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Strengthening Institutional Review Board Review of Highly Innovative Interventions in Clinical Trials

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Highly innovative approaches to disease treatment offer hope for therapeutic breakthroughs but also may cause serious unexpected adverse effects. For instance, repeated transplantation of neural stem cells resulted in multiple donor cell tumors,¹ and gene transfer using retrovirus vectors caused T-cell leukemia.² Such interventions can be considered to be highly innovative because the biological mechanisms are not fully understood, animal models do not reliably predict human effects, adverse effects cannot be minimized by starting with a low “dose,” and the interventions have never or only rarely been previously used in humans.³

Opportunities to Protect Research Participants

Even after the design of a clinical trial of a highly innovative intervention has received regulatory approval, protection for study participants can be significantly strengthened. In a phase 1 trial of a monoclonal antibody that activates CD28 receptors on T lymphocytes, all of the first 5 participants who were administered the antibody simultaneously developed immediate life-threatening hypotension.³ Regulatory agencies and an institutional review board (IRB) failed to suggest observing effects in 1 participant before administering it to the next, which would have allowed the trial to be stopped after the first life-threatening adverse event.

Centralized combined scientific and ethics review may better protect participants in highly innovative clinical trials. The Recombinant DNA Advisory Committee (RAC) at the National Institutes of Health (NIH) conducts in-depth, public review of proposed innovative clinical trials of gene transfer.⁴ In the vast majority of these reviews, the RAC makes suggestions to enhance safety,⁵ such as excluding participants at significantly increased risk of complications, making safety end points clearer and more specific, adding tests to detect serious adverse events, and monitoring a participant for adverse events before administering the study intervention to the next participant. However, the RAC process has been criticized for meeting only quarterly and recommending additional studies that are not essential but delay trials. Moreover, local IRB approval is still required.⁴

In contrast, the National Cancer Institute Centralized IRB Initiative (CIRB) reduces duplicative reviews.⁶ The CIRB performs in-depth review of multisite cancer clinical trials and makes

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detailed reviews, minutes, and correspondence with investigators available to local IRBs, which may choose to accept CIRB review rather than perform full local review.

Reporting Unanticipated Serious Adverse Events and Negative Results

Institutional review boards and scientific review panels need to be informed about unanticipated serious adverse events due to a highly innovative intervention, but these results might not be publicly reported. For example, in a clinical trial of a cell-free hemoglobin-based blood substitute, increased mortality was not reported until 5 years after the trial was stopped.⁷ When another controversial clinical trial with the product was proposed, IRBs were not aware of the results of the first study.⁸ In another example, when a trial found that a novel immunologic modifier for treating human immunodeficiency virus infection was ineffective, the sponsor tried to block publication.⁹

Sponsors may receive a competitive advantage by not reporting negative results and serious adverse events. Competitors may pursue a dead end, giving the sponsor time to develop new approaches. In addition, negative results may hamper raising new capital. However, it is ethically troubling to expose participants in trials to serious risks that had been identified but are not known to other researchers and IRBs. The recent Food and Drug Administration requirements to report basic results and serious adverse events on ClinicalTrials.gov do not apply to an intervention that is studied under an Investigational New Drug application and does not receive Food and Drug Administration approval.¹⁰ Negative results and safety concerns must be reported promptly. Proprietary information about the study product, including details of how it is manufactured, can be redacted for public presentation.

Learning From Previous Reviews

Institutional review boards cannot learn from previous reviews of trials of a highly innovative intervention because IRBs do not make their reviews publicly available. However, analyzing previous reviews would help IRBs identify pertinent ethical issues and suggest how to improve the benefit-to-risk ratio or informed consent process.

At a minimum, reviews should be available to other IRBs reviewing phase 1 clinical trials of similarly innovative interventions. However, there are good reasons for even wider access. Those who design highly innovative trials (including researchers, sponsors, biostatisticians, and ethicists) can strengthen protocols if they address concerns about risk and consent raised previously by IRBs. Making such reviews public would also enhance transparency, accountability, and public trust.

The Special Role of Academic Health Centers

Many trials of highly innovative interventions will require collaboration between industry and academic health centers. Such trials commonly require physician and staff expertise and special imaging and laboratory and pathology studies that are not available in community hospitals or contract research organizations. Academic health centers have a responsibility to promote the critical appraisal of evidence and provide appropriate role models. It is inconsistent for faculty members to require students and trainees to think critically but to withhold negative results from clinical trials.

At academic health centers, IRBs could require investigators involved in clinical trials of highly innovative interventions to post basic results and serious adverse events on ClinicalTrials.gov, even if they are not legally required to do so. Furthermore, IRBs should require investigators to state in the consent form that they intend to report negative results and serious adverse events in a timely fashion. Moreover, academic health centers should voluntarily make available on

their Web sites redacted minutes of their IRB reviews of such clinical trials. Posted materials should include the issues discussed by the IRB, questions posed to the principal investigator, and suggested and required protocol modifications.

Academic health centers should be on the cutting edge in developing ethical standards, just as they are in the forefront of scientific innovation. The top 10 or 20 NIH-funded research institutions, the NIH-funded Clinical and Translational Science Award programs, and the Association of American Medical Colleges could take the initiative to implement these measures. Such coordinated action would allay concerns that an academic health center acting unilaterally would be at a competitive disadvantage for obtaining industry contracts and grants.

The Special Role of the NIH

As the major funder of biomedical research and an advocate for the translation of bench discoveries to clinical therapies, the NIH has the stature and the resources to establish reforms. The NIH could establish and maintain a clearinghouse of redacted reviews by IRBs of clinical trials of highly innovative interventions. Medical journals could require that authors place IRB reviews of such trials in the NIH clearinghouse as a condition of submission and evaluation.

The NIH also could establish a centralized process to provide combined scientific and ethical review of clinical trials of highly innovative interventions. The NIH can convene experts free of conflicts to serve as reviewers, unlike IRBs at study sites or independent IRBs. To discourage duplicative reviews, the Office of Human Research Protections could issue guidance that local IRBs may defer to the review of this central IRB. Inviting chairs of IRBs at leading research institutions to serve on this central panel may help build acceptance. To reduce delays, the central IRB could use video conferencing between scheduled face-to-face meetings.

Conclusions

In summary, early phase trials of highly innovative interventions offer hope for therapeutic breakthroughs but also pose the risk of serious unanticipated adverse effects. To protect study participants and to strengthen trial design, IRB reviews of such trials and data on serious adverse events and negative results should be made publicly available.

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