companies with little research experience that are seeking Small Business Innovation Research ("SBIR") grants.

An organization of independent IRBs was formed in 1993 to provide a central discussion area concerning public policies and issues. The Consortium of Independent IRBs (CIRB) recently was incorporated as a non-profit corporation and has its headquarters in Washington D.C. One of their first actions was adoption of a Code of Ethics. For its members, the code makes clear that the major priority of the independent IRB is the protection of the research subject. (Appendix B)

IV The Mechanics of Operating an Independent IRB

Many questions have been raised about how Independent IRBs work, how members are recruited, clients found, and money handled. Whatever is said must be applied to the majority - but never to all - independent IRBs. There is no single model

Separation of Business and Review:

In any business there are departments or units to accomplish different tasks. Human resources, marketing, legal affairs, insurance, finance and accounting are essential to a business but are not central to the product being generated be they legal opinions, medical care, IRB reviews, computer chips, widgets, or aircraft.

Most institutions, independent or not, make an effort to shield the IRB from the business of the institution. Few academic IRB members know the amount of the grant budget requested²². Few Independent IRB members know the business relationship between the business and the client.

The majority of institutions with Independent IRBs maintain a distinct separation between the operation of running the business and the administration of an independent committee capable of rendering professional decisions. Members convene and render decisions, and, then, return to

their external lives and to prepare for the next meeting. Meanwhile, administrative employees translate those decisions for applicants, prepare the IRB correspondence, write the minutes, make sure that the files are filed, and the bills paid.

Recruitment of IRB Members:

Many academic institutions are able to assign faculty to the IRB and to define it as a part of their duties as professional staff. They also reach out to their community in order to obtain members unaffiliated with the institution or whose interests are not in the sciences. Appointments are often made at the CEO or Vice President level.

Recruitment of members for an independent IRB is usually from a broader pool. Some of the best members of independent IRBs are retired professionals who have the expertise, time and dedication to serve. Members may be from the same town as the IRB or may live elsewhere in the country. This allows independents to choose the best qualified members. Appointments are made according to the policies and procedures of the organization.

One hallmark of a typical independent IRB is that most members will have no other affiliation with the institution. Members are generally independent contractors.

Retention of IRB members:

Institutional IRBs work diligently to keep members interested, involved and attending. Some provide parking or meals while others provide educational opportunity. Release time is occasionally provided usually to the chair.

Independent IRBs generally pay their members. The amount and schedule of payment to members differs with each entity. Some payment schedules are on a flat fee basis with a different amount paid for initial, continuing, review, modifications or specialty reviews such as of adverse events or investigator's brochures. Others pay a flat fee per meeting. Some pay members for the amount of work reviewed. Some pay all members on an equal basis while others pay physicians more. The payment is never contingent on the decision of the member to approve or disapprove.

Most members of Independent IRBs find the fascinating variety of studies and the problems presented intellectually stimulating and enjoy being involved in questions that are presented in the daily news.

Setting and Collection of Fees:

The fees collected for study review must be sufficient to cover the costs of running the business. These costs include, but are not limited to, salaries and benefits to principals, staff, fees to members, overhead (copiers, lights, janitorial, phones, computers, computer service experts, etc), insurance (professional liability, workers compensation), marketing (trade shows, advertising), travel (lectures, site audits), education (of staff, members and investigators) and, of course, taxes.

Fees can be set to encourage submission of multi-site or single site studies. They can be flat fees (better for longer studies) or fees per action.

Liability concerns:

Actuaries have found it difficult to determine the potential liability faced by the company supporting an independent IRB. Initially there was no liability insurance available. Currently there are several brokers who have found companies willing to write liability insurance. Institutions with independent IRBs must also protect the members through indemnification agreements and insurance.

Professional reputation²³ concerns

The reputations of IRB are known to and shared among sponsors. Some IRBs are known to question everything or nothing, to meet frequently or rarely, to be distant and unapproachable or open and communicative. Independent IRB stress quality and professionalism as well as timeliness and pricing in their marketing; their reputations for meeting these claims are known to and shared among sponsors.

Effect of warning letters/closures

One protection against inadequate IRB review for all IRBs is the reality of federal oversight by the FDA and OHRP compliance programs. It has been amply demonstrated that an IRB can be closed by OPRR or by FDA and that it can be days or months before reinstatement.

The effect of IRB closure on the supporting institution is considerable. Since the user community is relatively small, and since FDA warning letters are published on their web site, adverse decisions or actions such as a warning letter about an IRB can become quickly known.

