JOURNAL OF CLINICAL RESEARCH BEST PRACTICES

Vol. 7, No. 6, June 2011 "Can You Handle the Truth?"

Streamlining the IRB Process: Avoiding Unnecessary Deliberation and Effort

By Tom Bechert

Introduction

Institutional Review Boards (IRBs) are required to fulfill two very important, and at times seemingly conflicting, responsibilities:

- The regulations task the IRB with ensuring compliance with federal, state and local regulations related to human research protections, and
- Institutional pressures simultaneously charge the IRB with ensuring that bureaucracy is minimized and review-process efficiency is maximized to ensure prompt and responsive reviews.

Unfortunately, achieving both compliance and service-oriented efficiency can be a considerable challenge in practice, and research administrators often find themselves making compromises related to regulatory compliance or efficiency to maintain their operations. Over time, these compromises can accumulate and ossify into standard practices that are perpetuated out of habit, which is why it is not surprising that an assessment of regulatory compliance and operational effectiveness at many IRBs identifies the following general themes:

> **Theme 1**. IRBs and IRB offices often do not do everything they need to do to comply with human research protections regulations.
>
> **Theme 2**. IRBs and IRB offices are commonly involved in administrative and review activities that are not required by the regulations and provide no human subject protection value, thereby limiting the efficiency and effectiveness of the IRB and IRB office.

Theme 1 is an area of common concern among organizations, given the potential consequences a noncompliant IRB may face from regulatory agencies and study sponsors, and is routinely addressed through a variety of publications, organizations and forums.

Theme 2, in contrast, is a relatively under-addressed issue, perhaps because there is less perceived risk associated with an inefficient IRB as opposed to a noncompliant one. However, it is important for organizations to realize that long approval delays and unnecessary requirements caused by inefficient IRBs come with significant negative consequences as well:

- They may result in missed deadlines that prevent the institution from participating in some studies.
- They may hinder enrollment by significantly narrowing the window of time that local investigators have to enroll research participants.
- In some cases, investigators may be discouraged altogether from conducting research if the approval

process (including the IRB review process) is considered to be overly burdensome.

In this uneven game of tug-of-war between efficiency and compliance, efficiency often loses out, to the detriment of human research itself. However, it is unnecessary to choose between the two; they can and do successfully coexist at many institutions.

Goal of this Article

This article highlights certain practices for IRBs to avoid in the interest of improving the efficiency and responsiveness of the human research protection program. IRBs and IRB offices are tasked with a significant amount of materials to review and numerous regulatory requirements to address. Given the limited resources allotted to IRB administration at many institutions, it is best to use those limited resources to focus on the relevant federal regulations and the regulatory criteria for approval, while avoiding the deliberation and focus on issues that are outside of the regulatory requirements and provide no additional protection to human subjects.

Regulatory Criteria for Approval

Throughout this article there are references to "regulatory criteria for approval." This phrase is used to refer to the Criteria for IRB Approval of Research found within the U.S. Department of Health & Human Services (DHHS) and U.S. Food and Drug Administration (FDA) regulations at 45 CFR 46.111 and 21 CFR 56.111 (below). These criteria contain all of the considerations that IRBs should apply when making approval decisions that protect human subjects (although properly understanding and applying each of these criteria is outside the scope of the current article).

Practices to Avoid

With the regulatory criteria for approval in mind, and with the goal of improving IRB efficiency without negatively affecting the level of IRB compliance, let's consider the following common IRB practices, both in terms of what these criteria specifically require and, perhaps more importantly, what they do not require.

Avoid unnecessary risk minimization

Even when an IRB's focus is limited specifically to the regulatory criteria for approval, consistency of interpretation among IRBs and IRB members will still vary. An example of this variation is the issue of risk minimization, an area that is commonly over-emphasized or misinterpreted at many institutions.

This is due to the widely-held — and incorrect — belief that one of the obligations of any IRB is to "minimize risks" or "minimize risk to the extent possible." In fact, this is a significant oversimplification of the role of the IRB, as the regulations do not give IRBs carte blanche to minimize risks. According to both the DHHS regulations (45 CFR 46.111(a)(1)) and FDA regulations (21 CFR 56.111(a)(1)), IRB Members must ensure that risks are minimized *subject to two reasonable constraints*:

- Using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk, and;
- Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

Stated more completely in this way, it becomes clear that the IRB's obligations with respect to risk minimization are much narrower than simply "minimizing risk." If the IRB minimizes risk in a way that no longer meets these constraints, for example by minimizing risk in a way that the research cannot be conducted with a sound design, the IRB has gone beyond the regulatory requirements in a way that is detrimental to research and human subjects protections. IRBs can avoid unnecessary deliberation and effort in the review process by focusing on the regulatory requirements within the DHHS and FDA regulations. For this regulatory criterion, the IRB should ensure that the risk level of the research cannot be reduced by changing or reducing the number or type of procedures performed or subjects involved in a way that will still allow the research question to be answered, and by avoiding unnecessary duplication of effort arising from conducting non-research-related procedures.

