IRBs and Randomized Clinical Trials

by Curtis L. Meinert

Introduction

A randomized trial may be undertaken only in so far as the treatments being tested are consistent with existing norms of care, and then only where there is a legitimate state of clinical equipoise[1] for choosing among them. The role of IRBs is to ensure that "risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk" (45 CFR 46.111(a)(1)(i)) and that "risks to subjects are reasonable in relation to anticipated benefits" (46.111(a)(2)). It can be argued that risks are not minimized or not reasonable if the trial does not rest on a legitimate state of doubt. The requirements of the Code of Federal Regulations 46.111 mean that IRBs should withhold approvals where the base of doubt is missing. They also mean that IRBs should withdraw approvals if the base of doubt disappears as determined by reviews "at intervals appropriate to the degree of risk, but not less than once per year" (46.109(e)) once a project is approved. Those reviews require an assessment of the current state of doubt to decide whether approval should be continued. The requirement that "significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation" (46.116 (b)(5)) are imparted to subjects implies the need for such assessments.

One of the criteria for IRB approval is that "when appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects" (46.111(a)(6)). "When appropriate" is left to the discretion of IRBs, but can be presumed to apply to all trials in which treatments have the potential for harm and when that harm is avoided or reduced by timely monitoring.

The regulations do not spell out what constitutes an "adequate provision for monitoring" but can be presumed to require IRBs to be satisfied that investigators have the competence, wherewithal, and expertise to receive, process, and analyze data in an ongoing and timely fashion, and that they have the means to alter or halt a trial when interim results indicate that such action is warranted. The expectation is that the monitoring is done by study investigators or a subset of them, or by a body specifically constituted for that purpose, typically referred to as a treatment effects monitoring committee, safety monitoring committee, or data and safety monitoring committee.[2-5]

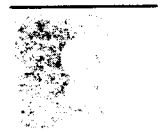
The Two Forms of Harm Common to Randomized Clinical Trials

Safety, as used in §46.111(a)(6), is the condition of being secure from harm, understood as physical or mental injury or insult arising from some purposeful act or accident or from disregard or neglect. Hence, harm can be the result of active or passive behavior.

Virtually any form of research, no matter how innocuous, involves the risk of active harm. Opportunities for passive harm are less common. In research pertaining to human beings such opportunities are largely limited to situations in which there is direct contact with study subjects and an investigator-subject relationship in which the investigator has obligations for care of subjects. This obligation is implicit in follow-up observational studies in which persons have health conditions amenable to treatment, and explicit in most clinical trials. Neglect of that obligation can result in a passive form of harm. For example, it was that form of harm that accrued to subjects of the Tuskegee Syphilis Study when investigators failed to offer treatment to subjects when one became available.[6]

The lion's share of the collective effort of IRBs goes to protecting against active forms of harm, as seen in the time and effort spent in ensuring disclosure of risks of direct forms of harm prior to asking for consent and in investigating occurrences of the direct form of harm. If there is less attention paid to protecting against the passive form of harm, it is because it is less common and because of the history underlying IRBs. They came into being because of "celebrated" cases of the active form of harm.[7,8]

Monitoring for Passive Harm



Passive harm in randomized trials arises when they are allowed to continue unaltered in the presence of data sufficient to indicate the superiority or inferiority of one study treatment relative to another. The harm comes from denying patients the superior treatment or in continuing to use an ineffective or inferior treatment. The safeguard against the harm lies in systems designed to prevent trials from continuing inappropriately by periodic looks at data as the trial proceeds.

IRBs would do well to withhold approval of a randomized trial until satisfied that monitoring will be done and that it will be adequate to protect against passive harm, or to be satisfied that the trial poses little risk of passive harm. IRBs would approve trials in the absence of provisions for monitoring only when investigators are able to convince them that the risk of passive harm is nil. In reality, however, IRBs tend to be laissez faire in regard to monitoring. The reason, no doubt, is that members of IRBs reflect reservations regarding monitoring extant in the clinical trials community.