Although the institution receiving a warning letter may suffer damage, it can recoup and reenter the research world often relatively unscathed. Re-entry is more difficult when the applicant has the ability to select an IRB that has not been cited for future reviews.

Diversity of services

As with academic IRBs, most Independent IRBs can review studies from a variety of disciplines. In order to distinguish its IRB from other independent IRBs, most companies supporting independent IRBs offer specialty areas. One IRB offers quality assurance monitoring, one is known for education, one specializes in review of studies with vulnerable populations and another specializes in review of medical devices.

V. Strengths of the Independent IRB

Because the independent IRB emerged as a result of the changing research environment described earlier in this paper, its development closely matches the needs created by that change.

While the benefits of independent IRBs continue to emerge with a still-changing environment, several benefits are apparent.

A. Independent IRBs Provide Review for Studies at Sites Without an Internal IRB.

Small organizations (e.g., private practice corporations, small clinics, and research centers) conducting research often have several choices for IRB review: they may form an institutional IRB, use the services of a neighboring (perhaps competing) IRB, or contract for IRB services.

Forming an internal IRB in this environment is frequently inappropriate. Few members of small organizations are versed in the regulations, issues and ethical requirements. There may be too few employees to provide appropriate IRB member diversity. There may be too little research to gain experience with IRB review. The time and cost associated with establishing an in-house IRB, if done moderately well, can be prohibitive in smaller research settings. In small organizations, there is also a substantial conflict of interest as all salaries are dependent upon approval and, frequently, many employees are also equity holders. Although some institutionally-based IRBs provide review for studies conducted outside their institutions, most do not.

Thus, the evolution of research with IRB review into the ambulatory setting probably could not have occurred without the emergence of independent IRBs to fill the void. To this day, the primary focus of Independent IRBs remains sites without other sources for IRB review.

B. Independent IRBs are Structured to Provide Efficient Reviews

Development of new drug and device products is costly and time consuming. Yet, patent laws restrict the period of time during which the proprietary company can prevent the entrance of generic copies of new drugs into the market. This time can be whittled away during the research and development phase. Thus, commercial study sponsors always seek means to reduce the research and development time. While these commercial sponsors expect less to perform research reviews properly, they also expect that such reviews will be performed quickly and efficiently.

Independent IRBs are geared to meet these multiple needs because they have IRB members who understand the need to meet, to discuss and decide on research proposals. Most independent IRBs meet weekly, some meet even more often. As a result, independent IRBs can often provide research sponsors with a decision quickly -- sometimes in a matter of days. In contrast, because most academic medical center IRBs are volunteer-based and meet on a less regular schedule, their review may take much longer.

C. Institutional Independence Supports Objective Reviews

IRB board members connected with the institution for which they provide review are subject to the influences associated with such connections. Specifically, they often have a collegial relationship with the investigators for whom they provide review, or they may share office space

with the institutional arm that obtains grants and contracts. They may also be concerned about the financial, well being and prestige of the institution that employs them factors that are often driven directly by research-related revenues. Further, they may develop specific viewpoints because they are limited to working within the institution. These factors could result in biases that affect an IRB member's decision whether to approve or disapprove a study. It can also affect the vigilance with which the IRB conducts continuing review.

Because independent IRBs are not connected with the organizations for which they provide review, they can avoid such influences. The avoidance of such influences, in turn, may lead to greater objectivity in review.²⁴

D. Independent IRBs Provide Consistency of Review in Multi-Site Studies

Because independent IRBs are not limited in their review to a single site, they are uniquely suited to review and oversee multi-center or national trials. A unified review eliminates the problems (e.g., conflict of modification requirements, uniformity of advertising methods, central knowledge of adverse events) associated with multiple IRB review of a single sponsor's research plan. A further advantage of an independent IRB reviewing a multi-center or national trial is that it can develop a better understanding of the overall safety profile of the drug, device, or biologic involved, since it receives a broad spectrum of serious adverse event reports and other medical data from multiple sites. Such a diverse information base may not be available to single-site IRBs.

E. Independent IRBs Provide Review for Unregulated research.

As an indication of the acceptance of IRB review as an ethical imperative, researchers who have graduated in the last two decades and have moved into positions of responsibility, assume that their research should be IRB reviewed. This is supported by peer reviewed journal requirements. Independent IRBs report an increasing number of requests for voluntary review of social and behavioral research that is not otherwise regulated by the federal government.

