Protecting Subjects: The IRBs Role Today
The Congressional Hearing that Led to the Questioning of IRBs is Past. Now Sponsors/CROs, IRBs, and Sites Can Learn from History

Safeguards Applied to Research

Applied Clinical Trials’ Editors

In early March, reports regarding the “sting" operation which involved Coast IRB began streaming in. On March 26, 2009, the hearings on the results of the investigation of for-profit Institutional Review Boards (IRBs) by the Congressional Subcommittee on Oversight and Investigations were heard.

Under direction of the House of Representatives Committee on Energy and Commerce (Rep. Bart Stupak, D-MI, and Rep. Henry A. Waxman, D-CA, and Chairman of the Committee), the Government Accountability Office (GAO) conducted an undercover investigation of the for-profit IRB review process. It based its decision on previous for-profit IRB warnings, as well as an increase in revenues over the past several years, which caused concern that IRBs could be “rubber stamping experimental research protocols in order to collect fees.”

During the hearing, Rep. Stupak stated that the GAO submitted a “fictitious study, led by a fictitious doctor, and submitted by a fictitious company.” This false medical device study and its accompanying protocol were submitted to three IRBs—all of them “for-profit” or commercial IRBs—not affiliated with a larger academic research institution. One, Coast, approved the study. The two other unnamed IRBs did not. During its investigation, the GAO also took to task the Department of Health and Human Services by registering a fictitious IRB, and getting proposed work through this falsified IRBs’ Web site.

The immediate outcome of this investigation was that Coast IRB made the decision to close its business, with other IRBs stepping in to help vet out the studies, since none of the studies that were under Coast’s oversight were deemed cause for closure.

Next Steps

When violations in human subject protection are assumed, there is outrage. Many within the industry questioned Coast’s approval of the fictitious study as the events unfolded. Others felt that Congress basically engaged in a witch hunt and abuse of taxpayers money. Others questioned why sponsors would continue to use an IRB that had citations and a warning letter already in its file. However, the long-term implications from the Congressional setup are not as cut-and-dry.

We have little insight into how events like the Congressional investigation of Coast actually impact the public’s perception of clinical trials and drug research. We have very little working knowledge on the best way to oversee human subject protections moving forward. We do know there already is a high level of mistrust of pharmaceutical companies, as well as the FDA, by the general public in regard to patient safety.

Protecting Subjects: The IRBs Role Today is intended to take the Congressional events, the current political climate, and the processes necessary to ensure subject protection one step further. The following articles apply clarity to a situation and a part of the industry, which to quote one author, “is cloaked in mystery.”

Many in the clinical trials industry have a working knowledge of what an IRB does, and the following articles assume
that kind of basic understanding. These articles also explore better relationships between all stakeholders in the clinical trial industry in regard to the IRB process; suggestions for IRBs to examine their own processes; as well as suggestions for sponsors who are looking at their IRBs and the ethics of human subject protection in research with new eyes.

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What Should Sponsors Ask Their IRB?

Cami Gearhart

Is there anything a sponsor can do to prevent the chaos and cost of a shutdown of its ethics board? By asking a few key questions, a sponsor should be able to minimize the risk of a suspended study and the cost of a re-review. Many independent and institutionally-based ethics boards provide excellent and reliable services. A sponsor can identify a reliable board by asking questions about the board’s documented processes, accreditation status, quality systems, and resources to handle the proposed project.

These questions can be asked of both independent review boards and institutionally-based review boards. The term “independent” review board describes a freestanding organization that focuses on providing ethics review services. An institutionally-based review board (also called a “local” review board) is often a committee or department of the university, hospital or research organization that will be doing the research. Through a quirk in the federal regulations, all of these types of ethics review boards are called “institutional review boards” (IRBs) in the United States.

What should a sponsor look for?

First, it is important for the IRB to have written procedures. The FDA has published a checklist of processes that an IRB should document (see http://www.fda.gov/oc/ohrt/irbs/irbchecklist.html). If the sponsor has the resources to conduct a pre-qualification audit, the FDA checklist provides a road map for the processes and documentation to review. Even if the sponsor is not able to visit the IRB on-site, most IRBs will provide a table of contents of their processes upon request to allow the sponsor to obtain an overview of the IRB’s written processes.

The sponsor also should insist on accreditation of the IRB. Earlier this year, Pfizer became the first pharmaceutical company to state publicly that it would use only accredited IRBs for its clinical research. Other major sponsors may soon follow suit. Many major universities, institutions, and independent IRBs are accredited. A number of accredited ethics review board organizations are available in Canada.

Why is accreditation important?

Through accreditation, an independent third party verifies that an organization has an adequate set of written processes and follows those processes. Until 2005 there were two accrediting organizations, but since 2005 there has been only one: the Association for the Accreditation of Human Research Protection Programs (AAHRPP).

AAHRPP maintains a number of categories of accreditation, such as full accreditation, qualified accreditation, and probation. The accreditation status of an IRB can be confirmed on the AAHRPP Web site at www.aahrpp.org. Accreditation is a rigorous process that includes a review of written procedures, a review of IRB member abilities and training, and interviews of sponsors, staff, board members, and investigators. A sponsor that chooses an accredited IRB knows that the IRB has built extensive safeguards.
into its operations and adheres to the highest standards for research.