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Monitoring, since it involves looking at emerging data, is seen as carrying risks to the integrity of the trial and raises statistical concerns. The risks come in the form of treatment-related feedback bias and in opportunities to "data dredge." Treatment-related feedback bias arises when knowledge of interim results produces a bias in the way in which patients are treated or in the way data are collected. The risk of the bias is nil (even if investigators see interim results) in masked trials where the masking is effective, and likely to be low (even in the absence of masking) with crisp treatment protocols and objective outcome measures. "Data dredging" is the product of ad hoc analyses to find differences that are statistically significant. Of necessity, monitoring must have an ad hoc quality to be protective and, therefore, can be confused with data dredging if monitoring leads to alteration of a trial for unanticipated reasons.The concerns come from statisticians interested in p values and hypothesis testing (the "looks" are seen as making it difficult to gauge the true statistical significance of results when they are published) and from sponsors and investigators desirous of unassailably objective results.

Sponsors, especially those of pivotal drug trials, are wary of monitoring to the extent that it can be seen as jeopardizing a new drug application (NDA). They tend to want to limit monitoring to that required for safety. Usually they are loathe to allow monitoring for efficacy for fear that it will lead to premature cessation of the trial and thereby threaten the NDA.

Worries regarding the possibility of treatment-related feedback bias have led to apartheid forms of monitoring, i.e., monitoring that does not involve study investigators, especially those responsible for enrollment and treatment, thereby keeping from them knowledge of the trend of interim results.[2,9,10] The structure is intended to isolate monitoring bodies from study investigators—an insulation that tends to place them beyond the reach of study investigators and in turn that of the IRBs to which investigators report.

The Parent-Affiliate IRB Structure for Multicenter Trials

The risk of passive harm because of failure to monitor increases with the size and duration of the trial. The likelihood of identifying treatment differences indicative of passive harm is low in the typical single-centered trial because of its usually small sample size and short duration. The greatest protective value of monitoring, therefore, is with large-scale, long-term trials. However, those trials, because of their size, tend to be multicentered and therefore are not under the review authority of any one IRB.

Typically, an IRB is content to review from the perspective of the center it is overseeing, as implied by the name *institutional* review board. The expectation in multicenter trials is that the IRBs of cooperating research sites together will provide a comprehensive review of the trial. However, that expectation is unrealistic because there is no IRB with review authority for the trial as such. As a result, some processes, e.g., that for soliciting consents, are reviewed by every IRB, whereas others, such as that for monitoring, may not be reviewed by any IRB.

The review and approval process could be streamlined by a parent-affiliate structure for the IRBs represented in the trial. The parent IRB would have broad oversight responsibilities for the trial and for ensuring adequate monitoring, in addition to overseeing the specific activities of the parent center. The parent center would be the center housing the lead clinical center, the chair of the study, or the coordinating center. Affiliate IRBs would be those serving the affiliate centers in the trial. Affiliate centers (clinics, reading centers, central laboratories, and the like) would not submit to their respective IRBs until the parent center had cleared its review.

The parent center, under this structure, would supply affiliate centers with a packet of material to be used in their submissions to their respective IRBs. The packet would include the study protocol, the investigators' brochure (in the case of IND drug trials), prototype consent forms, and other documents, as needed. The packet would include details of how monitoring is to be done and evidence that the monitoring plan was reviewed and approved by its IRB, as conveyed in the letter of approval from the parent IRB.

The prototype consent form would serve as the basis for consent forms prepared by affiliate centers and would indicate whether monitoring will be done and how persons studied stand to benefit from the monitoring. Affiliate centers would be allowed to modify the prototype form to meet local requirements, but not to delete detail considered essential for informed consent by the parent IRB.