The Logical Flaw in "Minimizing Risk"

Consider the logical flaw in any effort to simply "minimize risks" in a way that goes above and beyond the regulatory requirements. The dictionary definition of the term "minimize" is "to reduce or keep to a minimum." Given that the only way to completely reduce the risks associated with research is to not conduct the research at all, and given that the IRB is not tasked with disapproving any and all prospective research, then clearly "risk minimization" is an incorrect characterization of the IRB's responsibilities.

Furthermore, it is important to keep in mind that risk levels cannot be meaningfully lowered for any research already determined to be "minimal risk."

Avoid unnecessary reporting and review of adverse events

A sizable portion of meeting time for many IRBs is devoted to reviewing Adverse Event (AE) and Serious Adverse Event (SAE) reports. Typically, members discuss and vote on issues such as "relatedness" and "severity." IRB action seldom results from a single, usually blinded, data point, so the exercise is generally a waste of time. Protocols (for greater than minimal-risk research) should task an individual (e.g., the investigator) and/or a group (i.e., the data & safety monitoring committee) to monitor safety because they are better equipped to perform detailed data analysis than the IRB.

IRBs are often flooded with AE and SAE reports because overly cautious sponsors instruct their investigators to report such AEs or SAEs to the IRB.

In fact, there is no regulatory obligation for investigators to submit AEs or SAEs to the IRB, and there is no regulatory obligation for the convened IRB to review them. On this topic, DHHS regulations (45 CFR 46.103(b)(5)) and FDA regulations (21 CFR 56.108(b)) require the following of IRBs:

> Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Department or Agency head of: (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB*; and* (ii) any suspension or termination of IRB approval.

Criteria for IRB Approval of Research (21 CFR 46.111 and 21 CFR 56.111)

(a) In order to approve research covered by this policy, the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized:

(i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and

(ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted, and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative in accordance with, and to the extent required by §46.116 / 21 CFR Part 50.

(5) Informed consent will be appropriately documented in accordance with, and to the extent required by, §46.117 / §50.27.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

The regulations do not equate serious adverse events with unanticipated problems involving risks to subjects or others for three reasons:

- Most adverse events are not unexpected, insofar as their specificity and severity are accurately reflected within the informed consent document.
- Most adverse events that occur that are not already reflected in the informed consent document are not related to the research procedures being performed on the research participant.
- Most unanticipated problems involving risks to subjects or others are not adverse events. Most unanticipated problems involving risks to subjects or others represent new information from sponsors, the FDA, and the literature, rather than an isolated adverse event incident.

Rather than reporting any and all adverse events, investigators should instead report any harm experienced by a subject or other individual which, in the opinion of the investigator, are *unexpected* and at least *probably related* to the research procedures, keeping in mind that:

- A harm is "unexpected" when its specificity and severity are not accurately reflected in the consent document.
- A harm is "at least probably related to the research procedures" if, in the opinion of the investigator, the research procedures more likely than not caused the harm.

Such an approach is compliant with federal regulations and consistent with both federal guidance and the Association for the Accreditation of Human Research Protection Programs (AAHRPP) accreditation requirements. In implementing this approach, IRB offices should instruct investigators to stop reporting harms that are expected or not clearly caused by the research procedures, saving both investigators and IRBs a significant amount of time and effort at no cost to the IRB's level of compliance. When AE reports are submitted to an IRB, a designated reviewer can review the submission to determine whether the event is an unanticipated problem involving risks to subjects or others, and if it is not, the IRB office can send acknowledgement to the investigator saying as much.

Avoid unnecessary scientific review

Another opportunity to improve IRB efficiency and reduce unnecessary effort relates to scientific reviews conducted by IRBs. IRB members at many organizations frequently undertake more detailed scientific reviews than are necessary under the regulations. The term "detailed scientific review" is used here to refer to cases in which IRB members attempt to re-engineer the scientific design of a study in order to improve the scientific design for scientific design's sake. These reviews can result in requests to, for example, add additional control groups, conduct additional tests, or change the study hypothesis in an effort to make the science better.

"Scientific review" is a term that has multiple meanings. There is "merit review" to determine which scientific project gets access to limited resources. However, research that does not merit funding can still meet the regulatory criteria for approval and be ethical. There is also "peer review" to improve the quality of research. However, research that meets the regulatory criteria for approval and is ethical can usually be made better. Involvement or concern of the IRB in either type of review is mission creep and dilutes the IRB's ethical and regulatory responsibilities and attention.