**Is there any regulatory action against the IRB?**

Another important question to ask is whether a government agency has taken regulatory action against the IRB. A sponsor should ask an IRB for all documentation of all of its FDA audits. This documentation might include inspectional observations as reported on a FDA Form 483 or, of greater significance, warning letters (which are issued for violations of regulatory significance). A sponsor also can confirm whether an IRB has received a warning letter by searching under the FDA’s Web site at http://www.fda.gov/foi/warning.htm.

The other government agency most involved in IRB oversight is the DHHS Office of Human Research Protections, or OHRP (see http://www.hhs.gov/ohrp). OHRP has jurisdiction over many federally funded studies and a sponsor should ask for documentation of any adverse regulatory action by OHRP.

**Does the IRB support the research community?**

A sponsor also might want to ask about the IRB’s participation in organizations that support the research community. Many independent IRBs, for example, belong to the Consortium of Independent Review Boards, or CIRB, a non-profit organization with a central mission of assuring the protection and rights of human research subjects, while promoting the integrity, high quality, and effectiveness of the independent IRB process (see http://www.consortiumofirb.org).

IRBs also are active in national organizations such as Public Responsibility in Medicine and Research, or PRIM&R (see http://www.primr.org), or in regional nonprofit organizations that belong to the States United for Biomedical Research (http://www.statesforbiomed.org).

**How many studies does the IRB handle annually?**

Sponsors should inquire into whether the IRB has the capacity to handle the proposed project within the desired time frame. Both independent and local IRBs can become overwhelmed by one large study or by the demands of multiple studies. A sponsor should ask how many studies and sites the IRB handles annually. The sponsor also should make sure the IRB’s timelines for reviewing the study and generating approval documents are consistent with the researchers’ expectations.

**Does the IRB have a quality system in place?**

Finally, a sponsor should ask whether the IRB has a quality system to help minimize error. The usual elements of a quality system include process change control, an employee training program, quality control checks on approval documents, a “CAPA” (corrective and preventive action) program, and an audit program. Don’t hesitate to ask the IRB for details on how it approaches any one of these elements.

This year’s events have left many members of the research community worried about the reliability of their ethics review boards. By asking a few key questions, however, sponsors should be able to identify those organizations that are capable of maintaining the integrity and quality of their ethics review processes.

In the IRB World, An Application of Flexibility and Learning to Live with Shades of Grey is Helpful

Common Sense and the Rules

Erica Heath

In the IRB World, An Application of Flexibility and Learning to Live with Shades of Grey is Helpful

Common Sense and the Rules

Erica Heath

RC’s tag line; dedicated to the protection of human subjects through application of laws, regulations, and common sense, can pose a challenge to live up to. After all, what to one person is a reasonable, common sense solution to a problem is, to another person, mission-creep, overkill, and indicative of a lack of understanding.

Why is common sense an issue? Rules are often considered to be either black or white, there can be little flexibility. IRBs, however, were created specifically to consider shades of grey. There are conflicts between science and rights and there are conflicts of mission. Without an underlying appreciation of resources, policies, and the uncommunicated choices and strategies of our partners, common sense can turn to Babel. Common sense helps reconcile multiple problems.

IRBs operate in a constrained regulatory world. There are the FDA’s IRB and consent regulations and numerous ancillary regulations, the Common Rule, state rules, and of course HIPAA. Each institution and site has its own rules and culture.

A self-imposed constraint comes from accreditation. AAHRPP (Association for Accreditation of Human Research Protection Programs) requires an integrated Protection Program with the IRB integrated into an institutional protection network. Where there is a functional program, the IRB is able to pursue its original purpose: review of proposed or continuing studies. AAHRPP recognizes the individuality of each institution and simply asks for an integrated program. This means that each IRB is unique, as is each sponsor and site. A central IRB such as IRC’s cannot become fully integrated into the programs of multiple sponsors and sites but must know to whom to report issues.

Introducing common sense is like swimming upstream into a bureaucracy serenaded by “we have always done it this way.” It is easy to go with the flow but, when we do, changes will never be made. At IRC we continuously seek to push the envelope on behalf of subjects to write sensible, readable, and understandable consent forms.

With rules seen as black or white, with each IRB, institution, sponsor, and site having different concepts, and all is chaos, how can common sense be introduced? If the following ideas are used in planning, presenting, and reviewing studies, perhaps some common sense will enter the process.

Live the Belmont Report. When the Belmont Report was written, doctors still sat on thrones and subjects rarely knew they were subjects. Belmont’s authors tempered “Beneficence” with “Respect for Persons,” thus requiring a balancing of science and subjects. Within IRBs and among sponsors and investigators, there are people who place a higher value on scientific inquiry and those who value the rights of subjects more highly. Frequently there is no right or wrong but simply a balancing of ethics and healthy inquiry.