IRBs of affiliate centers with questions concerning monitoring would address them to the parent IRB (via letter to the principal investigator of the parent center). An IRB at an affiliate center would have the prerogative of requiring additional monitoring if the monitoring proposed is seen as inadequate by that IRB.

Under the parent-affiliate structure, the IRB at the parent center has to assume the broader responsibility implied in the parent designation and be prepared to review and act expeditiously. It would have to accept the additional responsibility, as well, for ensuring that the monitoring performed is adequate. The investigator at the parent center would be responsible for indicating whether monitoring will be done and, if not, for convincing the IRB that absence of monitoring does not increase the risk of passive harm.

When monitoring is proposed, the information provided to the IRB should include details such as:

1) Membership or composition of the monitoring body (list of persons or of disciplines and skills to be represented)

2) Representation of study investigators in the monitoring body and voting status

3) Appointing authority

4) Charge to the monitoring body and to whom it reports; if to report to sponsor, how sponsor will communicate recommendations to investigators

5) Likely frequency of interim looks

6) Imposed objectivity constructs (e.g., stopping rules, masked monitoring)

7) Route of recommendation from the monitoring body to study investigators and their respective IRBs

Monitoring tests. The parent IRB should be satisfied that the monitoring is adequate. Adequacy should be judged against questions such as:

1) Does the trial involve the risk of passive harm?

2) Is the process and organizational structure for acting on recommendations from the monitoring body adequate?

3) Is there a continuous and timely flow of data from the generation sites to the database used for monitoring? If not, are the delays or lags small enough so as to be unlikely to reduce the real-time value of monitoring?

4) Is the interval between "looks" reasonable and unlikely to allow important treatment differences to go undetected?

5) Is the monitoring body free of constraints on the number of "looks" that may be performed and of what may be looked at?

6) If monitoring is to be done under imposed objectivity constraints (such as masking), are the constraints compatible with competency requirements for monitoring?

7) Does the sponsor have the means to keep study investigators from learning of a recommendation?

8) Does the sponsor have the right to decide whether a recommendation is implemented?

Questions 2 through 8 are relevant only if question 1 is answered *Yes*. Adequate processes for monitoring should produce *Yes* answers to questions 2 through 6 and *No* to questions 7 and 8.

Questions 7 and 8 relate to linkage of monitors and study investigators. A *Yes* to question 7 or 8 opens the possibility of the sponsor being able to block or "orchestrate" recommendations. One way to ensure linkage is by constituting monitoring bodies to include key study personnel (e.g., the chair of the study and the director of the coordinating center) and by requiring them to report to study investigators. Another way is to require the chair of the monitoring body to report to study investigators, or to them and the sponsor at the same time.[11] Sponsors, in cases where recommendations flow to them, should be required to provide written assurances to parent IRBs that recommendations arising from monitoring bodies will be passed to study investigators in a timely and forthright fashion.

Comment

A recent article in this journal pointed to the need "for effective and timely communication between the sponsor and investigators, or direct communication among the DSMBs, the investigators, and the relevant IRBs"[5] in regard to monitoring. The authors argued, as here, that IRBs "are better positioned to determine whether interim findings are of relevance to human subjects" than sponsors.

There can be no doubt that among the interests represented in trials, those of subjects are supreme. There also should be no doubt that we need better, more cordial structures to ensure the interfaces needed to meet obligations to study subjects in multicenter trials. The need for proper interfaces is most evident in regard to the monitoring process and in dealing with recommendations generated by that process.

The temptation from the perspective of an IRB is to have a more central role in monitoring than is presently the case. However, that is not a suitable solution. IRBs are ill-constituted for the demands of monitoring. Nor should one be inclined to a solution suggested by Gorden et al. that "IRBs routinely receive DSMB reports."[5] Such an approach is unworkable in multicenter trials except, perhaps, in situations in which that distribution is limited to the parent IRB. However, even then there are reasons to be wary. One reason for the restriction on distribution of monitoring reports is to minimize the risk of "leaks" of interim results, and in so doing reduce the risks of treatment-related feedback bias and insider trading (in the case of trials involving proprietary products of publicly held companies). Distribution of monitoring reports to any IRB, even if only to the parent, increases both risks.