F. Independent IRBs allow institutional IRBs "breathing room"

Research review demands are increasing both within and without the hospital setting. Recently, independent IRBs have demonstrated their ability to provide "support" to over-burdened institution-based IRBs. Independent IRBs are now assisting a number of institution-based IRBs in meeting their increasing demands by conducting initial and continuing review of a percentage of the institution's research plans. It is reported that in at least one instance, this was an OPRR-recommended resource.

G. Independent IRBs provide a bridge between the worlds of the IRB and Industry

Although communication and mutual recognition of basic principles of research is beneficial, there is little communication between those proposing studies and those reviewing them. It is unusual for members of either profession to communicate with the other.

The independent IRB often provides a bridge to understanding. Most IRB speakers at industry events are from independent IRBs. Invitations to IRB events made to industry are often extended by independent IRBs. Better understanding among all the parties to research can help avoid errors from miscommunication.

V. Perceived Disadvantages

Independent IRBs are not traditional and have been criticized on several fronts. It has been suggested that independent IRBs have several disadvantages that are inherent in their structure.

- Concerns have been raised about the Independent IRBs' ability to meet their responsibilities as they pertain to local issues and attitudes.
- The fact that Independent IRBs are paid for their services by parties seeking research plan approval has been identified as a potential conflict of interest.
- Because the relationship between the independent IRB and the investigator is voluntary, the concern of "IRB shopping" has been raised.

While independent IRBs must be diligent in assuring that these perceived weaknesses do not become a reality, they all can be addressed through proper organizational structure and/or implementation of standard operating procedures.

A. *Internal Procedures Can Ensure that IRBs Identify and Consider Local Issues and Attitudes*

When the IRB structure was developed, it was recognized that "local" IRB review was important for the proper protection of human subjects. Clearly, independent IRBs must meet their regulatory responsibilities to be sensitive to local issues and attitudes. However, in our current "global village," the term "local" has evolved. It no longer means that an IRB's physical presence in the community is necessary to meet this requirement.

Independent IRBs have developed novel and effective approaches for assuring accurate and up-to-date knowledge of local issues and attitudes. Site-specific questionnaires are employed by many independent IRBs. Regular site telephone contact and written reports are also useful. The internet and other technological advances now allow for almost instantaneous flow of information between communities. Site visits, if necessary, can be arranged. At least one independent IRB employs "local consultants," while another has a contract with a professional monitoring group employing local monitors.

Non-local IRBs realize that local issues are often, in fact, national issues. Information and issues often transcend small communities.

The FDA has recognized local review alternatives in its Non-Local IRB Review Information Sheet.²⁵ The OPRR and the FDA have facilitated participation of an individual IRB member or

consultant from the local community by sanctioning IRB meetings by teleconference or other technologies that allow real-time interaction. With OPRR's recent issuance of a policy statement that allows IRBs to conduct meetings by phone, IRBs conducting federally-funded research now have the capability of appointing an IRB member who lives in the local community.²⁶

Although it is important to maintain a system that addresses local attitudes and concerns, when multi-center trials are involved, the local community is provided enhanced protections. With a central perspective, the central IRB has the ability to work with a number of sites involved in a particular study. Knowledge gained at one or more sites (e.g., serious adverse event reports) can be applied to all sites.

B. Conflict of Interest Associated with the Fee for Service Can Be Addressed Through Organizational Structure

Another frequently cited concern is that independent, for-profit, IRBs might compromise the review process in order to advance the financial well-being of the firm. It has been alleged that such independent IRBs are paid to "approve" studies. On the other hand, those in the community of Independent IRBs consider their reviews provided to be equally - or more - stringent than the institutional boards.²⁷

To view this concern in the proper light, it should first be understood that all IRBs are subject to the same regulations. Thus, independent IRBs have a responsibility to ensure that each and every research plan meets the ethical, legal, federal or state requirements for protecting human subjects.

Putting aside the Independent IRB's legal responsibilities to safeguard the rights and welfare of human subjects, the concern over profit motives is addressed through organizational structure and internal policies.

First, fees are based on the review function itself, and not on the review outcome. Most IRB fee schedules set fees for different aspects of the review process (initial review, continuing review, modifications, etc.). The fee is the same regardless of the review outcome.

Second, most Independent IRBs are structured so that administrative and review functions remain separate. IRB members are not involved in the business end of the IRB. For example, management policies are implemented to ensure that IRB members are not privy to financial information regarding the company.