Celebrate subjective rules. The regulations are very subjective: risks should be “reasonable” in relation to the “importance” of the knowledge that “may be expected”
to result, subject selection should be “equitable,” and informed consent should be “appropriately” documented. This gives remarkable interpretive leeway. The regulation writers in the 70s were well aware of this and it was intentional. They asked a diverse membership to use their judgment to work within this subjective framework in which absolute rules are inappropriate.

Use the rules flexibly. Is IRB approval required? Is the study FDA regulated? Are there human subjects? Can consent be waived? Assuming the answer and submitting an application to the IRB results in needing to comply with all aspects of the rules. Consider the need to obtain consent from anonymous donors. Consider the tone of recruitment materials used for a safety study of a marketed device. Knowing and using the rules correctly but flexibly can help avoid these conundrums.

Consider your mission and culture. Each party to research has a unique culture. A current example of conflict of mission is review of drug Safety Reports. IRBs have long considered these reviews to be onerous and without value. Industry has believed IRBs were required to review them for subject protection and rejection was seen as abdication of a duty. There are better alternatives being adopted that recognize both views. At IRC we seek to understand our clients’ mission and values.

Remember the subject. Subjects never read at a 5th or 8th grade level but at a range of levels. Some want to know every detail while others are satisfied with generalities. Within any given eligibility profile, some are more vulnerable than others. At IRC we seek a recruitment and consent process and form to match the circumstances. The more sensible the approach, the more subjects will benefit.

Share the rationale. When an IRB receives an investigators’ response to questions that says no alteration will be considered, it is nice to know who made that decision and why. Is it because, “the FDA demanded it,” or because it has already been reviewed by 50 IRBs; was there a safety issue or design demand that wasn’t appreciated fully; or did some intermediary just want to avoid making waves with their client? Reviewing a request is much easier when the recipient knows the reason for the request. No IRB should be asked to assume facts.

Avoid over-reaction. With each warning letter posted on FDA’s Web site, each 483, each guidance, and following most conferences, there are reactions. Questions are added to submission forms and checklists. Another paragraph goes on the template consent form. These changes never go away! Finding ways to remain compliant while avoiding reactive maneuvers involves creative thinking.

Communicate. No protocol stands alone; it is the end result of many hours of strategy with many people. IRB members have only a slice of a larger picture. Failing to paint the larger picture may derail an otherwise easy approval.

IRC, as a remote, central IRB, cannot occupy the room down the hall as an academic IRB might. By using our common sense and by communicating and brainstorming solutions with our clients, we seek to create a partnership.

Living in a completely black and white world would be easier, but we live in a world painted in shades of grey. Taking advantage of the inherent flexibility built into many of the rules, clarifying motivations, and creating clear communication will help us maintain the range of color that makes research so interesting and exciting.

A question was asked recently at an IRB Congressional hearing, “How many studies did you disapprove?” In the opinion of the Ethical Review Committee (ERC) an independent institutional review board (IRB), the question did not take aim at the real concern of potential IRB failure to protect the human participant in research. It is not the objective of the IRB to disapprove research. Our purpose is to help facilitate potentially valuable research in a manner that safeguards the human participant, promotes compliance with the FDA regulations, and takes into consideration the ethics and scientific design of the protocol.

The ERC views this objective with serious intention and attempts to achieve it through partner relationships and education rather than a “roadblock” mentality. At times a “cloak of mystery” seems to surround the IRB process. Even among experienced investigators and sponsors a lack of real understanding of what the IRB does and how determinations are made may exist. Asking questions of the IRB has been described as “asking your dad for the car keys as a teenager.” Most investigators in private research, as well as many of the staff representing the sponsors and contract research organizations (CROs), have never observed or participated in an IRB review meeting. They often do not understand the purpose for the information requested by the IRB committee or administrative staff.

In an alliance of partnership with the sponsor and investigator, the IRB can help accomplish the desired outcome of a higher level of compliance through education rather than from an enforcement perspective. This compliance helps protect the study participant’s safety and well-being. It also facilitates a more controlled research environment resulting in accurate data collection, which in turn supports the ultimate goal of a successfully conducted research project.

Noncompliance, or the failure to comply with the regulations, ranges in scale from inattention to details to intentional scientific misconduct. Serious noncompliance can result in the suspension or termination of IRB approval. The costs of noncompliance can have considerable impact on the research trial.

What are potential outcomes of scientific misconduct and questionable research practices?

**Increased risk to research participants:**
- May result in an increase of participant complaints and concerns.

**Inaccurate data collection:**
- Jeopardizes the reliability and validity of a clinical trial. Misconduct by a single investigator can have a broad impact on projects initiated by several sponsors.
- May result in the exclusion of data collected at that site, which wastes time, money, and the resource of participants.
- Potentially skews data that could affect the worldwide population such as drug recalls, lawsuits, and need for additional data collection.
May result in the FDA’s refusal to accept data from the research in support of a marketing application. This can increase drug development costs and postpone product approval, leaving some patients without effective treatments for longer periods of time.

**Budget and management increases:**
- Additional monitoring and reporting requirements.
- Increased involvement of Senior Management, Quality Assurance, and Legal departments for sponsor, CRO, and IRB.
- Potential FDA investigation.
- Potential damage to relationships between sponsor, CRO, and IRB.