In many regards, the best safeguards against harm to subjects of research reside in informed and caring investigators answering to demanding and vigilant IRBs. The tendency toward marginalization of study investigators in clinical trials and their diminishing role in monitoring, has, in turn, served to marginalize the IRBs in exercising their duties. The removal of investigators from monitoring, in effect, requires that they assign part of their duty to protect to distant and remote third parties, not answerable to any IRB. The separation is not consistent with the need for linked communication among investigators, monitors, and IRBs. It is up to study investigators and IRBs to ensure that monitoring bodies are answerable to them and that interface structures guarantee linkage of investigators, monitoring bodies, and IRBs.

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Subject Selection for Clinical Trials

by Council on Ethical and Judicial Affairs,
American Medical Association

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Introduction

This report addresses the interest of potential subjects in participating in clinical research protocols. Just as a patient does not have an unrestricted claim to certain treatments, there is no absolute right to research participation itself. At issue is whether patients should be assured of fair consideration for participation in clinical trial protocols. Initially, it is important to acknowledge that qualifying factors for participation in a research protocol often typically have a scientific basis. These scientific factors are generally considered valid exclusionary criteria, and will not be the focus of this report.

Subjects' Interest in Fair Consideration for Research Participation

A right to fair consideration for enrollment in clinical trials must be based on identifiable interests of research participants. To identify benefits it is important to observe the distinction between "experimental treatment" and "research." In the former case, a physician may try a treatment that is not yet considered standard therapy for a disorder, for the purpose of treating a patient with the disorder. There is no formal study protocol and no control group and the clinician is focused on treating the patient.

The Council recognizes the difficulty many patients have in obtaining reimbursement for the cost of experimental treatments; this issue implicates the broader concern with access to health care in general about which the Council has already taken a position. However, this report is not intended to address the issues associated with experimental treatments, but rather is designed to focus specifically on the issue of access to clinical research trials. "Research" is designed to yield generalizable knowledge. Although subjects may derive some collateral benefits from participation, the primary purpose is not to provide treatment, or individual therapeutic benefits. The long-term goal of any clinical research protocol is to provide better treatment for the class of subjects from which participants are drawn. For example, although a new AIDS protocol may not provide direct therapeutic benefit to the subjects enrolled, it may eventually lead to a treatment that will help all AIDS patients.

Presently, there is no absolute legal right to standard therapy in our society.[1] In a 1994 report, the Council discussed the right to basic health care and five criteria under which therapies may be judged and determined to fall into the category of "basic."[2] The five issues to consider are: (1) degree of benefit, (2) likelihood of benefit, (3) duration of benefit, (4) cost, and (5) number of people who will benefit.[3] Research entails uncertain degree, likelihood, and duration of benefit, as well as high cost and a low number of people who will benefit. Therefore, research fails to fit into the category of health care that society has an obligation to provide to all members regardless of ability to pay. Additionally, because clinical research trials are not necessarily designed to provide an established individual benefit, patients' interests in participating in research are smaller than their interests in receiving treatment in a therapeutic, clinical setting. There is a continuum along which patients' strongest interests (access to proven treatments) and lesser interests (access to experimental treatments or access to a research protocol) may be mapped. Since there is no absolute right of access in the first situation of strongest interest noted above, it is inconsistent to argue for a right of access in the research situation where the interest is weaker. That point not withstanding, we shall argue for a right to fair consideration—in other words, a right not to be discriminated against unfairly with respect to inclusion in a potential subject pool. If there is such a right to fair consideration, it must be based on the potential benefits of research participation. These potential benefits can be divided into three general categories: direct therapeutic, indirect therapeutic, and altruistic. Each of these is addressed below.