Finally, many independent IRBs ensure that the IRB membership contains very few, if any members who are part of the IRB's management structure or have an equity interest. Although the regulations require at least one external member, most independent IRBs have only one internal member.

Of course, conflict of interest is not unique to the Independent IRB. Many institution-based IRBs are subject to similar economic pressures to approve research contracts. In recent years many university IRBs have instituted fees for their service. Some of these fees are equivalent to the fees

of independent IRBs although their overhead costs are often much less. In addition, in an institution there are a number of interests including departmental conflicts, need to publish, power struggles, and the importance of very large grants that could affect votes of individual members or the pressures placed on the IRB. Conflicts of interest come dressed in many costumes only one of which is green.

C. IRB "Shopping" can be addressed through Regulations and Due Diligence to Assure that IRBs have Knowledge of Previous IRB Reviews

The concern regarding "IRB shopping" has also been raised as a problem associated with independent IRBs. The specific concern is that if a research plan is questioned or rejected by one IRB, the investigator may contract with another IRB without informing it about the prior board's determination.

Many independent IRBs support the implementation of an effort (ranging from concerted but voluntary IRB requirements or federal regulations) that would require study sponsors and investigators to inform IRBs about any prior review of the study plan, along with the findings, if known, of the prior review. Such a provision would largely eliminate the concerns associated with IRB shopping.

However, in the absence of such regulation, many independent IRBs already have procedures or policies in place to determine if a particular research plan has been previously reviewed by another IRB. These policies may involve direct questions to the research site or, where necessary, discussions with an IRB assumed to have primary jurisdiction over review of the particular study. For example, if an investigator is associated with a particular institution that has an in-house IRB, the independent IRB will question why the in-house IRB was not utilized. This question would be presented to both the investigator and the in-house IRB. These due diligence inquiries go a long way toward addressing the concerns related to "IRB shopping."

VI. The Future

What does the future hold for independent IRBs? The Independent IRB will always have as its primary goal the protection of human subjects involved in research. The future will require Independent IRBs to continually review the means of meeting that goal.

The IRB System will certainly change. Some changes are already occurring and others many suggested by the NBAC -- will be the, subject of future discussion. While federal action to improve IRBs and human research protection is effective in warning the research community of what is expected by the regulatory authorities, it may be that the rules and issues are changing more rapidly than they can be learned

- *Registration of IRBs.* It is believed that IRB registration requirements will soon be implemented providing government regulators with the ability to register IRBs and to exert more oversight. Most Independent IRBs welcome such registration requirements as they

provide another opportunity for "information sharing" among IRBs, and thus enhanced human subject protections.

- *Investigator certification.* It is also expected that some form of investigator certification will become a reality. Such certification will benefit Independent IRBs.
- *Accreditation.* IRB (or human subject protection program) accreditation seems likely within the next few years. Many Independent IRBs already seek external audits²⁸ and participate in federal and IRB-sponsored education programs. It is expected that many Independent IRBs will seek accreditation.
- *Assurances.* Change is expected in the assurance press. With the creation of the newly constituted Office of Human Research Protection (OHRP), how it will change remains unknown.

Methods of IRB Operations

As fast as the worlds of medicine, patient reimbursement, clinical research and industry are changing, IRB operations will also change

- *Models.* Independent IRBs are a valuable part of the research community, and it is believed that, as institutions increasingly participate in multi-site studies, Independent IRB policies and structure will be used as models.
- *Alliances.* Several new clinical research units have been formed to better cross institutional barriers. An example is university consortiums.²⁹ Cross alliances throughout the research world will allow better use of resources. Independent IRBs are already active in new alliances and this will certainly continue.
- *Cyberworld* The cyberworld will, allow cross-connections and information flow unimaginable today. Several independent IRBs are already working in these areas.

Independent IRBs will continue to fill areas of need created by new technologies, new populations and new demands

- *Reaching into non regulated areas.* The Information Age has benefited society with resources never before so readily available. The ability to conduct studies in new areas such as on the internet, and by new investigators without academic affiliation or training can open areas of research -- and research risks -- not encountered before. Much of this research is outside institutional settings. The Independent IRB is uniquely positioned to review these studies. Without the Independent IRB, the alternative would be further workload for institutional IRBs.
- *Reaching into underserved areas.* The federal mandate for pediatric safety and efficacy data on new drugs will benefit our children, but clinical studies involving children are sure to

increase with many new sites in private practice settings. Enhanced diligence will be necessary to ensure that the vulnerable population intended to benefit from this legislation is not harmed. Independent IRBs can help meet this need.