**Negative impact to research image:**
- Decreases public confidence in clinical research and raises questions about the effectiveness of trial monitoring and the responsiveness of the FDA.
- Significant noncompliance can place the sponsor, CRO, investigator, and the IRB in the “headlines” of public scrutiny and unfavorable publicity.

No IRB can be the “research participant’s protector” at each step of the research process. The philosophy of the ERC has always been that the most effective way to protect the participants in a research trial is to carefully review the qualifications of the investigators conducting the study. The investigator and research staff carries much of the responsibility for the protection of the participant. It is at the investigator level where the research decisions are made that has the greatest opportunity to affect the participant’s safety.

No one would choose to be on the opposite side of education, would they? The question is more to the issue of how to provide the education in an effective and efficient manner. Time is critical in the environment of research. Most investigators have demanding schedules and are heavily reliant upon their study coordinators, especially in late stage research that is often conducted in the primary care physician’s practice.

Training before research initiation can be the most effective tool in preventing noncompliance. This helps guard against errors that increase risk. Ineffective research, at the minimum, wastes the valuable resource of the human participant. As the IRB for many multi-site studies, the ERC attempts to find ways to educate the investigator and research staff in all communications. The communication contains regulatory explanation, which can help point the investigator to informed decisions leading to better compliance.

Opportunities for IRB to provide education include presentations at investigator meetings; information booklets with IRB and regulatory language in a “user friendly” format; on-line Web-based training; and more.

Within a climate of relationship and education, the IRB should be approachable and knowledgeable, supportive to the research objectives, flexible within the constraints of the regulations, and continually striving to raise the educational level in order to improve compliance and efficiency. In replacing the “cloak of mystery” that

**In an alliance of partnership, the IRB can help accomplish a higher level of compliance through education.**

seems to exist regarding IRBs with understanding and cooperation, the objective to promote valuable research while protecting the human participant will be much better served.

An International Perspective: Why Were Commercial IRBs Singled Out for Congressional Hearing?

U.S. Moves Are Ethically Unclear

Jack Corman

When the American elephant catches a cold, we in Canada get pneumonia. And the rest of the world is not immune either from catching U.S. ills, as the global financial collapse shows.

Those of us in other countries pay closest attention to our local clinical trial regulations, including ICH GCP. However, it is inevitable that events in the United States such as the Coast “sting” are noticed. America’s profound international economic influence is reinforced by the FDA in its guidance on acceptance of foreign clinical studies and the recent draft guidance and FAQs on the Statement of Investigator Form 1572, and the establishment of FDA offices in China, India, and elsewhere. It is inevitable that fallout from the Coast IRB investigation will have international impact.

A commercial board bias?

Earlier this year information started to come out about a congressional committee’s attempt to uncover evidence of poor quality ethics review by commercial ethics review boards in the United States. Despite past evidence from FDA, OHRP warning letters and other reports that non-commercial ethics committees were commonly in serious violation of federal regulations, this committee decided to single out the private sector. How did the deaths of Ellen Roche (Hopkins) and Jesse Gelsinger (Penn) go overlooked by Congress? Also recent U.S. regulatory inspection results show in 2009, of 18 OHRP initial and follow up determination letters describing apparent failures of institutions to follow DHHS regulations applicable to U.S. federally-funded research, only one was directed at a private clinic and its IRB. In addition, only one of 10 FDA Warning Letters directed to IRBs from May 2008 to May 2009 was directed to a commercial IRB (Coast). The other nine IRBs referenced in the warning letters were all embedded in public or not-for-profit organizations.

A recent anonymous posting to IRB Forum, an ethics discussion group, made public a recommendation by Penn’s legal department to dissolve its internal IRB and use an external commercial IRB due to concerns about internal conflicts of interest. Further, congressional focus on commercial IRBs is in stark contrast to other evidence of a solid and effective private IRB system, well researched and described in a recent article written for the American Health Lawyers Association (Lis JM, Murray, GM, The Ins and Outs of Independent IRBs, J Health & Life Sci Law, vol. 2 No. 1, Oct 2008).

What also seems odd is that the congressional committee did not follow the expected approach and ask the appropriate regulatory agencies to conduct inspections and audits of suspect IRBs. In hindsight, this choice seems to indicate both a selective mistrust of the private IRB system and lack of confidence in its governmental oversight mechanisms, hence the decision to include DHHS agencies in the sting’s crosshairs.
International reaction

Internationally this story seems to have generated some, but not a great deal, of attention, perhaps because few commercial IRBs exist outside North America, and research based outside large institutions is relatively uncommon—most countries have created a government agency to conduct or manage ethics review, e.g., UK’s Multicentre Research Ethics Committee (MREC) system, or the French government appointed regional ethics committees (CPPs). These governmental “accredited” independent ethics committees are presumed (rightly or wrongly) to be both competent to conduct scientific and ethical review, and free from conflicts of interest.

The fairly limited discussion and amount of coverage accorded to it is directly proportionate to the presence or absence of commercial ethics committees in that country. For example, The Research Ethics Blog in Canada, recounted in the BMJ April 20, 2009, and an editorial in Lancet (Vol. 373, #9673: 1400, April-May 2009) picked up by others such as Bioetica Latinoamerica blog, which also repeats the Institute of Medicine’s recommendations on management of conflict of interest. However, judging by the relatively limited space devoted to the story and related commentary, the incident appears to have been treated as essentially a problem for the United States.

