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Future Oversight of Recombinant DNA Research: Recommendations of an Institute of Medicine Committee

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VIEWPOINT

Future Oversight of Recombinant DNA Research

Recommendations of an Institute of Medicine Committee

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The National Institutes of Health (NIH) established the Recombinant DNA Advisory Committee (RAC) in 1974 in response to public concerns about the safety of manipulating genetic material through recombinant DNA (rDNA).¹ Jesse Gelsinger's death during a genetic therapy trial in 1999 further galvanized societal apprehensions.² The RAC—a federal advisory committee to the NIH director—performs multiple functions: reviewing all gene transfer protocols, selecting specific protocols for public review, and acting as a national forum for rDNA research.³ Through its Gene Transfer Safety Assessment Board the RAC also surveils, aggregates, and analyzes adverse events across all human gene transfer trials.

Although societal concerns have not entirely abated, the accumulation of 40 years of experience with gene transfer research has led to a better understanding and acceptance of the risks and potential benefits. Consequently, only approximately 20% of all protocols submitted to the NIH are currently selected for additional public review; the remaining are approved without additional review.⁴

As gene transfer research has matured, the complexity of the overall regulatory environment has remained. Gene transfer research continues to be subjected to multiple layers of review: the Food and Drug Administration (FDA), institutional review boards (IRBs), institutional biosafety committees (IBCs), and the RAC. By regulation, the FDA, IRB, and IBC must all approve rDNA research; although the RAC is technically advisory, in practice, it has become a prerequisite for the research to proceed. The partly overlapping functions of these regulatory bodies reveal tensions among competing values: protection of research participants while facilitating scientific progress; transparency while protecting personal privacy and proprietary data; and effective oversight while not needlessly encumbering scientific investigation.

It is within the context of overlapping regulatory authority and improved scientific understanding and social acceptance that the NIH commissioned the Institute of Medicine (IOM) to assess whether gene transfer research continues to warrant additional oversight, especially for individual clinical protocol review.⁵ The overarching goal was to ensure patient safety and the ethical conduct of research while not subjecting scientists to unnecessary regulatory burdens, which can impede or delay scientific exploration and medical innovation.

Limit RAC Oversight to Extraordinary Circumstances

The RAC engendered trust and public confidence in an emerging area of science, which, at the time of its founding, was deeply controversial. It provided expertise to inform the scientific community, alleviate public misgiv-

ings, and guide the NIH at the complex intersection of science and bioethics.

Most gene transfer research today, however, is no longer sufficiently novel, ethically problematic, or socially controversial to justify such intensive scrutiny—above the oversight afforded similar areas of clinical research. The concerns that led to the creation of the RAC have largely abated over 4 decades, including the creation of transmissible pathogens, unintentional germline modification or contamination, and harm to third parties or society at large.⁶ Existing regulatory bodies, moreover, are charged with and capable of effectively overseeing the vast majority of rDNA research.

The RAC's function of reviewing selected individual protocols, in particular, rarely adds value to the existing regulatory framework, while posing significant delays and administrative burdens.⁷ Although a small number of gene transfer protocols may continue to warrant public review, over time the FDA, IRBs, and IBCs should be able to effectively undertake all oversight functions. To achieve this goal, the expertise and capacities of existing regulatory bodies should be expanded. In addition, the criteria for the RAC's selection of individual protocols should be reformed, as described below.

The safety of human research participants remains the paramount concern, but additional oversight should not be required unless it affords a corresponding benefit; regulation without added value impedes scientific progress. The IOM committee therefore recommended that the RAC should review individual protocols only if other regulatory authorities could not adequately do so and the study meets one of the following criteria: (1) the protocol uses a new vector, genetic material, or delivery method representing a first-in-human experience, thus presenting unknown risks; (2) the protocol relies on preclinical safety data obtained using a new preclinical model system of unknown and unconfirmed value; or (3) the protocol involves a vector, gene construct, or method of delivery associated with possible toxicities that are not widely known. Beyond these discrete criteria, the NIH, in consultation with IRBs and IBCs, should be able to require public review of individual protocols if the director believes there are wider social and ethical concerns.

The expertise and authority of the RAC are best used to provide additional oversight only in exceptional circumstances when the above criteria are fulfilled. The central characteristics of the RAC, such as transparency and inclusive engagement—key principles of good governance—should continue. Notably, the IOM committee recommended that the NIH director, in consultation with IRBs and IBCs, should select protocols for

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review—as opposed to the existing mechanism for protocol selection by RAC members.

By working in consultation with the existing regulatory bodies, the NIH could enhance oversight capacities consistent with the authority and responsibilities for which they are entrusted. This ongoing collaborative process would also, over time, further reduce the necessity of the RAC's protocol review functions.

Evolution of Oversight of Emerging Clinical Research

Gene transfer research no longer poses risks or societal concerns that can be regarded as unique in modern science. Contemporary laboratory and clinical research often shares characteristics similar to those of gene transfer studies 40 years ago. Nanotechnology, for example, presents fundamental scientific questions about the chemical, optical, and other properties of familiar materials in unfamiliar sizes. In human applications, these novel questions may render it difficult to assess the safety of clinical trials, as well as the risks to the workforce handling the materials and the risks to the environment into which the materials are excreted. Synthetic biology can raise societal concerns about the appropriate scope of human endeavors to shape the natural world. Neurobiology can blur the line between what is commonly thought of today as body and soul as it probes the underexplored world of cognition and human behavior.

Gene transfer research no longer stands alone as the only human application of an emerging technology that could benefit from additional oversight. Nor is it even necessarily the most deserving of such attention. Consequently, the IOM committee

recommended that the NIH director charge a standing or new committee to examine the need for additional or different oversight for clinical applications of emerging technologies that pose novel risks. A new process for overseeing novel research across scientific realms could be modeled on the most innovative and effective functions of the RAC: providing a public forum for review and discussion of emerging science; partnering and consulting with and educating local review bodies; fostering scientific and public awareness; and enhancing the capacity to surveil, aggregate, and analyze adverse events across related trials of emerging technologies.

Although modeling a new process on the best features of the RAC could improve oversight, there are also equally viable options. A process to review multiple spheres of evolving science, for example, could be built around the widely discussed idea of a centralized IRB that could provide subject matter expertise for specific scientific enterprises. Whatever processes are adopted, however, they should complement, not duplicate or hamper, the work of existing oversight bodies. A key feature of future regulatory reform of human subjects research is that it must be limited to rare circumstances, such as when existing bodies lack the capacity or there is significant societal concern.

The future of clinical trial oversight needs to reinforce and augment existing institutional capacities and expertise so that the need for additional review becomes a rare occurrence. That would fulfill the admirable goals of rigorous safeguards for research participants, consistency of application across scientific realms, and the imperative of advancing important scientific discoveries.

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