- *Serving population studies.* Registries, Phase IV studies, pedigree studies and large epidemiological studies are very feasible with computer tracking. However, recruitment from many investigators requires review of many investigators. Independent IRBs are ideally suited for review of large-simple studies.

To handle the ever-changing research environment, independent IRBs are well suited to adjust, diversify, and meet the needs of the investigators, sponsors, research institutions, and government regulators, *while maintaining the protection of human subjects as their focus.*

Independent IRBs will continue to respond to the legitimate needs of human subjects and the ever-changing research community. The future will find Independent IRBs playing a critical role -- as members of the larger community of IRBs -- in the protection of human subjects of a wide-range of research.

VI. A Personal Evaluation

In its request for this paper, I was asked to include a personal reflection. As a participant in this world from almost its inception, I have been associated with a large academic IRB, an independent IRB and several community hospital IRBs. Making the adjustment from the academic IRB world to the independent IRB world necessitated learning new methods for ethically reaching the same goal of protecting human subjects. In each instance, the IRB has been a source of personal pride and of growth.

As in most facets of life, there is a continuum with a normal distribution. Most studies of IRBs have demonstrated, there is an inevitable distribution of practices and quality. There are excellent IRBs and poor IRBs among all families of IRBs: academic, hospital, college, industry, government, independent and others.

I have occasionally pondered - and there is no evidence to prove or disprove - whether the median quality independent IRB is somewhat better than the median quality institutional IRB. The program closures in academic centers in the past several years demonstrate that institutions will certainly lose money, time, contracts, and reputation. But in each case the institution has been able to eventually rebound and improve. Most of us involved with independent IRBs innately understand that if the IRB were found to be equally deficient, liability insurance premiums would soar, prestige would plummet, the client base would disappear and the business would be dead. This is a very large incentive to maintain quality.

Change has been a hallmark of the protection of human subjects. Every few decades the thinking about ethics has evolved. Nuremberg, Helsinki, Belmont, ICH and Helsinki again. Every decade or so the regulations have changed. There have always been new

issues: extension of clinical rules to broader social sciences, using computers to enhance IRB operations, working with regulations from different organizations, debating waiver of IRB or consent, or privacy needs, genetics issues, fighting off inappropriate changes to the IRB job and bureaucracy. Personally, about the time that boredom hit or I became fed up with fighting the same fights, new issues have emerged to engage me or to allow me to develop new skills.

Although the world of research continues to present new challenges, the pace of change seems to have quickened. Communication now spreads ideas, news, dangers, and gossip more quickly than our capacity to verify the information, challenge it or to change or ideas or procedures to meet it

There are currently new issues, new risks, new sites, new organizations to direct us and reinterpret the bureaucracy again, new requirements and new kinds of research. Each of these presents challenges to those of us whose focus is the human subject. Offering innovative channels for building protection of human subjects must happen if the needs of our current century are to be met.

APPENDIX A

List of Independent IRBs Gathered from Various sources

		ARENA Member *	HIMA NET	CIRB Member
Allendale Investigational Review Board	NJ		X	
Argots IRB	AZ		X	
Biomed IRB	CA	X	X	X
Chesapeake Research Review, Inc.	MD	X	X	X
CHSD	CA	X	X	
Clinical R&D Services IRB	NJ		X	
Copernicus Group IRB	NC	X	X	X
Essex Institutional Review Board, Inc	NJ	X	X	X
Ethical Review Committee	MO	X	X	X
Goodwyn IRB	OH	X	X	X
Independent Investigational Review Board	FL		X	
IntegReview	TX	X	X	X
Internet IRB	FL		X	
IRB Services (Canada)	ONT		X	
IRC Independent Review Consulting, Inc.	CA	X	X	X
New England IRB	MA	X	X	X
Quorum IRB	WA	X	X	X
Reliable IRB	CA	X		X
Research Consultants Review Committee	TX	X	X	X
Schulman Associates IRB, Inc;	OH	X	X	X
Southwest Independent IRB	TX		X	
St. David's Human Research Review Board	PA	X	X	X
Sterling IRB		X		
Triad IRB	IL		X	
Western Institutional Review Board	WA	X	X	X
Wyle Laboratories IRB	TX		X	

ARENA: Applied Research Ethics National Association is a membership organization. This column is marked if the CIRB representative or a known principle of the company is an ARENA member.