What can we learn from the investigation?

Writing as a Canadian, several questions remain unanswered. But one wonders what broader learning can come from this incident, or how it will help improve safety of research subjects.

For example, should entrapment become a standard tool used by the FDA or other regulatory agencies? Is there a chance that this could spread to even sponsor auditors? Does “one out of three” IRBs deliberately targeted by sting officials as possible “weak links” say anything about private ethics boards in general, or all ethics boards?

Historically, U.S. regulatory inspections uncovered major findings during routine inspections of academic ethics boards, leading to several suspensions and transfer of responsibility to commercial ethics boards fully compliant with regulatory requirements. Ethics boards elsewhere learned from the findings of these inspections; indeed some of these ethics boards openly shared what they had learned and changes they instituted as a result of the inspections that have been instructive for all of us. Presumably, Coast IRB had a satisfactory audit and inspection history. However, all of us will re-examine our review processes and documentation. It remains to be determined if a measurable improvement in subject protection results.

The U.S. system already suffers from what Greg Koski, MD, and former director of the OHRP, dubbed a “culture of compliance,” leading to what Yale’s Robert Levine has called “dysregulation of research.”

Given recent precedent, it is unlikely that the Coast IRB sting and regulatory or legislative reform it generates will alleviate the dysregulation or move us away from Koski’s “culture of compliance” to his dream of a “culture of conscience.” We can only hope changes will be thoughtful and collaborative, taking into full account the strengths as well as weaknesses of the present system to create a more ethical and accountable global clinical research system.

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Few commercial IRBs exist outside North America, and research outside large institutions is uncommon.
n the recent IRB “sting” operation described in the introduction, the GAO noted that one of the three IRBs approved the bogus submission, and concluded that “[t]he IRB system is vulnerable to unethical manipulation, which elevates the risk that experimental products are approved for human subject tests without full and appropriate review.” One could argue that the fact that two out of the three IRBs did not approve the submission shows that the IRB system does work. However, in light of the current scrutiny of IRB practices by Congressional subcommittees, it is more productive to pinpoint the nature of the deficiencies of the lone approving IRB, which has since closed its doors, and to make certain that existing IRBs are doing everything they can to properly review studies.

**Revisiting IRB Training and SOPs**

One of the first steps in providing comprehensive review is for an IRB to have a thorough human subject protection training program for all board members and staff. Everyone who touches an IRB submission needs to understand fully what is in the regulations governing human subject protection and what the specific requirements are for performing a proper review. After initial training, IRBs should have their members and staff regularly review these regulations and requirements through an organized continuing education program. There are numerous Web sites and books that can help in creating a program.

In addition, an IRB should be certain that it has sufficient expertise on its board to evaluate the type of studies it reviews. If an IRB doesn’t have the appropriate specialists needed to review a protocol and evaluate the study design and the risks and benefits it describes, it should use outside consultants to fill in any gaps. The outside consultants should also be knowledgeable about human subject protection requirements. This type of expertise will help the board determine whether it has all the information needed for proper review. If the IRB needs additional documentation from the investigator and/or sponsor in order to evaluate a protocol completely, it should withhold making a decision on approval until it has all the information it needs to make an informed decision.

Board members must also have a thorough understanding of conflict of interest principles. Any time financial or other personal considerations may compromise or even have the appearance of compromising an IRB member’s deliberation in reviewing research protocols, a possible conflict exists and must be identified. A board member who is paid $50,000 a year to consult for a biotech company should not be reviewing that company’s protocol submissions to the IRB. Other types of conflicts are not as clear cut, and need to be reviewed as soon as they arise. IRBs should train members to recognize and respond to a wide variety of conflict situations and reinforce this training frequently through continuing education.

Another step in performing a comprehensive review is for an IRB to have SOPs that require thorough initial and continuing review of submissions. This means
that the IRB should have comprehensive reviewing tools so that it can gather all the information necessary for complete review. IRB submission forms for investigators, sponsors or CROs should elicit all the information the IRB needs to get a full picture of how the study will be carried out. The form should require the investigator, sponsor or CRO to explain where the study will be conducted, the source of funding, the IND number or device status, if applicable, the intended study population, the existence of a data safety monitoring board and/or plan, and the type of recruitment methods and materials that will be used.

Submission forms for research sites should elicit all the information the IRB needs to get a full picture of the site’s ability to carry out the study while complying with human subject protection requirements. The site should be required to describe its research experience, education and training, its regulatory history with other IRBs, FDA, OHRP and state medical boards, plans for compensation of subjects, methods of recruitment, and types of populations targeted for recruitment.

A lesson learned from the GAO sting operation is that the IRB should independently verify as much of the information submitted as possible, such as by checking state Web sites to verify medical license and good standing.