What the IRB needs for scientific review is an "accuracy and explanatory review." For example, the IRB must determine whether risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. If a protocol accurately portrays and effectively explains the risks and anticipated benefits of the knowledge reasonably expected to result, all members of the IRB (including non-scientific members) can make a judgment call about the level of risk, the level of anticipated benefit, and the importance of knowledge gained. Then they can judge whether the level of risks to subjects are reasonable in relation to the level of anticipated benefits to subjects, if any, and the degree of importance of the knowledge reasonably expected to result. Many protocols need additional information to allow the IRB to determine whether the regulatory criteria are met. This is the role of scientific review in the sense of an "accuracy and explanatory review."

A focus on scientific validity will cause IRB members to ask a different, simpler set of questions when reviewing proposed research:

- Is the research protocol scientifically sound and does it have any scholarly merit?

- Does the protocol accurately describe the research in a clear, detailed way?
- Is the research likely to answer its proposed question as designed?
- Does the protocol fairly portray the importance of the knowledge expected to result, realizing that in many cases the knowledge to be gained may be fairly modest?
- Is the available background information adequate to support the proposed research?

Ultimately, any scientific design of a proposed research study can be incrementally improved, but this is the role of a peer review process, not the IRB. As long as the regulatory criteria for approval are still satisfied, the IRB should approve the research.

Avoid unnecessary wordsmithing of informed consent documents

Some IRB members will tell you that ensuring the readability of informed consent documents is their primary role on the IRB. They often cite a nonexistent regulatory requirement that consent documents be written at a fifth-, sixth- or eighth-grade level. It is thus common for IRBs to invest significant effort in rewriting the informed consent document and even the protocol for clarity and readability. Since most IRB members are not expert consent form writers, their recommendations may be counterproductive. Surely, correcting typos and grammatical errors has minimal impact on human subject protection. If editing efforts are absolutely necessary, IRB office staff, medical writers, or other administrative personnel can perform them, without consuming IRB time.

It is often said that informed consent is not a document, but a process. IRBs should thus ensure that the research team will communicate with the subject in a way that ensures that the subject will understand the information. Training and auditing programs can achieve this assurance. The primary mechanism of communication should be the discussion between the research team and the subject. Think of the consent document as a tool to reinforce and memorialize the information communicated by the research team to the subject. No matter how well a consent document is written, participants may misunderstand portions of it, regardless of their reading abilities. If an investigator just gives a consent document to a participant and walks away, the consent process will likely be unacceptable, regardless of how well the consent document is written. If the consent document contains language that the subject does not understand, but the investigator sits down with the participant and explains the study in a way that the subject understands, then the consent process will likely be effective, regardless of the consent document's language. When IRBs focus on the consent process, they soon realize that consent document readability, in and of itself, is neither necessary nor sufficient.

Avoid unnecessary full-board reviews

A great deal of unnecessary IRB and investigator effort is consumed when the IRB reviews submissions that do not actually require IRB review. In some cases, this may result from erroneous IRB office determinations that a protocol is exempt when, in fact, it is not, or eligible for expedited review when, in fact, it is not. Either circumstance is a cause for concern from a regulatory compliance perspective. They are also problematic from an operational perspective. Examples of protocol review at a level *above* the appropriate level include:

- Granting exemptions or conducting expedited reviews of activities that do not meet the regulatory definition of human research
- Conducting expedited or full-board reviews of exempt research
- Conducting full-board reviews of protocols that are eligible for expedited review

Limit the Number of Full-Board Reviews with Expedited Review Category 9

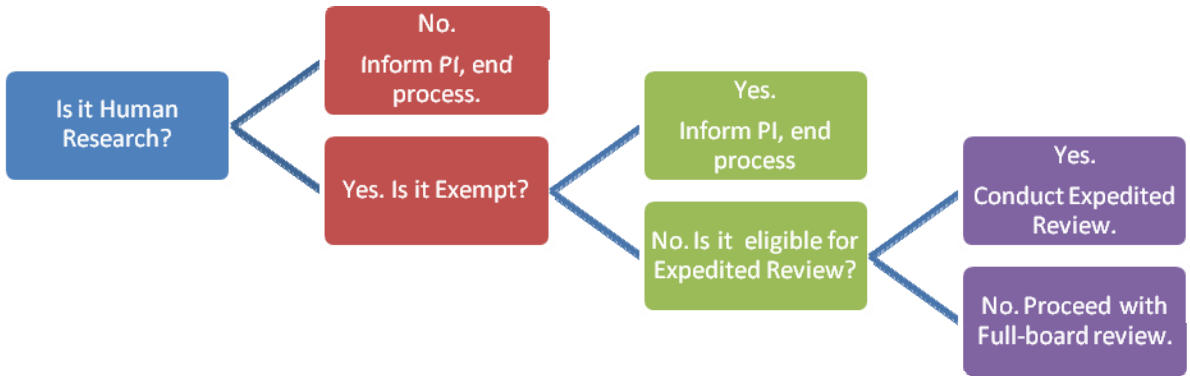
Efforts to correctly determine the appropriate level of review are equally important during the time of continuing review, not just at initial review. Automatically keeping a study at the same review level as the previous year can create unnecessary additional review efforts for IRB members for two reasons:

- A submission may have been incorrectly categorized in a previous year, making it worthwhile to reconsider the correct level of review each year with a fresh perspective.
- Any protocol reviewed by the full board in a previous year and determined (and documented) by the board to be minimal risk is eligible for Expedited Review under Expedited Category 9 the following year.

To eliminate full-board continuing review of minimal-risk research, the best practice is to have the convened IRB identify the correct risk level (minimal risk or greater than minimal risk) for all full-board studies during IRB meetings. Once this is documented, the staff can process via expedited continuing review the following year. The convened IRB does not have to agree or document that the protocol under review will be eligible for Expedited Category #9 the following year; it simply has to establish that the study is minimal risk.

IRB Office personnel should ask the questions in Figure 1 for every submission they receive:

Figure 1. Algorithm for IRB Office Staff Processing of Protocol Submissions



IRB Managers should ensure that the IRB office has formal processes in place to make a stepwise determination as to the correct review category for every submission. Putting an effective process in place can substantially reduce IRB member workload at many institutions.

Avoid unnecessary assent requirements

Avoid unnecessarily burdensome or inflexible requirements related to assent for research involving children (or for cognitively impaired adults). Commonly, such unnecessary requirements include the following:

- Mandating that investigators document assent using a written form (such as a simplified ICF)
- Mandating that all children above a certain age (e.g., age 12) must provide assent

The regulations do not set a specific minimum age for assent from children. In fact, the regulations generally require assent whenever the child is capable of providing assent. Some organizations attempt to simplify the determination process by setting a specific age at which assent will always be required. However, such rules ignore variations in child development. The reality is that there are bright 5-year-olds who may be perfectly capable of assenting to certain types of research, and certain cognitively delayed or impaired 17-year-olds who may not be capable of assenting. Setting the assent age at 12 for every participant, for example ignores the needs of both populations. It is best for IRBs to set guidelines based on the complexity and risk of each study, allowing the investigator discretion to evaluate the capability of individual children on a study-by-study basis.

Furthermore, the use of assent forms is burdensome and unnecessary. There is no regulatory requirement to document assent with an assent document; a progress note stating that the child gave assent is sufficient. Like informed consent, assent is not a document; it is a process by which the child (or cognitively impaired adult) obtains enough information to make a decision about the research, understands the consequences of participating in the research, and is capable of making and communicating his or her decision to participate.

Avoid IRB deliberations over "institutional" or "investigator" risks as opposed to research subject risks

Clinical studies create risks not just for participants, but also for investigators and institutions. Institutional risks include financial risks due to subject injury or even an extended hospital stay. A controversial study could generate negative publicity for the institution. The physical well-being of the investigator (and other personnel) may be at risk if the disease, treatment or subject population is dangerous.

Nevertheless, these risks are outside the IRB's purview. They should be considered by institutional officials or some other duly constituted committee. If a study involving unacceptable risks to the institution or to the investigator is submitted to the IRB, and otherwise satisfies all regulatory criteria for approval, the IRB should approve the research but inform senior officials of these potential risks. Under DHHS and FDA regulations, research that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution (45 CFR 46.112, 21 CFR 56.112). Therefore, these individuals have the power to stop research that the IRB has approved, even though the opposite is not true.

Conclusion

The examples above describe some of the more common sources of IRB inefficiency that can be eliminated within many organizations. These reductions have no detrimental affect on human subject protections. In fact, they improve protections by allowing the IRB to focus on its regulatory responsibilities.

Applying this mindset in assessing your own organization's efforts to streamline its human research protections operations can be done through the following basic process:

- Consider the regulatory criteria for approval.
- Consider your local IRB's requirements, common practices, and policies that have accumulated over time, and identify practices that do not have a basis in the regulations.
- Eliminate or reduce those unnecessary practices for a faster, more efficient, more responsive, less over-worked, and equally compliant IRB.

Author

Thomas Bechert, MS, MBA, CIP, is a Director in the Life Sciences Advisory Services practice at Huron Consulting Group. Contact him at 1.312.880.3331 or tbechert@huronconsultinggroup.com.