APPENDIX B

Code of Ethics

The Consortium of Independent Review Boards

Each member IRB of the Consortium of Independent Review Boards (CIRB) pledges to follow the articles of the CIRB Code of Ethics, as contained in this document.

1. The primary mission of CIRB members is to protect the interests, rights and welfare of human subjects in IRB reviewed studies.
2. CIRB members will be guided by the fundamental principles of research ethics put forth in the Belmont Report (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979) - Respect for Persons, Justice and Beneficence.
3. CIRB members will adhere to the letter and the spirit of laws and regulations requiring the protection of human subjects.
4. CIRB members will protect against conflicts of interest.
5. CIRB members will develop and follow a plan for its training IRB members.
6. CIRB members will protect the confidentiality of subject information and sponsor proprietary information to the extent allowed by law.
7. CIRB members will promote ethical recruitment practices for clinical research subjects.

Concerns *regarding* ethics violations shall be *communicated in writing* to CIRB's Executive Committee, and if appropriate, to CIRB's legal counsel for review and recommendations.

¹ See 21 CFR Part 56.107 or 45 CFR 46.107

² Title 45 CFR 46.102(c) and 21 CFR 56.102(f). As used in this part... Institution means any public or private entity or agency (including federal, state, or other agencies).

³ Heath, Erica, "The Noninstitutional Review Board: What Distinguishes Us from Them" IRB: A Review of Human Subjects Research, Vol 20, #8, Sept-Oct 1998

⁴ Katz, Jay, Alexander Capron, and Glass "Experimentation with Human Beings, Russell Sage Press, 1973, pp 9-65

⁵ Id. pp 1007-1010

⁶ Beecher, Henry, "NEJM".

⁷ Katz document at p855

⁸ Institutional Guide to DHEW Policy on Protection of Human Subjects, DHEW (NH 72-102) Dec. 1, 1971.

⁹ Although many new boards took the name IRB, many other boards became known by other names such as the Committee on Human Research (CHR), The Human Experimentation Committee (HEX), the Committee on Protection of Human Subjects (CPHS), etc. This has led to some confusion when investigators are asked if there is an "IRB" at their institution.

¹⁰ 43 Fed Reg 56174 (Nov 30, 1978).

¹¹ Although 45 CFR 46 is referred to as "The Common Rule" each signatory agency that adopted the same rule uses "The Common Rule" with its published distinctions. Thus, FDA's regulatory variant without reference to an assurance and split into two sections as 21 CFR 50 and 21 CFR 56, remains one version of "The Common Rule."

¹² 43 Fed Reg at 56177.

¹³ FD&C Section 505(1)(4) 1962 PL 87-781 10/10/62

¹⁴ 21 CFR 312(a)(2) 10C; FDA Compliance Program Guidance Manual March 15, 1977

¹⁵ 56 Fed Reg 28025, June 18, 1991.

¹⁶ FDCA Efficacy 505(b)(1)(A).

¹⁷ 46 Fed Reg. 8962 (Jan 27, 1981) Preamble comment #17.

¹⁸ Internet at www.himant.com, businesses supporting research: Independent IRBs.

¹⁹ “Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research, Office of the Inspector General.

²⁰ “Institutional Review Boards: The Emergence of Independent IRBs,” Report of the Office of the Inspector General, Department of Health and Human Services, June 1998.

²¹ Id

²² Whether this separation of money and review will continue if IRB members are asked to evaluate the effect of budgets on recruitment is an interesting question.

²³ During the writing of this sentence, my teen walked in with a food treat saying, “You want a bite of this. Its from (brand name) so you know its healthy and good.” What more can be said for the value of one’s reputation.

²⁴ Id

²⁵ Non-Local IRB Review, Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators, Food and Drug Administration (1998 update).

²⁶ See Memorandum from J. Thomas Puglisi, Director of the Division of Human Subject Protections, OPRR (March 28, 2000)

²⁷ A complaint frequently heard is that “77 other IRBs have approved this, why can’t you?” In most cases the 77 other IRBs are academic or hospital based.

²⁸ An informal survey of independent IRBs showed that most had experienced at least one external audit from a non governmental compliance auditor.

²⁹ Kowalczuk, Liz, “Medical schools join forces: Harvard, others aim to give drug firms faster OK’s on clinical trials” The Boston Globe, 7/2/00