Finally, in order to conduct a robust review of the research, the primary reviewer of a new study should have a detailed checklist of all the elements the IRB must consider, which may include targeting of vulnerable populations, cost, compensation for injury, risks and benefits, study design, confidentiality, data oversight, and regulatory criteria. If a Subpart B analysis is required for research involving pregnant women, or a Subpart D analysis is necessary for research involving children, the reviewer should have a list of the guidelines for these analyses.

**Improving the Public Image of IRBs**

IRBs today need to do everything they can to correct any misperception that they are remiss in their obligations for human subject protection. In addition to providing a thoughtful and thorough review, IRBs should consider applying for accreditation from the Association for Accreditation of Human Research Programs (AAHRPP), an independent non-profit body that provides an objective measure of quality using rigorous standards. Accreditation provides sponsors, institutions, researchers, and the public with confidence that accredited organizations meet or exceed federal standards for protecting human subjects.

**Preparing for Closer Scrutiny**

In the aftermath of the recent hearing about IRBs, and the pressure it has created on everyone in the clinical trials world to make certain that subjects are being adequately protected, IRBs can expect more scrutiny and more third-party audits. IRBs should have a documented process for how to prepare for and manage audits or visits from such entities as FDA, OHRP, AAHRPP or research sponsors. Additionally, in order to be in the best possible position to respond to third-party audits, every IRB needs to have a comprehensive program in place that covers the areas discussed here.

A lesson learned...is that the IRB should independently verify as much of the information submitted as possible.

Being in the IRB industry for more than 20 years, I attest that all independent IRBs are not representative of the particular IRB that was the recent target of the U.S. Government Accountability Office (GAO) sting.

It is very disheartening to hear a client tell us that an institutional IRB staff member stated that he did not trust independent IRBs since learning about the GAO sting. Ethical integrity has been proven by the fact that two other independent IRBs refused to approve the bogus study. To use a popular quote, “One bad apple does not spoil the bushel.”

**Common Goals and Integrity**
Independent IRBs do not wish to be competitive with institutional IRBs. Rather, we respect the role of the institutional review board and prefer to partner with them to achieve our common goal of adequate protection of human study participants. Given the opportunity, this partnership could be very beneficial to both parties.

Independent IRBs fulfill a niche in the industry that allows researchers who are unassociated with an institution the ability to be involved in the conduct of clinical research. Who would review their research if independent IRBs did not exist?

Quality and integrity are essential to the services IntegReview provides. Human research is a field that relies on accuracy, honesty, individualized attention to details, and the ability to respond quickly and effectively in a rapidly changing professional landscape.

Our key relationships with customers are based on and driven by our Core Values, Mission, and Vision Statement. Our board members and employees continually maintain high standards of quality, ethical integrity, and regard for human safety while being responsive to customer demands and needs for prompt, thorough, and professional services.

Employees work in a fast-paced, highly responsive, open, and adaptive culture that is reflected in the company’s mission, which states it will “Provide unsurpassed ethical review services while acting as an advocate for research study participants.” Furthermore, we have committed to a 24- to 48-hour turnaround time, in addition to complying with federal regulations, utilizing quality control processes, employing the latest technologies, and being flexible to customer needs.

**Flexibility and Turnaround Times**
Some have voiced concerns with the ability of an IRB to provide turnaround of study documents within 48 hours of board review. However, independent IRBs are businesses and, as such, must be cognizant of client expectations. As an independent entity, we are able to provide necessary resources as they are needed to ensure we continue to meet the expectations of our clients. The 48-hour turnaround time was a key policy and business practice improvement implemented by IntegReview in response to requests from our customers and to the changing environment in the human research field. Customers and clients re-
quested the flexibility to forward requests for approval of research with a shorter lead time, but still receive the high standards of scientific review, attention to detail, and responsiveness.

In response to these requests, IntegReview developed strategies and procedures to facilitate quality, thorough review with a rapid-turnaround process that our customers now rely on. To accomplish this, we trained staff as well as our group of consultants in guidelines and deadline goals for rapid-turnaround submissions. Since all materials for each research study are processed in multiple stages by various staff teams, this required us to analyze the flow of documents and materials at all levels. Once this was done, staff and consultants were trained in specific ways to process rapid-response requests in order to assure that quality standards are maintained at the same time flexibility and timeliness are addressed.

In 2005, IntegReview implemented a Corrective and Preventative Action (CAPA) program. This program identifies errors discovered internally versus those discovered by the client. It also assists in identifying the root cause that can result in process improvements. IntegReview’s staff and consulting committee members routinely handle approximately 3,100 documents per quarter, with an average accuracy rate of between 98% and 99%. Errors that might have been prevented through improving internal processes are used as learning opportunities for either staff training or for adopting new steps in processing or changes in quality checklists.

Among IntegReview’s successes in using the CAPA program to ensure high-quality customer service has been its regular examination and improvement of its checklist and review process.

Another area of importance is continuous training. At least annually, customer service training is provided to all staff. In 2008 we conducted a training session regarding how our core values impact everyday interactions, a series of workshops based on The 7 Habits of Highly Effective People, and training sessions on professional communication as well as conflict resolution.

At a recent conference where we were exhibitors, many attendees posed the same questions: “Would your IRB have discovered a bogus study and how would you detect this?”

