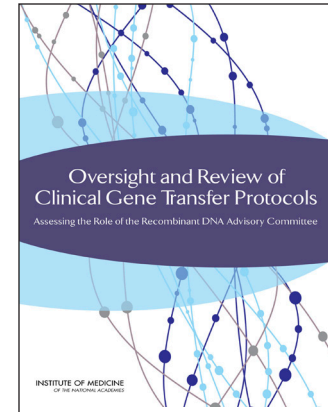


Oversight and Review of Clinical Gene Transfer Protocols

Assessing the Role of the Recombinant DNA Advisory Committee



In the 1970s, scientists first developed methods for manipulating DNA—resulting in what is called recombinant DNA. One of the applications of these methods, known as gene transfer, is an experimental technique involving the insertion of new genetic material into a human subject. This research sparked discussion and controversy over scientific, research participant safety, ethical, and other societal concerns.

In response to these concerns, the National Institutes of Health (NIH) established in 1974 the Recombinant DNA Advisory Committee (RAC) to provide oversight and a public forum for discussion. Today, NIH-supported researchers are still required to submit all research protocols—detailed plans of procedures—for human gene transfer trials, known as individual clinical trial protocols, to the RAC. The RAC then determines which of these require further review and public discussion by the RAC.

Human gene transfer research remains one of the most heavily regulated areas of clinical research. In addition to review by the RAC, before human subjects can be enrolled in a study, individual clinical trial protocols are subject to review by the U.S. Food and Drug Administration (FDA) at the federal level and by institutional review boards (IRBs) and institutional biosafety committees (IBCs). With the accumulation of safety data and increased experience with its applications, gene transfer research's associated risks are now better understood. Therefore many have argued that today RAC review is redundant and unnecessary in its current form. Responding to a request from the Director of the NIH, the Institute of Medicine (IOM) convened a committee to determine whether gene transfer research continues to raise concerns that warrant extra oversight by the RAC of individual clinical trial protocols involving gene

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transfer. In addition, the committee was asked to recommend criteria to guide when the RAC should, if deemed necessary, review protocols.

In its report, *Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee*, the committee concludes that patient safety will not be compromised if the RAC does not review all individual protocols. Instead, the RAC should review only those protocols that are considered to raise exceptional or unknown risk—as defined by one of three criteria outlined by the committee—and when another oversight or regulatory body (e.g. FDA, IRB, and IBC) cannot adequately review the protocol.

More Clinical Trials, Fewer Concerns

When recombinant DNA technology was new, and the many risks concerning individual clinical trial protocols were uncertain, the public, scientists, and policy makers raised important questions about potential dangers—such as whether this technology could harm patients, create new infectious organisms, or make genetic alterations that could be passed down to future human generations.

In its report, the IOM committee finds that the major concerns about recombinant DNA from 40 years ago do not raise the same level of concern today, as hundreds of gene therapy clinical trials have evaluated the technique's safety and effectiveness.

Focusing on Exceptional Cases

The committee finds that while some gene transfer research continues to raise important scientific, social, and ethical questions, not all of gene transfer research can be considered sufficiently novel or socially controversial to justify RAC oversight. Therefore, the committee recommends that individual clinical trial protocols

should be reviewed by the RAC only in exceptional circumstances.

The committee determines that the NIH Director, in consultation with institutional oversight bodies, should identify those exceptional protocols. This will serve to optimize safety and to assist IRBs and IBCs in their own review with the goal of increasing their capacity over time. In order to minimize administrative burdens for applicants, investigators can use the same submission materials that are required for FDA review of investigational new drugs. This reduced administrative burden could help facilitate progress with important scientific investigations.

Exceptional cases that would warrant RAC review would be those that otherwise could not be adequately reviewed by other regulatory and oversight processes such as IRBs, IBCs, and FDA and that meet one or more of the following criteria:

- The protocol uses a new vector, genetic material, or delivery methodology which represents a first-in-human experience, thus presenting an unknown risk.
- The protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value.
- The proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known which may render it difficult for local and federal regulatory bodies to rigorously evaluate the protocol.

Furthermore, the NIH Director, in consultation with appropriate regulatory and/or oversight authorities, should consider broader societal issues and ethical concerns when identifying protocols for review.

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Oversight for Applications of Emerging Technologies

While gene transfer research continues to advance and still can present heightened risks to research participants, other applications of emerging technologies in clinical research may pose similar or even greater risks and may generate comparable scientific, safety, and ethical concerns. For example, in nanotechnology, where familiar materials are manipulated at a very small scale, uncertainty remains about how these very small particles could adversely affect the body.

Therefore, the IOM committee recommends that the NIH Director consider exploring the necessity of oversight of applications of other emerging areas of science in human clinical intervention in addition to gene transfer. To accomplish this, the committee recommends that the NIH Director convene a working group that will consider whether additional oversight and public deliberation is needed for other applications of these technologies. The focus of this task should be on those human clinical applications that may be of particular interest to the public or that feature uncertain risk, may pose harms to individuals or to the public's health, and which could not otherwise be adequately assessed by existing regulatory and oversight processes.


If additional oversight is deemed appropriate, the RAC should be used as one possible model, particularly with regard to

- providing a public forum for the review and discussion of emerging areas of science,

including the capacity to consult with, inform, and educate IRBs and IBCs;

- providing a venue to foster scientific and public awareness regarding emerging science in order to address concerns about clinical investigation and future societal implications;
- integrating the capacity to survey, add up, and analyze adverse events across related trials of emerging technologies; and
- performing an additional level of review of individual protocols that are identified by the NIH Director, in consultation with one or more IRBs and IBCs, based on exceptional issues as defined above.

Conclusion

Four decades ago, the RAC was established in response to the application of an emerging technology of great public interest and with risks and benefits only barely understood. Over time, it has provided successful oversight of complex technology. In addition, by engaging the public in its process, it has engendered trust and credibility. While some aspects of human gene transfer may continue to merit RAC review today, much of this review can be done through the other existing regulatory and oversight bodies, and applications of other emerging technologies could benefit from the lessons learned and structures built for the responsible development of this field. 



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