Given the detail of quality assurance performed by our Quality Assurance Department, we feel comfortable that we would not fall victim to a similar situation. The numerous checks and balances employed by our Quality Assurance Department would not allow the clinical study to be assigned to any of our boards for review. As part of our quality assurance process, extensive checklists are utilized that would allow us to identify potential issues of concern.

Ethical integrity can be demonstrated in a number of ways. I believe that independent IRBs are very dedicated, committed, and focused on ensuring compliant behavior and play an increasingly important role in providing adequate protection of human study participants.


Independent IRBs fulfill a niche that allows researchers who are unassociated with an institution the ability to be involved in the conduct of clinical research.
How to Choose a Central IRB

William Dirkes, MD, MBA

Recent events have focused increased scrutiny by sponsors and CROs on the capabilities of the IRB providing study oversight. The selection of an IRB should be considered carefully. A quality IRB potentially enhances a study, both before startup and throughout the process. The wrong choice, however, could cause delays, or in the case of the recent closure of an IRB, the need for re-review of the study. Both can be very costly.

The new era will view the IRB as a trusted consultant that can prevent costly errors, and works with the sponsor/CRO to support decisions made if they are ever questioned.

Accreditation by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) provides assurance that an independent entity has reviewed the board and administrative processes.

However, additional criteria should be considered. First and foremost, IRB selection should be based on the membership of its board. Considerations include the members’ scientific or non-scientific backgrounds, ability to evaluate and validate the scientific basis of the study, longevity with the IRB, years of IRB experience, training in regulatory requirements, continuity as a group, access to outside experts, willingness and availability to convey rationale supporting decisions, frequency of meetings, ability/willingness to convene ad hoc meetings on short notice, and financial relationship to the commercial entity.

**BACKGROUND.** Look at the IRB’s membership roster and request CVs of the members. Does the group provide breadth and depth of experience in not only medical/scientific areas but regulatory, statistics, ethics, legal, and non-scientific areas to adequately review your protocol? A simple screen might include checking the IRB Web site. Is its membership posted? Will they stand behind their reviews if they are not willing to publicly acknowledge their memberships?

Is the IRB willing to validate the scientific basis as well as the project design as a whole? Developing a project entails a broad range of decisions before it is even presented to an IRB. These decisions include the type of patient to be studied, drug dosage, the use of a wash-out period and/or placebo, testing procedures, and statistics. In order for a study to be validated by the IRB, its members must be capable of analyzing all of the study’s complex components. The questions the board asks after reviewing a protocol represent indicators of this capability.

**EXPERIENCE AND CONTINUITY.** As in other roles, members of an IRB grow through experience and training. Ask for information regarding the members’ years of experience on the IRB being considered, as well as other IRB experience. Board turnover speaks to the continuity of the team. Rapid turnover could signal problems with the IRB itself, or with the administrative team. Are the board members provided regular training in new ethical considerations and regulatory requirements? Does the board request and have
a means to access outside assistance if deemed beneficial? Will the same board review amendments?

**COMMUNICATION.** Does the board routinely object to certain aspects of a protocol, or does it provide suggested changes to enhance the project? This provides insight as to whether the board views its role as limited to human subject protection, or if its membership also considers research a societal good. In most cases both objectives may be achieved through open discussion of the thought processes regarding decisions, and creative suggestions that both protect human subjects and advance science.

**FREQUENCY OF MEETINGS.** Frequency can impact a study significantly. All IRBs require adequate time for review of materials by the board before a meeting. Sponsors and CROs should ask for the standard review time allotted to the board and determine if it is adequate for a thoughtful review. Frequent meetings allow for a review more rapidly. Once a study is started, unpredictable things occur and may require a more rapid review. How quickly can an ad hoc IRB meeting be convened? If board members are employees, some sponsors/CROs might consider them conflicted. The IRB function and capability is significantly linked to the administrative team.

**REGULATORY EXPERIENCE.** Although board members should be cognizant of the applicable regulations, the administrative team is frequently responsible for knowing, researching, and informing the board of guidance updates and suggesting avenues that traverse the maze to a successful conclusion. Do staff members have regulatory experience in both sponsor/CRO and IRB environments?

**CONTINUITY.** While each project is unique, sponsors/CROs frequently have “usual practices” that distinguish its work. Having an administrative liaison that is company-specific (or at least project-specific) reduces frustration and contributes to quality outcomes.

**DOCUMENT MANAGEMENT.** The electronic environment can provide instant access to all documentation as well as tracking of the submission process. Systems must be validated. IRBs that distribute documentation to their board via paper will have a longer turnaround time unless they shorten the time for review by the board. Again, the primary emphasis should be on a sound board review. Allowing adequate time for review by the board is critical.

**QUALITY.** Ask for samples of documentation. Is the documentation detailed enough to provide your staff with the information they need? Documentation in the research environment requires meticulous attention to detail. Ask for quality metrics.

**SUPPORT.** Does the IRB provide support for investigators? When an investigator or site staff call with a question, is a response provided within a reasonable time frame? Does the IRB provide initial and ongoing training?

The choice of an IRB should be an important decision in the research process. The right IRB engenders the confidence of the C-suite and legal department of a sponsor/CRO. The IRB you choose should be the one you want sitting next to them in a Congressional hearing, if something is questioned.

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**In order for a study to be validated by the IRB, its members must be capable of analyzing all of the study’s complex components.**
All Stakeholders in Human Research Protection Would Benefit from a Cooperative Enterprise That Moves Forward Without Blame

Transparency and Cooperation

Currien MacDonald, MD, CIP

Americans love competition. Free enterprise embraces the notion that more competition is good for the consumer and business; describing the pharmaceutical research field as “highly competitive” gives a positive impression. However, it also is a direct cause of investigator, sponsor, human research protection program, and government error. We put Sisyphus to shame (and spend billions) in pushing against this system’s inherent tendencies, struggling to police integrity. The solution is simple, if not easy. The stakeholders in research—sponsor companies, researchers, and the general public—need to cooperate. By taking simple steps to increase transparency in research, we in human research protection programs (HRPPs) can support the cooperation that is needed to change the research field from a financially inefficient machine of mistrust into a comfortable vehicle to meet all stakeholders’ needs.

The problems with the current system are not unfamiliar, though completely misunderstood and have led to non-existent public trust. Contrary to current opinion, the FDA and OHRP, despite a boost to their budgets and staff, were never designed to be the first line of defense in subject research protection. Pharmaceutical companies are not training grounds for avarice and their executives do not hang their morals on a peg outside of the boardroom. They do provide treatments we all desperately need. Researchers, also known as caring and compassionate people who believe cures are out there to be found, deserve our support, not a watchful eye.

Despite the publicity of a GAO sting, HRPPs are made of diligent, hard-working people who balance, juggle, and perform contortionist routines to apply ethereal theory to messy and complicated real-world ethics. We are all aware of the problems of the system, but blame and punishment can never correct them. The real problem is not that there are a few bad apples in the barrel, but keeping apples crammed in a dark barrel in the first place.

The currently proposed quick-fixes to the current system, such as separating the FDA into drugs/devices and the rest of its responsibilities, do not address the underlying systemic issues. Any system that has competition at its foundation is doomed to fail, and there is a plethora of evidence that proves competition encourages inefficiency, duplicity, and scarcity, regardless of the performance of its components.

The transition from our current system to a cooperative one would require effort. A cooperative research enterprise would allow efforts to align, producing rapid, profitable, effective outcomes that cost less. Yet how can the stakeholders get from where they are to a cooperative system?

Transparency in the HRPP

One way is through transparency. Anyone can trust when seeing what the other party is doing. Transparency, one of the new Obama-era buzzwords, appears to be a verb. The FDA just opened its black box, in a big-government sort of way, to produce “regulatory changes to improve
the FDA’s ability to provide...useful and understandable information about FDA activities and decision-making to the public." Research institutions, such as Harvard, MIT, and 34 others have dedicated their published research as open-access and free on-line. PubMed does the same, and its connection to ClinicalTrials.gov imparts information as studies begin. Pharmaceutical companies are lining up to post their financial relationships for all to see. What could HRPPs do to be transparent, to facilitate cooperation?

While it may appear that OHRP registration could fulfill part of this, the process does not mean that the registered HRPP is compliant with regulation, that their written procedures have been vetted or there is any review of what is actually being done to protect research subjects and their information. Having significantly raised the standard, AAHRPP is a vanguard for a transparent system.

What else could a transparent, cooperative system entail? HRPPs could have something like WikiSOPs, modified for use at an individual site, but templates built in cooperation, transparent for all involved. Individual HRPPs could be “audited” in real-time by their peers and stakeholders; and as every HRPP and stakeholder would be able to contribute and cooperate, there would not be any big surprises to anyone. Best practices could be common practice. Regular self-reporting, similar to Australian ethics boards’ annual reports, could be hosted by ClinicalTrials.gov or something similar and provide benchmarking data for transparent, cooperative quality improvement for research oversight programs. Of course, financial, commercial, affiliate, even preferential disclosures by stakeholders would allow HRPPs to become independent, objective managers of stakeholders’ conflicting interests.

Cooperation is the Future of Research

While current financial incentives are available for comparative research, going beyond that to collaborative research would provide the stakeholders the ability to meet each of their needs most effectively. The chemical cooperation required to combat HIV defenestrated old treatment paradigms, and is starting to do the same for old, insular concepts of treatment research and notions of industry cooperation in those concepts.

Research is our most powerful tool to produce objective evidence to answer real questions. Each of the stakeholders in research wants the same thing—to know the answers to those questions. We, the HRPPs, have a unique opportunity, as we were created to meld the perspectives of the medical research system.

HRPPs were created, not only to protect research subjects, but also to protect research from losing the perspective of its necessary support and responsibility, the society that allows it to continue. We, therefore, could continue to be champions of cooperation, leading by example. We ideally would demonstrate that we cannot only work together, but unite as facilitators in having research produce the ends to benefit all stakeholders.

The future of research is a positive and cooperative one. The only question is will it be a joyous transition, or one that has people fighting the whole way to a better place. Join with others who are making a change for the better; grasp the hand of an HRPP. As a wise and kindly revolutionary put it, become the change you want to see.

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